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Aims and Scope

Neurospine provides spine clinicians and researchers with peer-reviewed articles on basic and clinical investigation of spine and spinal cord to enhance patient management, education, clinical or experimental research, and professionalism. The journal will consider submissions in areas on craniocervical to lumbosacral spine including the followings: neuroscience and pain research, bone and mineral research, disc and joint research, bio and industrial technology, pathophysiology, risk factors, symptomatology, imaging, treatment, rehabilitation of spine, spinal cord and peripheral nerve diseases. Specifically, basic and technology researches include the most influential research papers from all fields of science and technology, revolutionizing what physicians and researchers practicing the art of spinal neurosurgery worldwide know. Thus, we welcome valuable basic and translational technology research articles to introduce cutting-edge research of fundamental sciences and technology in clinical spinal neurosurgery. Clinical or basic research articles, review articles, case reports, technical notes, and letters to the editor written in English will be accepted.

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Contact Neurospine

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nd #407, Dong-A Villate 2 Town, 350, Seocho-daero, Seocho-gu, Seoul 06631, Korea

Tel: +82-2-585-5455 • Fax: +82-2-523-6812 • E-mail: ksns1987@gmail.com

Editorial Office

Department of Neurosurgery, Spine and Spinal Cord Institute, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea

Tel: +82-2-2228-2172 • Fax: +82-2-313-5970 • E-mail: theneurospine@gmail.com

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Michael C. Prabhu, Kevin C. Jacob, Madhav R. Patel, Hanna Pawlowski, Nisheka N. Vanjani, Kern Singh

Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

The minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) is a popular surgical technique for lumbar arthrodesis, widely considered to hold great efficacy while conferring an impressive safety profile through the minimization of soft tissue damage. This elegant approach to lumbar stabilization is the byproduct of several innovations throughout the past century. In 1934, Mixter and Barr's paper in the New England Journal of Medicine elucidated the role of disc herniation in spinal instability and radiculopathy, prompting surgeons to explore new approaches and instruments to access the disc space. In 1944, Briggs and Milligan published their novel technique, the posterior lumbar interbody fusion (PLIF), involving continuous removal of vertebral bone chips and replacement of the disc with a round bone peg. The following decades witnessed several PLIF modifications, including the addition of long pedicle screws. In 1982, Harms and Rolinger sought to redefine the posterior corridor by approaching the disc space through the intervertebral foramen, establishing the transforaminal lumbar interbody fusion (TLIF). In the 1990s, lumbar spine surgery experienced a paradigm shift, with surgeons placing increased emphasis on tissue-sparing minimally invasive techniques. Spurred by this revolution, Foley and Lefkowitz published their novel MIS-TLIF technique in 2002. The MIS-TLIF has demonstrated comparable surgical outcomes to the TLIF, with an improved safety profile. Here, we present a view into the history of the posterior-approach treatment of the discogenic radiculopathy, culminating in the MIS-TLIF. Additionally, we evaluate the hallmark characteristics, technical variability, and reported outcomes of the modern MIS-TLIF and take a brief look at technologies that may define the future MIS-TLIF.

Keywords: MIS-TLIF, Minimally invasive, Lumbar fusion, Transforaminal lumbar interbody fusion

INTRODUCTION

Degenerative disc disease of the lumbar spine is a common disabling condition, often resulting in low back pain, radicular leg pain, and spinal deformity. In the case of conservative treatment failure, the discogenic radiculopathy is often treated surgically in the form of a lumbar interbody fusion. Several approaches are used for this procedure, differing in their strategic access route to the disc space.¹

In the mid-1900s, surgeons began exploring posterior access corridors for lumbar arthrodesis. One such technique, the transforaminal lumbar interbody fusion (TLIF), was developed in 1982 and thereafter gained traction among the surgical community due to its innovative respect for neurological elements that can be harmed while approaching the disc space. In 2002, the TLIF was modified to incorporate tissue-sparing retraction, and the minimally invasive TLIF (MIS-TLIF) was born. In the present article, we deliver a historical perspective on the development of the MIS-TLIF, as well as an evaluation of its current outcomes and a look at further innovations on the horizon.
A LOOK TO THE PAST: SETTING THE STAGE FOR THE MIS-TLIF

The history of the MIS-TLIF begins when clinicians reached a consensus on the focal significance of lumbar disc herniation in radiculopathy after decades spent poised at the brink of clarification. This pathophysiological understanding was imperative before surgeons could make purposeful strides toward a technical solution. Thus, the story of the MIS-TLIF begins nearly 70 years before its inception in 2002.

1. Understanding Discogenic Radiculopathy: 1896–1934

In August of 1934, the New England Journal of Medicine published an article from 2 Boston physicians that would change the landscape of lumbar spine surgery, William J. Mixter and Joseph S. Barr, working out of Massachusetts General Hospital, wrote of the phenomenon of intervertebral disc herniation, and its critical role in lumbar instability and sciatica. They suggested nerve root decompression and spinal fusion as the preferred treatment, prompting surgeons to develop novel access methods and specific tools to accomplish these goals.

Though Mixter and Barr’s connection has had a profound impact, notable advancements had previously been made. One 2013 historical investigation led by Stienen et al. has elucidated the early progress in the treatment of disc herniation, preceding the work of Mixter and Barr, by physicians published in German. As early as 1896, spinal trauma related to disc rupture had been noted by Swiss surgeon Emil Theodor Kocher, and in 1909 a report of degenerative disc resection was delivered by German physicians Hermann Oppenheim and Fedor Krause.

At that time, however, no correlation was drawn between disc herniation and sciatica. A 1927 case report from Zurich neurologist Otto Veraguth and his surgeon colleague Hans Brun detailed successful transdural resection of herniated L4–5 disc fragments. Veraguth accurately correlated clinical and radiographic findings with a lesion of the lower lumbar segment (though he was unable to identify its true origin in the disc space), and Brun’s operation successfully relieved the patient of radicular pain.

Interestingly, another Boston duo demonstrated insight regarding the discogenic radiculopathy before Mixter and Barr. In 1911, Joel Goldthwait uncovered a correlation between annulus fibrosus rupture, neurologic signs, and symptomatic sciatica after anatomical studies on a patient following treatment by neurosurgeon Harvey Cushing (a former student of Emil Theodor Kocher), who performed a laminectomy for cauda equina decompression. In 1929, Baltimore neurosurgeon Walter Dandy published his surgical experience removing loose cartilaginous fragments transdurally, which he postoperatively concluded to be consistent with disc material and traumatic in nature. Dandy described the disc material as bulging out like a tumor into the spinal canal, compressing the nerve roots of the cauda equina and causing radicular motor and sensory paralysis.

Despite these advances in identification, pathophysiological understanding, and surgical treatment of intervertebral disc herniation, it was not until Mixter and Barr’s seminal 1934 paper that a consensus was reached. However, it is thanks to the work of those that came before that the stage was set for Mixter and Barr to uncover the phenomenon of the discogenic sciatica and usher in a new era of surgical disc repair.


Spurred by the new information of the discogenic sciatica as well as Mixter and Barr’s surgical advice, in 1944 Briggs and Milligan published a landmark paper describing their novel
surgical technique, the posterior lumbar interbody fusion (PLIF). Using the term “chip fusion,” their technique consisted of exposing the spine posteriorly and removing chips of bone from the spinous processes, as well as partially excising the lamina and facet joints. These excisions exposed the disc space, and the disc was removed and replaced with a round bone peg. The bone chips initially obtained were placed over the dura and facet joints after insertion of the bone peg. Though Briggs and Milligan saw promising results in their PLIF patients, several issues remained: patients faced a long and arduous recovery in the hospital, the procedure carried an imposing complication profile particularly with neurological complications and pseudarthrosis, and it proved difficult for surgeons to adopt. Briggs and Milligan may have achieved some success in postoperative fusion, though they did not report any. As such, it failed to gain complete acceptance throughout the spine surgical community.

Despite the early work of Briggs and Milligan, later investigation has revealed that a neurosurgeon from Hawaii named Ralph Cloward actually demonstrated the earliest PLIF attempt. After noticing an opportunity to insert spinous bone fragments into the disc space during a discectomy in 1940, Cloward essentially attempted the first PLIF, though the patient died and he did not pursue the technique further. In 1943, however, he reattempted the procedure and noted fusion success, after which he devoted much of his career to continually enhancing the PLIF.

Over the next 40 years, the PLIF underwent several modifications, including replacement of the bone peg with bone grafts from the ilium or cadavers, addition of Harrington rod instrumentation, and preservation of certain structures like the proximal facet joint and cortical plate. One concept that would prove particularly valuable was the alteration of facet screws to form longer screws to be placed through the vertebral pedicles. This innovation emerged from a keen insight that pedicle screws can provide three-column fixation and thereby maximize lumbar stability during fusion. Pedicle screw instrumentation was brought to the PLIF in the late 1980s by a team led by orthopaedic surgeon Art Steffee, who intuitively recognized that placement of pedicle screws through the anterior spinal column delivered an optimization of stabilization and facilitation of fusion that had eluded facet screws.

Interestingly, the work of 2 innovators during this time foreshadowed future spine surgical techniques. In 1968, American surgeon Leon Wiltse wrote of a novel technique for posterior lumbar spinal access. Later referred to as the Wiltse paraspinous approach, this technique called for dissection of the natural cleavage between the multifidus and longissimus paraspinous muscles as a pathway to the vertebral column. Wiltse’s insightful conceptualization of a muscle-splitting route to the spine served as a unique glimpse into the later field of minimally invasive spine surgery.

In 1973, Philadelphia orthopaedic surgeon Parviz Kambin introduced a transforaminal route to the disc space, exploiting an access corridor free of significant vascular and neural structures. Kambin initially explored this pathway in percutaneous posterolateral resection of herniated L3–4 and L4–5 discs, using fluoroscopic guidance and an incision 8–9 cm from the midline. "Kambin’s triangle" (recently described three-dimensionally as "Kambin’s prism" by Fanous et al.) is enclosed anteriorly by the exiting nerve root, inferiorly by the proximal endplate of the lower vertebral body, posteriorly by the superior articular process of the lower vertebra, and medially by the traversing nerve root and thecal sac. Without necessitating bone removal, this anatomical prism enabled Kambin to perform endoscopic discectomy procedures while avoiding neural retraction.

In 1982, 2 German surgeons sought to entirely rethink the posterior approach to lumbar fusion, via a transforaminal access route similar to that explored by Kambin. Harms and Rolinger published their new technique, the TLIF, which employed a unilateral corridor through the intervertebral foramen to directly access the anterior disc space and implant titanium mesh packed with bone graft. With this new procedure, and with Harms and Jeszenszky’s subsequent refinement of the
technique in 1998 to incorporate a complete removal of the facet joint, surgeons could now posteriorly access the disc space with impressively reduced damage to nerve roots and other key anatomic complexes. Though reminiscent of Kambin’s transforaminal insight, the TLIF called for excision of the facet joint, pars interarticularis, and hemilamina, and as such moved beyond Kambin’s prism to create an expanded transforaminal corridor which facilitated insertion of an interbody device.

The improvements delivered by the TLIF were intuitive. The unilateral approach inherently demanded less soft tissue damage than the PLIF’s bilateral approach. The PLIF required substantial neural retraction, and subsequently held a particularly dangerous risk of injury to nerve roots and dura mater, among other structures. Incorporating a complete facetectomy, the TLIF dramatically reduced thecal sac traction, protecting patients from much of these potential neurological injuries. Accordingly, the TLIF steadily gained recognition as an effective and safer surgical option. Studies conducted in 2017, 2018, and 2021 comparing PLIFs and TLIFs in 2,825 total patients found TLIFs to exhibit impressive reductions in operative time, blood loss, dural tears, and nerve root injuries. An additional advantage of the TLIF is the superior restoration of lordosis, a critical aim when surgically correcting spondylolisthesis. A 2022 study reporting an 8-year dual-center comparison of single-level PLIFs and TLIFs noted markedly similar clinical and radiographic outcomes, while PLIFs held a 5-time greater risk of dural tears.

3. Inception of the MIS-TLIF: Turn of the 21st Century

While Harms and Rolinger’s TLIF demonstrated significant improvement in the search for optimal lumbar stabilization, surgeons would remain discontent with its efficacy. The success of posterior-approach lumbar arthrodesis was curtailed by exposure-related adverse events that would garner the general term of “fusion disease.” Extensive retraction and muscle stripping resulted in an imposing amount of injury to soft tissues, paining the way for postoperative issues including prolonged back pain and poor long-term outcomes. In light of these unwanted issues of paraspinousiatrogenic injury associated with the open TLIF, further innovations to posterior-approach lumbar stabilization were inevitable.

In 2002, Kevin Foley and Michael Lefkowitz of the University of Tennessee published an article in Clinical Neurosurgery entitled “Advances in minimally invasive spine surgery” detailing their adaptation of the TLIF to employ tissue-sparing mechanisms. Though certainly not the first change to posterior-approach lumbar interbody fusion, the proposed MIS-TLIF brought a new type of change.

By the early 2000s, minimally invasive techniques had found their way into several spinal procedures. Notably, lumbar discectomies had seen successful applications of laparoscopic and microendoscopic techniques. Issues of lengthy hospital stay, significant costs, and increased morbidity associated with open procedures had aroused increasing concern for spine surgeons of the time. The danger of substantial muscle retraction especially revealed itself. Studies of this time reported significant damage to lumbar musculature and subsequently increased incidence of low back pain, increased levels of ischemia, increased weakness, and persistent pathological alterations of paraspinal muscles, all in direct association with the extensive use of muscle retractors in open spine surgery. Dr. Foley, a pioneer of the microendoscopic lumbar discectomy, recognized the innovative significance of minimally invasive surgery far different from the innovations that lumbar procedures had seen in the past. The TLIF improved the PLIF by altering it conceptually, changing the access window to the disc space. In contrast, the MIS-TLIF improved upon the open TLIF in a more nuanced manner, keeping it conceptually unaltered but refining it to further enhance its safety profile for patients, with a reduced “surgical footprint.”

Foley and Lefkowitz’s MIS-TLIF incorporated 2 mirroring 1-inch paramedian incisions. The first incision was used for the insertion of a tubular retractor to the facet joint for facetectomy, discectomy, and placement of an interbody implant and bone graft. Upon tubular retractor removal, both contralateral paramedian incisions were then used for pedicle screw fixation using a percutaneous screw-rod system. The use of a tubular retractor enabled the surgeon to reach the disc space and perform the TLIF through a circumferentially defined surgical window, with impressive mitigation of soft tissue disruption along the way. Preservation of soft tissue was the innovative hallmark of the MIS-TLIF, aimed at improving the patient experience perioperatively (Fig. 3).

IN THE PRESENT: CHARACTERIZING THE MIS-TLIF

1. Technological Advancements of the MIS-TLIF

Technological innovations in surgery have paved the way for procedures like the MIS-TLIF. Perhaps the quintessential piece of equipment enabling this procedure is the tubular retractor (Fig. 4), introduced by Foley and Smith in 1994. The first tu-
The evolution of MIS-TLIF

The tubular retractor system allowed surgeons to split muscles, rather than cut them, on the path to the spine. This was accomplished using a series of sequential tubular dilators with consecutively increasing diameters, and placement of a tubular retractor over the final dilator. Surgeons could therefore access the spine via a tissue-sparing pathway, and still incorporate previously developed microsurgical instruments including Kerrison rongeurs and nerve root retractors. The resulting decrease in muscle damage was the pivotal change necessary to temper the chronic back pain and other postoperative symptoms faced by open TLIF patients.

Though tubular retractors yielded a beneficial preservation of soft tissue and subsequent reduction of access-related back pain, the use of this technology came at a certain cost. Tubular retractors dramatically limit operative visualization and subsequent understanding of the spatial positioning of anatomical structures. In an open TLIF, a large surgical incision maximizes the view of anatomical landmarks to direct operative steps. The small operative window of the MIS-TLIF restricts the ability to place a large interbody spacer, threatening the potential to adequately restore lordosis. The insufficient ability for a discectomy and large cage insertion, as well as the incorporation of only a unilateral facetectomy, may put the MIS-TLIF at further risk regarding postoperative pseudarthrosis.

To account for restricted visualization, MIS-TLIF surgeons rely on diagnostic imaging modalities such as intraoperative fluoroscopic guidance and neuromonitoring. Diverging from the open technique, surgeons must continuously interpret these modalities and integrate them fluidly within the operation. Additionally, surgeons must be prudent in managing intraoperative fluoroscopy so as to minimize radiation exposure to patients and staff. Thus, to perform the MIS-TLIF successfully, operating surgeons must conduct diligent preoperative planning to overcome decreased visualization, as successful patient outcomes rely on fluid integration of imaging with MIS techniques. In addition, MIS techniques carry a considerable surgical learning curve, rendering it imperative that surgeons take appropriate training measures and hold in high regard the importance of preoperative planning and the anatomical makeup of the operative field which loses direct visibility.

2. Modern Variability of the MIS-TLIF

In a 2020 effort to define the modern MIS-TLIF, Lener et al. evaluated the technical and procedural aspects reported in 75 MIS-TLIF-related articles published between 2010–2018. Their
comprehensive analysis of 4,920 total patients yielded 3 criteria most characteristic of MIS-TLIFs, related to the processes of retraction, incision, and visualization. The first of these is the use of tubular retractors in approaching the facet joint for cage insertion. The second is the use of paramedian incisions, thus excluding procedures using midline incisions from MIS standing. The third is that the considerable reductions in operative visualization are mitigated by the use of a microscope or endoscope. The intersection of these 3 hallmarks of the MIS-TLIF is illustrated in Fig. 5.

Though Lener’s team has admirably differentiated MIS-TLIFs from mini-open or traditional open techniques, the very need for their analysis is related to one interesting quality of the MIS-TLIF: that it contains within itself much variability. For while the 3 aforementioned criteria set a broad framework for the procedure to take form, there exist within that framework different variations of the technique. Fortunately, Lener and colleagues’ comprehensive and systematic investigation of the MIS-TLIF yielded some definition to its variability.

The first point of diversion among MIS-TLIFs involves the type of retractors used to access the facet joint. Though 81% of their included studies reported the use of tubular retractors, there remained variability as to which type of tubular retractors were used. 35% of studies discussed nonexpandable tubular retractors, 21% discussed expandable, and 25% discussed both types. Despite this slight variability, the general use of tubular retractors appears to be invariable in MIS-TLIFs, excluding procedures that use nontubular retractors or endoscopic access.

The primary point of MIS-TLIF diversity pertains to the properties of the interbody cage implanted into the affected disc space. Cages can vary in 3 distinct qualities: shape, material composition, and dynamic ability. Regarding cage shape, the 2 most common designs are banana-shaped and straight-shaped. Of the studies in Lener and colleagues’ analysis that reported the type of interbody cage used, 65.2% disclosed straight-shaped, 15.2% disclosed banana-shaped, and 15.2% mentioned either. A 2018 randomized controlled trial by Choi et al.57 assigned 44 patients to receive banana-shaped cages and 40 patients to receive straight-shaped. Their results indicated similarly favorable fusion rates and clinical improvements in disability and pain, though straight-shaped cages ended up in concluding favor based on the discovery that banana-shaped cages were associated with significantly higher rates of postoperative cage subsidence.

The material of interbody cage composition takes 2 primary forms: titanium and polyetheretherketone (PEEK). Lener’s team found that 82.8% of studies reporting cage material used PEEK, while 10.3% used titanium. Fusion rates reported in the literature are comparably favorable between the 2 cage materials,54 though a 2017 systematic review59 evaluating 410 patients did identify a significantly higher rate of postoperative cage subsidence from titanium cages. Based on these findings, the general favorability of PEEK cages over titanium may be related to a greater chance for successful fusion, similar to the general favorability of straight-shaped cages over banana-shaped.

The final area of cage variation concerns its dynamic capabilities. Interbody cages can be either static or expandable. The traditional use of static cages rendered the TLIF’s ability to adequately restore sagittal alignment controversial, due to its small window of disc space access relative to anterior-approach procedures. To mitigate this, expandable cages were developed such that they may be inserted into the disc space and then expanded to achieve the desired restoration of disc height and lordosis.56,61 Since their inception, expandable cages have become commonplace in MIS-TLIFs, used in 88.1% of studies in Lener’s review that reported type of interbody cage, in contrast to the 11.9% reporting use of static cages. Despite the intuitive benefits of expandable cages regarding lordosis restoration, the comparative effects between static and expandable cages remain unclear.62 A recent study60 comparing long-term radiographic outcomes between these cage types revealed that while expandable cages do appear to produce an environment more suitable to restoration of sagittal alignment and disc height, they also showed higher rates of cage subsidence, which may threaten their true advantage. Such subsidence may be related to the force of expansion required in the considerably small disc space, potentially placing unwanted stress against vertebral endplates and
leading to subsequent cage migration. In contrast, Li et al.'s analysis of 284 osteoporotic MIS-TLIF patients spoke to the fusion-related advantages of expandable cages, finding similar lordotic angles but significantly higher rates of intraoperative subsidence, postoperative subsidence, and cage migration with static cages. Teams led by Hawash and Russo found expandable cages to provide significantly greater and longer-lasting restoration of disc height, foraminal height, and segmental lordosis following MIS-TLIF than static cages, as well as improved postoperative disability scores. More comparative investigation is required, particularly in fusion rates.

Along with the cage implanted into the disc space, a bone graft is typically used to induce successful fusion. Though several variations exist, including bone morphogenetic protein and allograft transplants which continue to be explored, nearly 80% of studies in Lener's analysis reported the use of autograft, which typically comes in the form of iliac crest bone graft (ICBG). ICBG, taken from the hip of the patient receiving the MIS-TLIF, has been shown to lend itself kindly to successful fusion.

After interbody implant placement, the surgeon is left with the insertion of percutaneous pedicle screws for increased stabilization of the fused vertebrae. This step contains further diversity among MIS-TLIFs. Foley and Lefkowitz's initial concept employed a bilateral approach for pedicle screw fixation over 2 contralateral paramedian incisions. In the years since, however, surgeons have explored the idea of unilateral fixation. The unilateral technique utilizes the same incision that was made for cage insertion to insert pedicle screws, without necessitating a mirroring incision. In a prospective trial exploring the operative and clinical results of these 2 techniques, Choi et al. randomized 26 patients to undergo unilateral fixation and 27 patients to undergo bilateral fixation. While their unilateral fixation cohort demonstrated significantly lower operative time and blood loss, the perceived benefit of this technique stopped with these perioperative improvements. Both cohorts saw notable clinical improvements in disability and pain through 2 years. The most significant finding of this trial, however, is the observed difference in fusion rates. 84.6% of unilateral fixation patients showed radiographic evidence of successful fusion at 2 years, while 96.3% of bilateral fixation patients fused at 2 years. Choi et al. provide rationale for the unrivaled importance of fusion rates in this comparison, identifying this as the key measure of successful pedicle screw fixation, the aim of which is simply to facilitate fusion. Reflecting this, the investigators concluded that bilateral fixation is a superior option, providing more impressive lumbar stabilization and thereby delivering an environment more likely to promote successful fusion following MIS-TLIF.

Throughout the entirety of the MIS-TLIF, there remains the challenge of restricted operative visualization. While Lener's team did find that invariably some sort of magnification is used, the vast majority of procedures additionally incorporate some type of intraoperative imaging to guide their surgical effort. 79% of the 75 reviewed articles reported the use of standard fluoroscopy, while 3-dimensional (3D) fluoroscopy was noted in 11% of articles and intraoperative computed tomography (CT) imaging in 3% of articles. The demand for intraoperative guidance due to reduced visualization has shown to result in significantly greater fluoroscopy times for MIS-TLIFs relative to open TLIFs, posing a threat of extended radiation exposure to both patients and operative staff. Though cone-beam CT imaging systems provide reductions in surgeon radiation exposure relative to traditional fluoroscopy, standard fluoroscopy remains most prominent in MIS-TLIF procedures. Furthermore, it has been suggested that cone-beam CT imaging may provide simply a nonsignificant reduction in surgeon exposure while unnecessarily increasing radiation exposure to the patient.

3. Current MIS-TLIF Outcomes

Recent studies have explored MIS-TLIF outcomes, often pursuing a comparison to the open TLIF. Due to the characteristic reduction in muscle disruption, the relative superiority of the MIS-TLIF is primarily perioperative. Operative time, blood loss, hospital stay, and narcotic administration have seen encouraging reductions in MIS-TLIF populations. In addition, short and long-term outcomes in disability, back pain, and leg pain have favored MIS-TLIF patients relative to their open TLIF counterparts. Seng et al. compared MIS-TLIF to open TLIF with 5-year follow-up, observing similar midterm and long-term outcomes for disability, neurogenic symptom score, back/leg pain, and physical function as well as similar 1-year fusion rates. While long-term clinical trajectory was similar, the authors observed important MIS-TLIF benefits, specifically noting improved initial postoperative pain, decreased bleeding, earlier rehabilitation times, and shorter hospitalization. These findings have been echoed by teams led by Lau et al. and Wang et al. in comparative studies of open versus MIS-TLIF in obese populations, where authors reported significant perioperative benefits, reduced complications, and improved postoperative back pain for MIS-TLIF patients. A 2016 systematic review by Hu et al. noted that MIS-TLIF held significant advantages over open TLIF in blood loss, length of hospital stay, and complication rates, but it was also discovered that MIS-TLIF patients were faced with
significantly greater radiation exposure during surgery, suggesting that heightened fluoroscopy use may threaten long-term success. These findings were echoed by a 2020 systematic review from Miller et al. The widely demonstrated perioperative advantages of the MIS-TLIF over the open TLIF also appear to translate to financial benefits, with authors reporting reduced hospital costs and considerable preservation of hospital resources due to reductions in operative time and length of hospital stay. Cost-effectiveness of the MIS-TLIF may be further increased given recent trends of transitioning cases to the outpatient setting, where intuitively the imposing costs of hospitalization can be avoided.

Similar to its relationship with the open TLIF, the MIS-TLIF is evolutionary linked to the PLIF, and the inherent differences between the 2 procedures are well represented in comparisons of their outcomes. In a 2016 systematic review evaluating 856 MIS-TLIF patients and 806 open PLIF patients, Goldstein et al. found the 2 procedures undifferentiated by way of patient-reported clinical outcomes, though MIS-TLIFs demonstrated significant favorability in blood loss, time to ambulation, length of hospital stay, and perhaps most notably adverse events. These advantages of the MIS-TLIF are intuitive; with reduced muscle disruption through the use of muscle-splitting tubular retractors, it follows that the MIS-TLIF can deliver great perioperative benefit over its open procedural counterparts. Another systematic review by Goldstein et al. in the same year revealed both direct and indirect cost-savings associated with MIS-TLIFs relative to open TLIFs and PLIFs, further suggesting that the advantages of the MIS-TLIF lay primarily in the perioperative realm. The MIS-TLIF yields similar clinical outcomes to the TLIF and PLIF while improving the safety and economic considerations of lumbar fusion surgery.

One region at which the MIS-TLIF may remain limited is the L5–S1 vertebral level. The biomechanical significance of L5–S1 demands a strong effort in sagittal restoration, and the 2 surgical techniques most commonly used to achieve this are the TLIF and the anterior lumbar interbody fusion (ALIF), both of which have demonstrated successful fusion induction. A recent study by our team comparing MIS-TLIF to ALIF at L5–S1 discovered that ALIF patients on average experienced more favorable postoperative clinical outcomes in physical function, back pain, and leg pain, as well as significantly fewer incidences of postoperative fever. The ALIF is widely considered to be particularly suitable for lordosis restoration at L5–S1 due to its increased and direct vertebral access window, allowing for implantation of a larger interbody cage. Open TLIFs also have potential for considerable lordotic restoration, accomplishing comprehensive bilateral anterior column stabilization through a unilateral approach. In particular, surgical methods such as the cantilever technique (c-TLIF) incorporate bilateral facetectomy and posterior column compression in conjunction with expansion of the anterior column through release of the anterior or longitudinal ligament (ALL), mechanically inducing further sagittal correction. In this regard the open TLIF can approach the lordotic success of the ALIF; though this potential evades the MIS-TLIF as the restricted operative view eliminates the ability for contralateral facetectomy or safe ALL release. Current data regarding lordosis restoration following MIS-TLIF is variable, highlighting the need for further investigation. Nonetheless, the MIS-TLIF may be well-equipped to restore disc height and sagittal alignment at this vertebral level through the use of expandable cages. As previously mentioned, long-term radiographic and clinical data will be required to confirm the lordotic potential of expandable cages in MIS-TLIF.

LOOKING AHEAD: CONTINUED EVOLUTION OF THE MIS-TLIF

In the evolution of the TLIF, innovations have been characterized by refinement. Through a series of minor improvements, the MIS-TLIF has emerged as a technique capable of granting patients significant clinical and radiographic improvement while minimizing soft tissue damage and associated adverse events. Recent trials suggest that this trend will continue, with surgeons around the world conceptualizing robotic-assisted pedicle screw fixation, augmented reality-enhanced intraoperative navigation, and more.

1. Robotics

The experience of Cui et al. with robotic-assisted pedicle screw placement in 23 MIS-TLIF patients revealed significant favorability in pedicle screw accuracy, intraoperative blood loss, postoperative pain, postoperative drainage, recovery time, and paraspinal muscle atrophy relative to 25 open TLIF patients. Lin et al. compared 75 MIS-TLIF patients who underwent robotic-assisted pedicle screw fixation to 149 patients receiving freehand fluoroscopy-assisted fixation, noting similar postoperative outcomes between cohorts, with robotic-assisted patients experiencing significantly reduced blood loss, as well as reduced operative time for procedures on more than 3 vertebral levels. Vo et al. recently commented on the current state of robotic applications in spine surgery, indicating that robotics are
most highly investigated in the capacity of instrumentation guidance. Their analysis highlights the infant nature of spinal robotics, citing one early randomized controlled trial\(^4\) that demonstrated less accuracy from robotic-assisted pedicle screw fixation relative to freehand. Though aforementioned later trials have shown more promise, this remains an area requiring comprehensive investigation and long-term data.

2. Augmented Reality

Jamshidi et al.\(^5\) recently published a video and abstract of their experience with augmented reality visualization to improve pedicle screw accuracy following endoscopic TLIF surgery. The innovative head-mounted display, integrated with a tracking camera, enables the surgeon to view navigation assistance in the same field as the operative site. After demonstrating successful and accurate pedicle screw placement in cadavers,\(^6\) this technology underwent a recent first-in-human trial,\(^7\) showing clinical accuracy and technical precision. Though such technologies currently exist in infancy and have yet to prove their true efficacy, the future appears open to further refinements of the MIS-TLIF. A recent systematic review\(^8\) noted pedicle screw malpositioning among the most frequent of MIS-TLIF complications, second only to radiculitis, suggesting that pedicle screw fixation may be the area of the MIS-TLIF most vulnerable to change.

3. Interbody Implant Alternatives

A 2021 detailed review has shown that MIS-TLIF interbody implants may also be subject to change. Lo et al.\(^9\) indicate that the commonplace usage of ICBG may fade given concerns regarding the difficulty of autologous harvesting as well as potential for infection development, and suggest that bone grafting may shift towards materials such as ceramics and cell-based regenerative therapeutics (including stem cells, cellular bone matrices, and platelet-derived biomaterials). In addition, 3D printing may find a profound role in designing interbody cages of optimal characteristics.

CONCLUSION

The story of the MIS-TLIF reveals a consistent commitment to innovation, ultimately yielding the tissue-sparing refinement of posterior-approach lumbar arthrodesis. Through the use of muscle-splitting tubular retractors in conjunction with fluoroscopic guidance, surgeons can perform the TLIF, as designed by Harms and Rolinger in 1982, in a manner that minimizes tissue trauma and perioperative morbidity, all while maintaining or improving the clinical outcomes of the open technique.

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ORCID

Kevin C. Jacob: 0000-0002-5703-9294
Madhav R. Patel: 0000-0002-1865-717X
Hanna Pawlowski: 0000-0002-9475-2574
Kern Singh: 0000-0002-6118-7273

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The Change of Spinal Canal According to Oblique Lumbar Interbody Fusion in Degenerative Spondylolisthesis: A Prospective Observational Study

Young-Seok Lee1,*, Dong-Hyun Lee2,*, Dae-Chul Cho3, Inbo Han4, Chi Heon Kim5, Heum-Dai Kwon6, Kyoung-Tae Kim3

1Department of Neurosurgery, Chung-Ang University College of Medicine, Seoul, Korea
2Department of Neurosurgery, Bio-Medical Research Institute Kyungpook National University Hospital, Daegu, Korea
3Department of Neurosurgery, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea
4Department of Neurosurgery, CHA Bundang Medical Center, CHA University, School of Medicine, Seongnam, Korea
5Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea
6Department of Neurosurgery, Pohang Stroke and Spine Hospital, Pohang, Korea

Objective: Oblique lumbar interbody fusion (OLIF) involves inserting large cages into the interbody disc space. This expands the spinal canal and neural foramen by stretching the ligament flavum and releasing the facet joint, resulting in indirect neural decompression. Our objective was to investigate the changes in the spinal canal and ligament flavum over time after OLIF.

Methods: This was a prospective observational study involving 30 patients who underwent OLIF L4–5 between 2015 and 2018. In total, 27 of the 30 patients underwent preoperative, early follow-up (<5 days), and late follow-up (10–14 months) magnetic resonance imaging to measure the area of the spinal canal and ligament flavum. Based on the results, the patients were divided into subsidence and nonsubsidence groups for further analysis.

Results: After OLIF, the spinal canal area gradually increased during the preoperative, early postoperative, and late postoperative periods (p < 0.001). The thickness and area of the ligament flavum decreased gradually over the same periods (p < 0.001). Low-grade subsidence (2–4.4 mm) did not influence the effects on the spinal canal and ligament.

Conclusion: After OLIF, the spinal canal and ligament flavum gradually change, which is effective for indirect neural decompression. In addition, the effects of low-grade subsidence on the remodeling of the spinal canal and ligament flavum are insignificant.

Keywords: Oblique lateral interbody fusion, Indirect decompression, Spinal canal, Ligament flavum, Subsidence

INTRODUCTION

Oblique lumbar interbody fusion (OLIF) reduces the risk of injury to the lumbar plexus and psoas muscle compared with direct lumbar interbody fusion (DLIF). It is increasingly used as an alternative to conventional anterior or posterior procedures.1,2 OLIF is useful for sagittal and coronal balance correction, allowing large cages to be inserted into the disc space while preserving the anterior and posterior longitudinal ligaments.3,4

In OLIF, the disc height is increased by inserting a large cage into the interbody space. This results in indirect neural decompression by correcting spondylolisthesis, stretching the ligament flavum, and releasing the facet joints. Oliveira et al.5 investigated indirect neural decompression using stand-alone extreme
lateral interbody fusion (XLIF). They reported an increase of 41.9% in disc height, 24.7% in the foraminal area, and 33.1% in the central canal diameter. However, if postoperative subsidence occurred, it reduced the effect of indirect neural decompression.

Many studies have reported that DLIF, XLIF, or OLIF provide efficient indirect decompression by releasing the spinal canal and foraminal areas. However, the study used computed tomography (CT) and magnetic resonance imaging (MRI) examinations shortly after surgery. There is no research on the long-term effects of indirect decompression.

In our prospective study, we examined the effect of indirect decompression using MRI in the preoperative, early postoperative, and late postoperative periods. In addition, since subsidence frequently occurs after OLIF, we investigated whether subsidence could affect the spinal canal and ligament flavum remodeling.

MATERIALS AND METHODS

1. Patients and Methods

We enrolled 27 patients who underwent OLIF L4–5 between 2015 and 2018 in this prospective observational study.

The study included 27 patients diagnosed with degenerative spondylolisthesis on L4–5 for back pain and radiating pain after more than 6 months of conservative treatment. We included only patients who underwent L4–5 level OLIF to enable consistent measurements. We excluded patients with spinal tumors, infections, vertebral fracture, and revision surgery from the study. The age, sex, and degree of osteoporosis of the patients were examined.

Twenty-seven patients underwent MRI before surgery, within 5 days of surgery (early follow-up), and 10–14 months after surgery (late follow-up). The postoperative results were evaluated by the Oswestry Disability Index (ODI) and visual analog scale (VAS). Plain radiography was done to evaluate spondylolisthesis and the intervertebral disc height (IVH) preoperatively, 3 days, 3 months, 6 months, and 12 months postoperatively (Fig. 1A). IVH was defined as the distance between the superior and inferior endplate at the midpoint of the anteroposterior diameter of the inferior vertebral body.

Subsidence was defined as a decrease in the IVH of more than 2 mm immediately and 12 months after surgery. Patients were divided into subsidence (+) and subsidence (−) groups according to the degree of subsidence.

The fusion rate was graded with the Bridwell fusion grading system (Table 1). Based on this classification system, grade 1–2 was a successful fusion. We evaluated fusion using plain radiography 1 year after surgery.

We obtained informed consent from all the patients. The study was carried out in accordance with relevant guidelines and regulations. The study was approved by the Institutional Review Board of Kyungpook National University Hospital (No. 2014-10-034-001).

2. Surgical Technique

OLIF involves minimally invasive lateral interbody fusion using a left-sided retroperitoneal approach and percutaneous pedicle screw fixation.

Table 1. Fusion grading system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fusion status</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Completely remodeled with trabeculae across the disc space</td>
</tr>
<tr>
<td>II</td>
<td>Graft intact with no lucent lines seen between the graft and adjacent endplates</td>
</tr>
<tr>
<td>III</td>
<td>Graft intact, but a radiolucent line is seen between the graft and an adjacent endplate</td>
</tr>
<tr>
<td>IV</td>
<td>Lucency along an entire border of the graft or around a pedicle screw or subsidence of the graft</td>
</tr>
</tbody>
</table>

Fig. 1. (A) Measurement of intervertebral disc height (IVH) and spondylolisthesis distance (LD) on plain radiograph. (B) The area of the spinal canal and the thickness and area of the ligament flavum (LF) on middisc level T2-weighted magnetic resonance imaging.
The intervertebral disc was exposed through an open corridor between the psoas muscle and aorta. The sympathetic chain and ureter were mobilized anteriorly. The procedure was performed using an OLIF system (Medtronic, Memphis, TN, USA), fusion material (Grafton, Medtronic, Memphis, TN, USA), and a percutaneous pedicle screw fixation system (Longitude system, Medtronic, Memphis, TN, USA). We determined the height of the cage to be inserted by using the presurgery CT scan. If the intervertebral disc space was < 6 mm, a 10-mm cage was inserted. If the intervertebral disc space was ≥ 6 mm, a cage 4 mm greater than the disc height was inserted. The indirect decompression effect on the constant disc height was evaluated. We did not perform posterior decompression on any of the patients.

3. Measurement of the Spinal Canal and Ligament Flavum

The MRI scans were acquired on a 1.5-T EXCITE whole-body imaging system (General Electric, Milwaukee, WI, USA). An axial localizing sequence was then done to identify the lumbar L4–5 disc-space intervals. Four slices per level were obtained, with 4.0-mm thickness at 1.0 mm intervals. T2-weighted images were then obtained using the following imaging sequence: repetition time, 3,800 msec; echo times, 102 msec; matrix, 416 × 224; excitations, 4; and field of view, 20 cm. The images were displayed and analyzed using PiView (INFINITT, Seoul, Korea) digital image viewing software. The cross-sectional areas of the spinal canal and ligament flavum area were outlined using a graphic cursor. The thickness of the ligament flavum was averaged by measuring the greatest thickness of the ligament on both sides (Fig. 1B). The areas of the spinal canal and thickness and area of the ligament flavum were measured by MRI at the L4–5 middisc level preoperatively and at < 5 days (early follow-up) and 10–14 months (late follow-up) postoperatively. The radiography measurements and evaluations were performed by 2 other surgeons who reviewed and confirmed the results. The interobserver reliability for measurements was excellent (intra-class correlation coefficient, 0.91; 95% confidence interval, 0.80–0.96).

4. Statistical Analysis

The parametric and nonparametric variables preoperatively and at 3 days, 6 months, and 12 months postoperatively were compared using repeated-measures analysis of variance. A post hoc comparison was also performed using the paired t-test. The comparison of variables between the subsidence (+) and subsidence (−) groups preoperatively and at 3 days, 3 months, 6 months, and 12 months postoperatively was made using the t-test and Mann-Whitney U-test. A p-value of < 0.05 was considered statistically significant. Statistical analyses were done using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Patient Demographics

Of the 27 patients who underwent OLIF at L4–5, 3 (11.1%) were male, and 24 (88.9%) were female. Subsidence occurred in 7 patients (25.9%). The subsidence was 1.5 ± 1.8 mm on average, and it occurred within 5 mm in all patients. The Bridwell fusion grades were grade 1 in 12 patients, grade 2 in 13, and grade 3 in 2. Therefore, the fusion rate was 92.6%, with grades 1–2 regarded as successful fusion (Table 2).

2. Changes in Spondylolisthesis and IVH

After OLIF, the correction of spondylolisthesis was from 5.3 ± 2.3 mm before surgery, to 2.5 ± 1.6 mm at 3 days, 2.5 ± 1.8 mm at 3 months, 2.4 ± 1.7 mm at 6 months, and 2.5 ± 1.8 mm at 12 months postoperatively (p < 0.001). After OLIF, the IVH changed

Table 2. Patient demographic data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.0 ± 9.1</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (88.9)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>6 (22.2)</td>
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</tr>
<tr>
<td>Subsidence &gt; 2 mm</td>
<td>7 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Fusion rate</td>
<td>25 (92.6)</td>
<td></td>
</tr>
<tr>
<td>Spondylolisthesis (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>5.3 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>3 Days after surgery</td>
<td>2.5 ± 1.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 Months after surgery</td>
<td>2.5 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 Months after surgery</td>
<td>2.4 ± 1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>2.5 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intervertebral height (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>8.2 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>3 Days after surgery</td>
<td>13.6 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3 Months after surgery</td>
<td>13.4 ± 1.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 Months after surgery</td>
<td>12.5 ± 1.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>12.2 ± 1.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

*Compared to preoperative.
from 8.2 ± 2.4 mm preoperatively to 13.6 ± 1.5 mm at 3 days, 13.4 ± 1.5 mm at 3 months, 12.5 ± 1.6 mm at 6 months, and 12.2 ± 1.6 mm at 12 months postoperatively (p < 0.001) (Fig. 2).

3. Changes in the Spinal Canal
After OLIF, the spinal canal area gradually increased from 78.5 ± 42.8 mm² preoperatively, 112.5 ± 47.8 mm² at early follow-up, and 151.8 ± 62.4 mm² at late follow-up postoperatively (p < 0.001) (Fig. 3).

4. Changes of Ligament Flavum
After OLIF, the ligament flavum thickness gradually decreased from 4.2 ± 1.1 mm preoperatively to 3.7 ± 0.9 mm at early follow-up and 2.6 ± 0.74 mm at late follow-up postoperatively (p < 0.001). In addition, the ligament flavum area gradually decreased from 123.5 ± 37.1 mm² before surgery to 102.2 ± 28.3 mm² at early follow-up and 70.1 ± 26.1 mm² at late follow-up (p < 0.001) (Fig. 4).

5. Changes of the Spinal Canal and Ligament Flavum According to Subsidence (>2 mm)
The spinal canal area of the subsidence (+) and subsidence (−) groups were compared between the preoperative and follow-up periods. The spinal canal area was 81.7 ± 48.8 mm² in subsidence (+), 77.4 ± 42.9 mm² in subsidence (−) at preoperative. At early postoperative follow-up, the spinal canal area was 110.8 ± 48.9 mm² in subsidence (+) and 113.2 ± 49.8 mm² in subsidence (−). At the late postoperative follow-up, the spinal canal area of subsidence (+) was 121.4 ± 52.7 mm² and subsidence (−) was 162.5 ± 64.8 mm² (p > 0.05).

Fig. 2. Changes of spondylolisthesis and intervertebral height after surgery. Preop, preoperative; POD, postoperative day; POM, postoperative month. **p < 0.05.

Fig. 3. Changes in the spinal canal area after surgery. Preop, preoperative; POD, postoperative day; POM, postoperative month. **p < 0.05.

Fig. 4. Changes in the ligament flavum area (A) and thickness (B) after surgery. Preop, preoperative; POD, postoperative day; POM, postoperative month. **p < 0.05.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperative</th>
<th>Early follow-up (&lt;5 days)</th>
<th>Late follow-up (10–14 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subsidence (-)</td>
<td>Subsidence (+)</td>
<td>Subsidence (-)</td>
</tr>
<tr>
<td>Spinal canal area (mm²)</td>
<td>77.4 ± 42.9</td>
<td>113.2 ± 49.8</td>
<td>162.5 ± 64.8</td>
</tr>
<tr>
<td></td>
<td>81.7 ± 48.8</td>
<td>110.8 ± 48.9</td>
<td>121.4 ± 52.7</td>
</tr>
<tr>
<td>Ligament flavum thickness (mm)</td>
<td>4.2 ± 1.2</td>
<td>3.7 ± 1.0</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>4.2 ± 0.6</td>
<td>3.6 ± 0.7</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>Ligament flavum area (mm²)</td>
<td>127.6 ± 38.9</td>
<td>105.6 ± 31.0</td>
<td>69.3 ± 29.0</td>
</tr>
<tr>
<td></td>
<td>111.9 ± 34.5</td>
<td>92.5 ± 20.3</td>
<td>72.4 ± 20.2</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

Table 3. The changes in the spinal canal and ligament flavum after surgery according to subsidence (> 2 mm)

The ligament flavum thickness and area of the subsidence (+) and subsidence (−) groups were compared between the preoperative and follow-up periods. The ligament flavum thickness was 4.2 ± 0.6 mm in subsidence (+) and 4.2 ± 1.2 mm in subsidence (−). And at early postoperative follow-up, it was 3.6 ± 0.7 mm in subsidence (+) and 3.7 ± 1.0 mm in subsidence (−). There was no statistical difference in subsidence (+) of 2.6 ± 0.6 mm and subsidence (−) of 2.6 ± 0.8 mm at late follow-up after surgery (p > 0.05). The ligament flavum area was 111.9 ± 34.5 mm² in subsidence (+) and 127.6 ± 38.9 mm² in subsidence (−) preoperatively. It was 92.5 ± 20.3 mm² in subsidence (+) and 105.6 ± 31.0 mm² in subsidence (−) at early follow-up. There was no statistical difference in ligament flavum area at late follow-up after surgery: 72.4 ± 20.2 mm² in subsidence (+) and 69.3 ± 29.0 mm in subsidence (−) (p > 0.05) (Table 3).

6. Clinical Outcomes

The ODI was 27.6 ± 4.7 preoperatively, 13.5 ± 4.8 at 3 months, 13.4 ± 5.2 at 6 months, and 11.1 ± 4.5 at 12 months postoperatively. ODI improved significantly at 3, 6, and 12 months postoperatively (p < 0.001). The VAS-leg was 7.2 ± 1.1 preoperatively, 1.8 ± 1.2 at 3 months, 2.0 ± 1.5 at 6 months, and 1.5 ± 1.3 at 12 months postoperatively. The VAS-back was 4.2 ± 1.5 preoperatively, 2.7 ± 1.4 at 3 months, 2.8 ± 1.5 at 6 months, and 2.4 ± 1.3 at 12 months postoperatively. VAS-leg and -back improved significantly at 3, 6, and 12 months postoperatively (p < 0.001) (Table 4).

DISCUSSION

There has been much research into indirect neural decompression in lateral lumbar interbody fusion (XLIF, DLIF, and OLIF). These procedures allow the insertion of large cages at intervertebral disc space. As a result, the height of the intervertebral disc can be increased. The indirect neural decompression is effective because the spinal canal and the neural foramen are expanded. In this study, we performed an MRI series to investigate the changes and remodeling that result from indirect neural decompression.

OLIF, a lateral lumbar interbody fusion procedure, is effective in treating lumbar foraminal stenosis. One study reported that the foraminal area increased from 110.3 mm² preoperatively to 142.6 mm² postoperatively, an increase of 36.4%. The foraminal height also increased from 16.0 mm to 20.3 mm, an increase of 29.5%. In a previous study, we also found that the foraminal area of the cage insertion side (left) after DLIF increased from 99.5 ± 31.1 mm² preoperatively to 159.2 ± 44.8 mm² postoperatively, while it increased from 102.9 ± 32.9 mm² to 151.2 ± 39.1 mm² on the contralateral side (right).

OLIF is also effective in expanding the spinal canal. After lateral lumbar interbody fusion, the spinal canal area showed an...
A systematic review found that the central canal area increased by 25.4%, and the central canal diameter increased by 33.1%. In our study, the spinal canal area increased by 43.3% at early follow-up and 93.4% at late follow-up. This change in the spinal canal area is caused by a reduction of the disc bulge, stretching of a buckled ligament flavum, atrophy of ligament flavum due to spinal stability, facet joint release, and spondylolisthesis correction. These changes occur early or late. Early effects come from stretching the disc annulus and ligament flavum, correction of the spondylolisthesis, and release of the facet joints. The late effects are caused by atrophy of the disc annulus and ligament flavum.

In our study, we found that ligament flavum was remodeled by stretching and atrophy after OLIF. Ohtori et al. reported a ligament flavum changes from 150 mm² to 78 mm² after anterior lumbar interbody fusion. This study was conducted with an inconsistent periods MRI scan within 10 years of surgery. In contrast, our study demonstrated the stretching effect of the ligament flavum in the early follow-up (<5 days) MRI and the atrophic changes in the ligament flavum resulting from spinal stability through the late follow-up (10–14 months) MRI. The results showed the thickness and area of ligament flavum decreased by 11.9% and 17.2% from stretching (early effect) and decreased by 29.7% and 29.5% because of atrophic change (late effect) after OLIF (Fig. 5).

Hypertrophy and buckling of the ligament flavum are the leading causes of spinal stenosis. Hypertrophy of the ligament flavum leads to fibrosis due to a decrease in elastic fibers and an increase in collagen fibers. Altinkaya et al. suggest that buckling of the ligament flavum influences the ligament flavum thickness in spinal stenosis. In our study, as the buckling of the ligament flavum was released early follow-up, the area of the spinal

Fig. 5. (A, D) Two cases of L4–5 oblique lumbar interbody fusion. Panels A–C are the same patients, panels D–F are the same patient. Central spinal stenosis in preoperative axial magnetic resonance images (B, E), early (postoperative 2 days), late (postoperative 12 months) axial images (C, F). In panels B and E, the area of the foramen and spinal canal were enlarged by facet joint release (arrows) and ligament flavum and disc annulus stretching (early effects). In panels C and F, the area of the foramen and spinal canal were widened by atrophy of the ligament flavum and disc annulus (late effects).
Early effects
1. Stretching of disc annulus/LF
2. Correction of spondylolisthesis
3. Facet joint release

Late effects
1. Atrophy of disc annulus/LF

Fig. 6. Early and late effects of remodeling of the spinal canal and ligament flavum (LF) after oblique lumbar interbody fusion in degenerative spondylolisthesis.

canal increased, and the thickness and area of the ligament flavum decreased. Mechanical stress affects hypertrophy of the ligament flavum.\textsuperscript{16} Since the surgical site was stabilized by fusion and fixation, the decrease of mechanical stress on the ligament flavum led to its late atrophy (Fig. 6). However, the effect of indirect decompression of OLIF on spinal stenosis caused by calcified discs and disc fragments has not yet been clearly elucidated.

A previous study reported an incidence of subsidence after lateral lumbar interbody fusion of 13.8\%; however, the incidence of subsidence gradually decreased because of the use of wider cages and the improvement in surgical techniques.\textsuperscript{17-19} However, subsidence still occurred at 25.9\% in this study. We investigated whether subsidence after OLIF caused deterioration of the indirect neural decompression. The subsidence causes a decrease in the stretching effect on the ligament flavum and a reduction in spondylolisthesis correction. In our study, subsidence ranged from 2.0 to 4.4 mm. Applying the evaluation of cage subsidence described by Marchi et al.,\textsuperscript{20} subsidence was classified using the following scale: grade 0 (0\%–24\%), grade I (25\%–49\%), grade II (50\%–74\%), and grade III (75\%–100\%) loss of postoperative disc height. All patients in our study had grade 0 or I (low-grade subsidence). Thus the occurrence of low-grade subsidence did not affect the spinal canal area. It also did not affect the thickness and area of the ligament flavum. However, high-grade subsidence (> 5 mm) might affect the indirect neural decompression effect by reducing disc height and thus the neural foramen.

Also, Lang et al.\textsuperscript{19} found that the use of 26 mm wide cages in OLIF significantly reduced the incidence of subsidence compared to 18- and 22-mm cages. The use of larger cages may preserve the indirect neural decompression effects by a reduction in the incidence of subsidence.

Our study showed similar results to others for the release of the spinal canal. However, we confirmed the remodeling of the spinal canal and ligament flavum by examining serial MRIs. In addition, the remodeling effect of the spinal canal and ligament flavum was not affected even if low-grade subsidence occurred (2–5 mm).

The main limitation of our study is its small sample size. However, only patients who underwent a single level of surgery, L4–5, were selected to enable a direct comparison of the effects of indirect neural decompression. Longer follow-up observations may be necessary, but a 1-year follow-up has yielded adequate results. In addition, as the disc height increases for each patient, the area of the spinal canal increases, and the ligament flavum...
stretching effect may be different. However, we tailored the height of the cage to the patient, using CT, before surgery.

CONCLUSION

After OLIF, the spinal canal and ligament flavum undergo remodeling over time. A decrease in the ligament area and thickness were induced by ligament flavum stretching and atrophy. In addition, changes in the spinal canal area were caused by increased disc height, spondylolisthesis correction, and changes in the ligament flavum. In addition, low-grade subsidence after OLIF did not affect the changes in the spinal canal and ligament flavum.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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ORCID

Young-Seok Lee: 0000-0002-6881-812X
Dong-Hyun Lee: 0000-0003-0093-3110
Dae-Chul Cho: 0000-0002-2899-8015
Inbo Han: 0000-0002-0834-9325
Chi Heon Kim: 0000-0003-0497-1130
Heum-Dai Kwon: 0000-0003-1657-6234
Kyoung-Tae Kim: 0000-0003-4867-6854

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Corresponding Author
Roger Härtl
https://orcid.org/0000-0003-2442-8944

Department of Neurosurgery, New York-Presbyterian Hospital, 525 E 68th Street, Box 99, New York, New York 10065, USA
Email: roh9005@med.cornell.edu

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Safety and Feasibility of Augmented Reality Assistance in Minimally Invasive and Open Resection of Benign Intradural Extramedullary Tumors

Fabian Sommer, Ibrahim Hussain, Sertac Kirnaz, Jacob Goldberg, Lynn McGrath, Rodrigo Navarro-Ramirez, Francois Waterkeyn, Franziska Schmidt, Pravesh Shankar Gadjradj, Roger Härtl

Department of Neurosurgery, Weill Cornell Medicine, New York Presbyterian Hospital/Och Spine, New York, NY, USA

Objective: Surgical resection of benign intradural extramedullary tumors (BIETs) is effective for appropriately selected patients. Minimally invasive surgical (MIS) techniques have been described for successful resection of BIET while minimizing soft tissue injury. Augmented reality (AR) is a promising new technology that can accurately allow for intraoperative localization from skin through the intradural compartment. We present a case series evaluating the timing, steps, and accuracy at which this technology is able to enhance BIET resection.

Methods: A protocol for MIS and open AR-guided BIET resection was developed and applied to determine the feasibility. The tumor is marked on diagnostic magnetic resonance imaging (MRI) using AR software. Intraoperatively, the planning MRI is fused with the intraoperative computed tomography. The position and size of the tumor is projected into the surgical microscope and directly into the surgeon’s field of view. Intraoperative orientation is performed exclusively via navigation and AR projection. Demographic and perioperative factors were collected.

Results: Eight patients were enrolled. The average operative time for MIS cases was 128 ± 8 minutes and for open cases 206 ± 55 minutes. The estimated intraoperative blood loss was 97 ± 77 mL in MIS and 240 ± 206 mL in open procedures. AR tumor location and margins were considered sufficiently precise by the surgeon in every case. Neither correction of the approach trajectory nor ultrasound assistance to localize the tumor were necessary in any case. No intraoperative complications were observed.

Conclusion: Current findings suggest that AR may be a feasible technique for tumor localization in the MIS and open resection of benign spinal extramedullary tumors.

Keywords: Minimally invasive surgery, Benign extramedullary intradural tumor, Augmented Reality, benign intradural extramedullary tumor

INTRODUCTION

Benign spinal extramedullary tumors (BIETs) are a complex clinical entity affecting patients of all ages. Due to narrowing space in the intradural compartment, these tumors often cause pain and neurological symptoms related to compression of the neural elements. Surgical excision is indicated for BIETs with progressive clinical symptoms, radiographic growth, and decreased quality of life. Where possible, the tumor should be entirely resected while simultaneously preserving neural integrity and as much surrounding tissue as possible. Localization of the surgical
level(s) is typically performed by confirming the level of pathology from the preoperative magnetic resonance imaging (MRI) with intraoperative x-rays. The transfer of the tumor location from MRI images to the patient's radiographic anatomy for localization is the obligation of the surgeon. Surgical approaches often require more soft tissue and muscle dissection than necessary, especially in obese patients, resulting in higher approach-specific morbidity. Following laminectomy, intradural tumor location can be confirmed via sonography to determine the extent of dural opening. Until recently, this was a prohibitive criterion for minimally invasive approaches, as traditional “hockey-stick” ultrasound transducer probes could not fit through the tubular retractor. Nonetheless, evolutions in technology were sought so that patients undergoing BIET resection could benefit from the established advantages of tubular minimally invasive surgical (MIS) procedures, including lower blood loss, infection risk, less postoperative pain/opioid usage, shorter hospital length of stay, and preservation of the posterior tension band.

Augmented reality (AR) is an emerging technology that allows the surgeon to highlight anatomically relevant key structures and pathologies, which are displayed in the microscope’s field of view during surgery. For spinal tumor surgery, this technology can be particularly helpful since it can support the surgeon from the beginning of the surgery during incision planning and tubular insertion trajectory, thus minimizing soft tissue injury. Once the bony anatomy is exposed, highlighting of the tumor precisely determines how much bony resection is required for adequate dural exposure. Additionally, AR can localize the tumor in the crani-caudal as well as mediolateral dimensions, which is especially helpful for laterally positioned tumors that require medial facetectomy, since this can help minimize iatrogenic instability. These advantages could be particularly helpful when using surgical approaches with limited visualization for resection of BIETs, as with tubular MIS approaches.

The use of an early version of AR for the open resection of cervical and thoracic intradural tumors has been described with promising results from Carl et al. We have developed a protocol for how to implement AR for the resection of BIET and evaluated the clinical feasibility of this technique in a case series of open and tubular minimally invasive approaches. To our knowledge, this is the first description of AR-assisted resection of BIET via the tubular minimally invasive approach as well as the use of AR for lumbar tumors.

MATERIALS AND METHODS

1. Patient Characteristics

We conducted a prospective case study of AR-assisted resection of BIET between 11/20 and 08/21 at a single tertiary medical center.

Age, sex, American Society of Anesthesiologists (ASA) physical status classification, body mass index (BMI), and neurological symptoms were collected. In addition, intraoperative blood loss, complications, and the length of hospital stay were recorded. Clinical evaluation including sensorimotor examination and wound assessment was performed immediately postoperatively and 2 weeks after surgery.

2. AR Application

The AR application was planned utilizing Brainlab (Munich, Germany) Element’s software. Planning was based on the MRI images available as part of the diagnostic workup of the patient’s pathology. The MRI should have a high resolution with slices not exceeding 2 mm in thickness to avoid inaccuracy. The tumor was highlighted using the software’s “smart brush” function, which uses automatic algorithms to merge the structures highlighted on individual plane (2-dimensional, 2D) layers into a structured (3-dimensional, 3D) shape. Additionally, the software was used to calculate the tumor volume based on the highlighting on the MRI. The software fused the 2D markings to a 3D model of the tumor. This allowed even the calculation of irregular shaped tumors (Fig. 1).

The decision if a MIS or open tumor resection was performed was based on the suspected tumor pathology, size, and the location. Based on our experience, the MIS tubular approach is most suitable for small, benign tumors located in the lumbar spine.

To facilitate the surgeon’s orientation to the surgical site, the closest disc space was also highlighted and, if desired, projected into the microscope’s view. The surgeries were performed using total 3D navigation and the setup of the operating room was the same as a standard navigated surgery with navigation system and infrared cameras. The only additional equipment was a navigation array that was attached to the microscope to enable tracking by the navigation system (Fig. 2).

At the beginning of each procedure, an intraoperative low-dose navigation computed tomography (CT) was performed. Subsequently, the preoperative MRI, including the highlighted structures, was fused with the intraoperative navigation CT to transfer the localization of the tumor from the MRI to the CT image. Since the intraoperative CT was performed in prone po-
For this procedure, one vertebra in the MRI scan needs to be manually matched with the same vertebra on the CT scan, then the software corrects the curvature differences of the other levels. For maximal accuracy of the AR projection, we recommend manually matching the vertebra that is closest to the pathology to minimize deviation caused by the digital correction software (Fig. 3).

After each image fusion, the accuracy of fusion was verified and approved by a fellowship-trained orthopedic spine surgeon who was not involved in the surgical procedure. To avoid inaccuracy during the fusion process, the responsible person should have a basic understanding of the spinal anatomy. After validation of the digital image fusion, the highlighted tumor was visible on the navigation CT scan and could immediately be used for approach planning without any additional workflow steps (Figs. 4–8).

To integrate the surgical microscope view with the navigation system, calibration of the microscope to the AR software is necessary. For that purpose, a reference array is attached to the microscope and the microscope is connected to the navigation system using a dedicated data-cable for the transmission of the AR signal. For calibration of the microscope, the patient’s reference array, which is attached on an anatomical structure close to the
pathology, must be viewed and focused through the surgical microscope's field of view. The patient's reference array is automatically detected by the navigation system in calibration mode when focusing the microscope on it and can be calibrated to the microscope (Fig. 9).

After calibration, the pre operatively highlighted structures were projected into the surgical microscope (Zeiss Pentero, Carl Zeiss Meditec, Jena, Germany) via the AR module. All procedures were recorded through the microscope. During surgery, the tumor location, and margins were projected into the surgeon's field of view via the microscope. The surgeon could turn the projection off if a clearer view of the surgical area was required (Figs. 10-16).

Surgery-specific data including the volume of the tumor, duration of surgery in minutes, and intraoperative blood loss were recorded. Also recorded was the time required for calibration of the AR. Additionally, when a tubular MIS approach was used, the time from tissue dilation until the tumor was reached was also recorded.

RESULTS

A total of 8 consecutive patients were included in our series (5 males) with a mean age of 56 ± 12 years. The mean BMI was
The ASA PS classification was II in 7 patients and 1 patient had an ASA PS classification of III, respectively. The demographics of our study group are summarized in Table 1. Four tumors were located at the lumbar spine (50%) and 4 (50%) in the thoracic spine. The average overall tumor volume was 1.4 ± 0.6 mL. Divided into MIS and open procedures the average volume of MIS resected tumors was 1.0 ± 0.5 mL and the average tumor volume of open cases was 1.5 ± 0.6 mL. According to histological evaluation of the intraoperative specimens, 5 of the cases were World Health Organization (WHO) grade I schwannoma, 1 WHO grade 1 meningioma, 1 WHO grade 1 paraganglioma, and 1 WHO grade 2 myxopapillary ependymoma. All tumors were located intradural and extramedullary.

A tubular MIS technique was used to resect 3 tumors (38%), while the other 5 tumors (62%) were resected using a traditional open approach. The skin incision in the MIS cases was around 3 cm and either 24-mm or 26-mm tubes were used. The overall average procedure time was 177 ± 58 minutes and the average overall blood loss was 186 ± 183 mL. Divided into open and MIS procedures the average operative time for MIS cases was 128 ± 8 minutes and for open cases 206 ± 55 minutes. The estimated intraoperative blood loss was 97 ± 77 mL in MIS procedures and 240 ± 206 in open procedures. The median overall hospital stay

Fig. 5. The highlighted neoplasm can be displayed in 3-dimensional shape on the intraoperative computed tomography scan (sagittal view [A] and coronal view [B]).

Fig. 6. Alternatively, the highlighted neoplasm can be displayed in 3-dimensional shape on reconstructed x-ray images from every angle to facilitate the orientation. A reconstruction of an anteroposterior view x-ray (A); A reconstruction of a lateral view x-ray (B).
was 4 ± 4.6 days. A detailed list of surgical times and treated pathologies is shown in Table 2.

Preoperative weakness was reported in 6 cases (67%) and numbness was reported in 3 cases (33%). Postoperatively, the muscle weakness was improved in 5 cases and only 1 patient showed persistent weakness. Numbness improved in 2 cases and only 1 patient reported new numbness after surgery.

In all cases, the AR support was available at the time the microscope was used and no additional delay was caused. The elastic image fusion took place in the background to the actual surgery and the navigation system was fully operational in parallel, therefore this also did not lead to any delay in the actual surgical procedure. The only additional step that had to be integrated into the surgical workflow was the calibration of the microscope. This step required an average of 1.6 ± 1.2 minutes to calibrate the microscope to the navigation system.

The precision of the AR was sufficiently accurate in all cases and corresponded to the actual limits of the tumor. The accuracy of navigation was regularly checked during surgery using exposed anatomic landmarks such as the spinous processes. Subjective accuracy on the part of the surgeon was reported to be < 2 mm. Neither correction of the approach trajectory or ultrasonic assistance was required in any case nor a conversion to an open procedure in any MIS case. No intraoperative complications were observed. The intraoperative pathology result showed be-
Fig. 9. Intraoperative calibration of microscope to patient reference array. (A) Microscope view pre calibration. The virtual frame does not match the reference array. (B) Microscope view after calibration. The virtual frame matches the reference array.

Fig. 10. (A) Surgical site before skin incision. (B) Surgical site after dissection of the skin. The projection stays in place. After calibration of the microscope, the highlighted neoplasm is projected into the surgeon’s field of view (blue shape). The shape of the augmented reality (AR) projection matches with the navigated planning of the approach (cross on image A). Soft tissue preparation for the tubular approach after skin incision with AR visible (blue shape).

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benign tumors in all cases. Depending on location, either a total resection of the tumor was performed or if the tumor affected a motor nerve root, maximally-safe debulking was performed to avoid injury of the motor nerve. The regular follow-up recommendation for these patients is an MRI scan after 3 months. There were no revision surgeries in the 2-week short-term follow-up.

DISCUSSION

AR technology offers a promising advancement for tumor resection utilizing the tubular MIS technique. Until recently, resection of BIET was limited via tubular minimally invasive approaches due to the lack of ultrasound probes small enough to be inserted through a tubular retractor.5,6 Today, ultrasound probes are available that are small enough to be used through tubular retractors.6 However, handling remains challenging, requires a high level of experience and interrupts the surgical workflow. In addition, the ultrasound probe can first be utilized after the dura exposure and is not available during the approach planning or to determine the bone removal to approach the tumor. Orientation up to that point is accomplished by x-ray or navi-
Fig. 11. Confirmation of the approach trajectory after placement of the tubular retractor using 3-dimensional navigation in coronal (A) and sagittal view (B). Panel C shows the intraoperative view through the microscope after placement of the tubular retractor. The size, shape, and location of the neoplasm (blue shape) is visible during the soft tissue dissection.

Fig. 12. Confirmation of the anatomy after soft tissue dissection but before laminectomy in coronal (A) and sagittal (B) view. Panel C shows the microscopes view on the exposed left sided lamina of L4. The neoplasm is highlighted blue.

Fig. 13. Projection of the tumor site during removal of the bony structures (A) and when the dura is exposed (B).

By using AR, it is possible to see the actual position and the size of the tumor even during the approach planning as shown in Fig. 10. This allows precise planning of the skin incision and accurate placement of the tubular retractor, which minimizes soft tissue damage. As a result, a precise laminectomy can be performed to provide enough space to approach the tumor safely. This limited resection of bone further reduces iatrogenic in-
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Fig. 14. (A) The projection allows an exact incision of the dura. (B) After the incision, the dura is held open using holding sutures on both sides of the tubular retractor.

Fig. 15. (A, B) Exposure and resection of the neoplasm. After the incision of the dura, the neoplasm is found at the location of the augmented reality projection. Panel C shows the resection of the neoplasm under neuromonitoring.

Fig. 16. Closure of the dura after resection of the neoplasm. Panel A shows the conditions at the surgical site after the removal of the neoplasm and the size of the neoplasm (blue shape) in relation to the dura incision. (B) After resection, the augmented reality support is turned off and the dura is closed by suture via the tubular approach. Panel C shows the final result after closure of the dura.

stability of the spinal segment and avoids long-term postoperative complications.

The integration of AR into the regular surgical procedure was efficient in our case series. The image fusion between the
preoperative MRI with AR planning and the intraoperative CT can be performed in parallel with the other surgical steps and did not interrupt the workflow, nor did it not cause any delay of the surgical procedure in our evaluation. The only additional step that needed to be performed was the calibration of the microscope to the navigation system to accurately perform the AR projection. In our case series, the calibration of the microscope took 1.6 ± 1.2 minutes, which is an insignificant delay.

The accuracy of projecting the AR into the microscope corresponded exactly to the position of the tumor in all cases. The correct visualization of the cranial and caudal tumor borders is essential here since the surgical approach is chosen according to these 2 borders and the laminectomy is performed in reference to the BIET’s location. Extension of the approach was not necessary in any of the cases. Furthermore, in 1 case of tumor with an irregular shape and extension of the tumor into the neuroforamen, AR-guidance was key to achieving gross total resection.

This study, to our knowledge, is the first study on AR-assisted resection of BIET involving the lumbar spine. In contrary to the cervical and thoracic spine, most lumbar BIET do not cause compression of the spinal cord but rather the nerve roots of the cauda equina.11 This bundle of nerves provides flexibility which the surgeon can use to their advantage in terms of retraction and manipulation. In some situations, the tumor suspension in cerebrospinal fluid can cause variation in positioning concomitant with the respiratory cycle. This creates an obstacle for accurate AR projection, since the projection shows only the preoperatively planned position and does not dynamically adapt to changes in tumor position during surgery. This theoretical limitation of accuracy was not observed in our study. In our case series, there was no relevant cranial or caudal dislocation before finding the tumor. Likewise, opening the dura did not result in any relevant inaccuracy of the AR projection. The opening of the dura was always performed at the level of the AR projection and corresponded to the actual position of the tumor in all cases. This observation is consistent with the previously described high accuracy of the AR projection in other studies.8,12 Nevertheless, during the actual tumor resection particularly for schwannomas, attention should be paid to begin resection and disconnection from the cranial rather than the caudal end to avoid subsequent cranial retraction of the tumor which may require extension of the laminectomy.

After resection of the tumor, AR was found helpful in the lumbar spine to inspect the resection site for any residual tissue before closing. Since it is often not possible to remove the tumor en bloc, continued projection of the original tumor margins after resection helped to thoroughly explore the intradural space in the highlighted area and search for possible tumor fragments to ensure that all tumor components were completely re-

Table 1. Demographics of the study population

<table>
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<th>Patient No.</th>
<th>Sex</th>
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<th>Preop. numbness</th>
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<td>24.6</td>
<td>II</td>
<td>T6/7</td>
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BMI, Body mass index; ASA PS, American Society of Anesthesiologists physical status; T, thoracic; L, lumbar; preop., preoperative.

Table 2. Final pathological results, tumor volume, procedure time, estimated blood loss, hospital stay, and surgical approach

<table>
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<th>Estimated blood loss (mL)</th>
<th>Hospital stay (day)</th>
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WHO, World Health Organization; MIS, minimally invasive surgical.
moved. This is especially challenging in the lumbar spine where tumor fragments can easily be overlooked due to the many mobile nerves of the cauda equina.

There are limitations of our study. First, the low number of patients in this series is too small to draw general conclusions. Whether the positive first impression of the use of AR in resection of BIETs can be maintained in a larger and more diverse case series needs to be investigated. Second, the software used required manual marking of the tumor on the preoperative MRI, which increases the preoperative planning time. In all cases, preoperative marking required only a few minutes and did not add a significant effort to the procedure workflow. In the future, advancement of the software may allow automatized identification of the pathology and reduce the preoperative planning time. Additionally, highlighting the tumor manually may present error, since irregular tumor borders on MRI or incorrect margins due to surrounding nerves which appear like the tumor may cause the person doing the marking to incorrectly outline the tumor.

Another limitation of the technique is that intraoperative navigational CT is required, which exposes the patient to additional radiation. However, the use of total intraoperative navigation is at present a well-established and frequently used technique. For surgeons who are already using navigation as part of their surgical workflow, the use of AR does not require any additional radiation, since the software uses the navigation data set. AR thus represents a useful extension to existing navigation capabilities. In addition, intraoperative navigational CT’s typically use low-dose protocols, which keep patient radiation exposure low. Operating room staff can even leave the operating room during the CT and completely avoid radiation exposure. Overall, the use of AR in the detection of spinal tumors is a safe and effective alternative or adjunct to existing intraoperative orientation methods such as ultrasound, particularly for minimally invasive approaches.

CONCLUSION

The use of AR in the resection of intradural extramedullary tumors allows reproducible accurate visualization of the tumor level and position within the dura. AR-guidance can be integrated into the workflow of surgery without significant alterations to the standard routines and does not cause significant prolongation of surgery. Further studies are required to further elucidate the advantages of AR over ultrasonic guidance especially for minimally invasive surgical approaches in combination with 3D navigation.

NOTES

Conflict of Interest: Roger Härtl is a consultant for Ulrich, Brainlab, DePuy-Synthes and has royalties from Zimmer. Fabian Sommer received speaker fees from Baxter.

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ORCID

Fabian Sommer: 0000-0002-6284-7042
Jacob Goldberg: 0000-0003-0827-9387
Pravesh Shankar Gadiradj: 0000-0001-9672-4238
Roger Härtl: 0000-0003-2442-8944

REFERENCES

Comparison of the Clinical Efficacy of Transforaminal Endoscopy and Microtubular Technology for the Treatment of Lumbar Dumbbell-Shaped Tumors

Rui Wang*, Ze Yan Liang*, Yan Chen, Chun Mei Chen
Department of Neurosurgery, Fujian Medical University Union Hospital, Fuzhou, China

Objective: To analyze differences in feasibility and efficacy between the paravertebral approach and microtubular tumorectomy (PAMT) or percutaneous transforaminal endoscopic tumorectomy (PTET) for the treatment of lumbar dumbbell-shaped tumors.

Methods: Clinical data of dumbbell-shaped lumbar tumors in patients treated with PAMT or PTET in our hospital between June 2015 and November 2020 were retrospectively analyzed. The gross total resection (GTR) rate, operation time, estimated blood loss, postoperative hospital stay (PHS), postoperative neurological function, and spinal stability were compared between the 2 surgical methods. Neurological improvement was assessed using the pain visual analogue scale (VAS) and the Japanese Orthopaedic Association (JOA) score.

Results: Fifteen cases of GTR (93.8%) and 1 case of subtotal resection were included in the PTET group, whilst all 18 patients in the PAMT group achieved GTR. There was no significant difference in the GTR rate, operation time, and PHS between the PAMT and PTET groups. The estimated blood loss was significantly lower in the PTET group than in the PAMT group. At the last follow-up, there was no significant difference in the VAS or JOA scores between PTET and PAMT. No tumor recurrence or spinal instability was observed in either group during the follow-up period.

Conclusion: Both PAMT and PTET can achieve Eden type III-IV lumbar 1-stage tumor resection without additional spinal internal fixation due to reduced muscle, ligament, and facet joint damage. No lumbar instability and tumor recurrence occurred, and neurological function was improved.

Keywords: Lumbar spine, Dumbbell-shaped tumor, Eden grade, Microtubular technique, Spinal endoscopy, Gross total resection

INTRODUCTION

Dumbbell-shaped tumors of the lumbar spine are rare spinal canal tumors that often compress the peripheral nerve tissue, of which surgical resection is the preferred treatment method. Eden's classification and pathological types of dumbbell-shaped lumbar tumors aid surgeons in their decision regarding the appropriate surgical strategy. The traditional treatment of lumbar spine dumbbell-shaped tumors achieves adequate exposure and resection of the tumor by excising the facet joint, opening the intervertebral foramen, and performing fusion and internal fixation to maintain spinal stability. With the development of minimally invasive techniques and the concept of minimally invasive spine surgery, many surgeons elect to use the anatomical features of the spine to remove tumors while reducing the impact of surgical operations on the stability of the spine and the impact of internal fixation on the functional activities of the patient's spine.
In 2015, Chunmei et al. detailed the paravertebral approach and microtubular tumorectomy (PAMT) for the treatment of lumbar spinal tumors and reported that lumbar spinal tumors could be completely removed, and damage to the paravertebral muscles, articular processes, and spines could be avoided. They highlighted that PAMT for the treatment of lumbar spinal tumors resulted in less trauma, faster recovery, less complications, and good lumbar spine stability. In recent years, the percutaneous transforaminal endoscopic technique has been widely used in the treatment of lumbar disc herniation. In addition, we have reported on full-endoscopic surgery to remove lumbar dumbbell tumors. Alternatively, percutaneous transforaminal endoscopic tumorectomy (PTET) is a novel, safe, and effective surgical approach for lumbar spine dumbbell-shaped tumors, which can help avoid the spine and minimize the damage to the normal structure of the spine while completely removing the tumor inside and outside the lumbar intervertebral foramen. Spinal stability is conducive to the early recovery of patients. At present, with regards to the minimally invasive surgery of intraspinal tumors, there is no published work detailing the difference between endoscopic spinal surgery and tubular spinal surgery. This study assuming that PTET is not less efficacious compared with PAMT in patients with lumbar dumbbell-shaped tumors, and aimed to compare the gross total resection (GTR) rate, perioperative period data, postoperative neurological function, and complications to evaluate their safety and efficacy.

MATERIALS AND METHODS

1. Patients

Patients with lumbar dumbbell-shaped tumors treated with PAMT or PTET (according to their decision) in our hospital between June 2015 and November 2020 were retrospectively studied.

The inclusion criteria for this study were as follows: (1) patients with tumor classified as Eden type III or IV and a tumor located in the epidural layer; (2) the diameter of the intraspinal canal tumor was ≤ 2 cm; (3) the diameter of the paravertebral tumor was ≤ 5 cm; and (4) the patient has signed an informed consent form. The exclusion criteria were as follows: (1) infectious lesions in the surgical path, (2) tumor invading ≥ 2 intervertebral foramina, (3) the segment where the tumor was located with a history of surgery, (4) vascular tumor or tumor with rich blood supply, (5) lumbar instability, and (6) severe lumbar scoliosis.

2. Ethics Approval

This study has been granted approval by the Ethics Committee of Fujian Medical University Union Hospital, Fuzhou, China (approval number: 2021YF022-01).

3. Clinical Data and Imaging Examination

The clinical manifestation and presentation of each patient were also assessed. Radiographic examination, 3-dimensional computed tomography (CT) reconstruction, and magnetic resonance imaging (MRI) with enhanced scanning were performed on the lumbar vertebrae before surgery to obtain a definitive diagnosis.

4. Intervention: PTET

The puncture point and path of the intervertebral foramen were designed based on MRI and 3-dimensional reconstruction CT images taken prior to surgery, including the distance from the skin to the tumor surface and the distance from the skin to the intervertebral foramen. After the induction of general anesthesia, the patient was placed in the prone position and x-ray fluoroscopy was used to locate the surgical segment and puncture point. The puncture point was located 15 cm lateral to the posterior midline (adjusted according to the patient's body shape), the intervertebral foraminal puncture path pointed to the paravertebral tumor, and intervertebral foramen in the extending direction. Under x-ray fluoroscopy guidance, when the puncture needle reached the paravertebral tumor tissue, a guide wire was inserted. A skin incision of approximately 7 mm was made, and a soft tissue dilator and a tubular working sheath were sequentially placed along the guidewire. Tumor resection (from outside to the inside of the spinal canal) under endoscopy (Spinendos, Germany) was performed as follows: (1) First, the paravertebral tumor was excised after the nerve roots, tumor capsule, and normal muscle tissues were identified in the tubular working sheath. Electrocoagulation was used to cut off the blood vessels supplying the tumor, and the paravertebral tumor tissue and the tumor-bearing nerve root were excised to protect the normal nerve root. (2) If the intervertebral foramen was small, foraminoplasty was performed using an endoscopic burr or trephine. In most cases, tumor growth led to the expansion of the intervertebral foramen, and the tubular working sheath can easily enter the spinal canal. (3) Resection of tumors in the intervertebral foramen and spinal canal to avoid a dural tear. The direction of the tubular working sheath was adjusted such that the endoscope could gradually penetrate the intervertebral foramen and enter the spinal canal in the tumor capsule,
and the tumor tissue could be removed in pieces. A drainage tube was placed outside the intervertebral foramen, the working sheath was removed, and the wound was sutured (Figs. 1-3). A typical case was presented (see Supplementary materials).

5. Intervention: PAMT

1) Anesthesia and position

After the induction of general anesthesia, patients were placed in the prone position to minimize lumbar lordosis/thoracic kyphosis and avoid compressing the abdomen.

2) Approach and exposure

A 20- to 25-mm skin incision was made approximately 20–35 mm lateral to the midline (adjusted according to the patient’s body habitus), and the accurate target level was confirmed by x-ray fluoroscopy.

The paravertebral approach involved the paravertebral muscles, which were bluntly dissected using the muscle splitting

![Fig. 1](https://doi.org/10.14245/ns.2244152.076)

**Fig. 1.** Preoperative T2-weighted magnetic resonance imaging on axial (A) plane, T1-weighted enhanced sagittal (B) plane, 3-dimentional (3D) sagittal (C), and 3D coronal (D) planes, revealing a dumbbell tumor in the left L1–2 foramen (arrows). (E) 3D computed tomography scan shows the enlarged foramen (arrow).

![Fig. 2](https://www.e-neurospine.org)

**Fig. 2.** Surgical diagrams illustrating the percutaneous transforaminal endoscopic tumorectomy operation process. (A) A tubular working sheath was placed along the guidewire above the surface of the paravertebral part of the dumbbell tumor in lumbar vertebrae on the axial plane. (B) The paravertebral tumor and the tumor-bearing nerve root were excised after the nerve roots, tumor capsule, and normal muscle tissues were identified in the tubular working sheath on the sagittal plane. (C) The tubular working sheath reached the internal space of the foramen after foraminoplasty on the axial plane. (D) The tubular working sheath’s direction was adjusted so that the endoscope could gradually penetrate the intervertebral foramen and enter the spinal canal in the tumor capsule. The tumor tissue could be removed in pieces on the coronal plane. (E) After confirming that the tumor was removed entirely, the working sheath was withdrawn.

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https://doi.org/10.14245/ns.2244152.076

Fig. 3. Postoperative T1-weighted enhanced magnetic resonance imaging on axial (A), sagittal (B), and coronal (C) planes. Any remnant of the dumbbell tumor could not be identified (arrows) after 3 months.

Fig. 4. Preoperative T1-weighted enhanced magnetic resonance imaging on sagittal (A) plane, coronal (B) plane, and axial (C) plane, revealing a dumbbell tumor (Eden II) in the left L4–5 foramen (red arrows).

technique. After the smallest dilator was inserted to reach the lamina or peripheral bone structure, the dilators were sequentially placed on top of each other, and a working tubule (diameter, 14 mm or 16 mm) was inserted over the dilators. The dilators were removed, and a tubular surgical path was established. The tubule was fixed using a flexible arm mounted on the operating table. Due to the flexible fixed arm, the tubule was able to be angulated to expand the operating field. The tumor resection was performed under a microscope (OPMI Pentero, Carl Zeiss AG, Oberkochen, Germany).

In Eden type III tumors, tumor resection was first performed in the intraspinal tumor, followed by the paraspinal tumor. The microtubules first reached the lamina to facilitate intraspinal tumor removal. A high-speed drill combined with Kerrison punches was used to remove part of the lamina, and the ligamentum flavum was excised to expose the dura and the spinal nerves. The intraspinal canal and intervertebral foraminal tumors were excised which was located in the epidural area. Any obvious tumor-bearing nerves were removed. The bone window of the spinal canal was temporarily sealed using gelatin sponge. If the diameter of the paravertebral tumor is ≤ 2 cm, the direction of the tubule can be directly adjusted to expose and remove the paravertebral tumor. If the diameter of the paravertebral tumor (Figs. 4-6) was ≥ 2 cm, the microtubule was required to be reinserted to reach the region between transverse processes and establish a second paravertebral muscle tubular path (dual-tubule path); if necessary, remove the part of the transverse process and expose and remove the extraforaminal tumor and paravertebral tumor. For Eden IV tumors, the microtubule directly reached the paravertebral transverse process, exposing and resecting the extraforaminal tumor and paravertebral tumor. The paravertebral muscles were repositioned, and the muscle fascia, subcutaneous tissue, and skin were sutured layer-by-layer.
3) Postoperative measurements

The drainage tube was removed within 24 hours after surgery, and patients underwent passive lower extremity and walking training protected by a belt brace as soon as possible. A belt brace was used for 1–2 weeks after surgery.

6. Outcome Measurements and Data Collection

Neurological improvements were assessed using the pain visual analogue scale (VAS) and Japanese Orthopaedic Association (JOA) scores. The baseline data included sex, age, body mass index, comorbidities, target segment, clinical performance, and preoperative VAS and JOA scores. The primary outcome measure was the GTR rate. The extent of resection was defined as GTR if there was no residual tumor on postoperative MR images and subtotal resection (STR) if the residual tumor was present. Secondary outcome indicators included operation time, estimated blood loss (EBL), postoperative hospital stay, postoperative VAS score, postoperative JOA score, tumor recurrence.

Fig. 5. Surgical diagrams illustrating the paravertebral approach and microtubular tumorectomy operation process. (A, B) A working tubule (diameter, 14 mm or 16 mm) reached the lamina by dissecting the paravertebral muscle bluntly. The intraspinal canal and intervertebral foramen tumors were excised, which were located in the epidural area after removing part of the lamina and the ligament flavum. (C, D) The microtubule was reinserted to reach the region between transverse processes and establish a second paravertebral muscle tubular path (dual-tubule path); if necessary, remove the part of the transverse process and expose and remove the extraforaminal tumor and paravertebral tumor. (E) The microtubule can be angulated to expand the operating field. (F) After confirming that the tumor was completely removed, the microtubule was withdrawn.

Fig. 6. Postoperative T2-weighted magnetic resonance imaging on axial (A), and T1-weighted enhanced on coronal (B) planes. Any remnant of the dumbell tumor could not be identified after 6 months (red arrows). (C, D) The axial plane and 3-dimensional computed tomography scan showed the bone window of L4 and L5 lamina (red arrows).
7. Statistical Analysis

Data were analyzed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). For continuous variables, Student t-test was used for independent samples. Contingency tables will be constructed for the categorical variables, assessing the independence between variables using Fisher exact test. Statistical significance was set at p < 0.05. An exploratory subgroup analysis was performed to investigate whether the treatment effect varied across subgroups of patients.

RESULTS

1. Participants’ characteristics

Thirty-four patients were included in this study in accordance with the inclusion and exclusion criteria. The PTET group included 16 cases, 8 of which were Eden type III and 8 were Eden type IV, with an average age of 42.81 ± 16.86 years. The PAMT group included 18 cases, 12 of which were Eden type III and 6 were Eden type IV, with an average age of 48.17 ± 17.31 years. The pathological report showed 24 cases of schwannoma, 3 cases of inflammatory granuloma, 1 case of a cyst, 1 case of cavernous hemangioma, 1 case of ganglionoma, 1 case of neurofibroma, and 3 cases of metastases. The 3 metastatic cases included 1 small-cell lung tumor, 1 acute lymphocytic leukemia (B cell), and 1 acute leukemia metastasis (myeloid) (Table 1).

2. Primary and Secondary Outcomes

1) GTR rate

There were 15 cases of GTR (93.8%) and 1 case of STR in the PTET group whilst all 18 patients in the PAMT group achieved GTR. Due to an insufficient sample size, the Fisher exact test was used and determined no statistically significant difference in the GTR rate between the 2 groups (p = 0.47) (Table 2).

2) Surgical data

The mean operative time in the PTET group was 101.3 ± 25 minutes, and the mean operative time in the PAMT group was 112.2 ± 18.96 minutes (-10.97 minutes; 95% CI, -26.37 to 4.42; p = 0.16). There was no significant difference in postoperative hospital stay between the PAMT and PTET groups (-0.59 days; 95% CI, -1.33 to 0.15; p = 0.11). However, the EBL in the PTET group was significantly lower than that in the PAMT group (-32.71 mL; 95% CI, -63.53 to 1.89; p = 0.04) (Table 2).

3) Neurological function improvement

Lumbar or leg pain, lower-limb weakness, and other symptoms were significantly relieved in both the PTET and PAMT groups, and no new neurological dysfunction was observed. There was no significant difference in preoperative VAS (0.88; 95% CI, -0.40 to 2.15; p = 0.17) and JOA (-1.92; 95% CI, -4.75 to 0.90; p = 0.16) scores between PTET and PAMT, indicating that data were comparable between groups. At the last follow-up, there was no significant difference in the VAS (-0.19; 95%
CI, -0.58 to 0.20; p = 0.34) and JOA (0.47; 95% CI -0.24, 1.18; p = 0.19) scores between the PTET and PAMT groups (Table 2).

4) Adverse events
Postoperative complications included cerebrospinal fluid leakage in 1 case (PAMT group), cavity effusion in 4 cases (2 cases in the PTET group and 2 cases in the PAMT group), wound infection in 3 cases (2 cases in the PAMT group and 1 case in the PTET group), and relief after management and medication. No tumor recurrence or spinal instability was observed in both groups (Table 2).

5) Subgroup analysis
Subgroup analysis was performed according to the different Eden types. For Eden type III lumbar tumors, the JOA score at 6 months after surgery was significantly lower in the PTET group than in the PAMT group (-2.29; 95% CI, -4.48 to -0.1; p = 0.04), while the EBL in the PTET group was significantly less than that in the PAMT group (47.08 mL; 95% CI, -85.45 to -8.72; p = 0.02). For Eden type IV lumbar tumors, there was no significant difference in operation time, EBL, PHS, VAS score or JOA score between the PTET and PAMT groups (p > 0.05) (Table 3).

DISCUSSION
Based on preliminary reports on the feasibility and safety of PAMT and PTET, this study aimed to compare the efficacy of the 2 approaches and summarize the advantages and disadvantages of each technique in dumbbell-shaped lumbar tumors. Our findings indicated that both the microtubular and full-endoscopic approach can achieve satisfactory outcomes, which is a novel addition to current literature.

Most dumbbell-shaped lumbar tumors are benign. The tumors were located below the facet joints and reached the spinal and extravertebral canals through the intervertebral foramen. They can stimulate or damage the spinal nerves and cause clinical symptoms, including pain. Total tumor resection is often accomplished by open surgery for dumbbell-shaped lumbar tumors. Open surgeries result in sufficient exposure and reduced tumor recurrence, but they can result in damage to the paraver-
Table 3. Subgroup analysis for Eden classification of lumbar dumbbell tumors

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<td>(-85.45 to -8.72)</td>
<td>0.02*</td>
<td>8</td>
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<td>PHS (day)</td>
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PTET, percutaneous transforaminal endoscopic tumorectomy; PAMT, paravertebral approach and microtubular tumorectomy; CI, confidence interval; SD, standard deviation; JOA, Japanese Orthopaedic Association; VAS, visual analogue scale; EBL, estimated blood loss; PHS, postoperative hospital stay.

*p < 0.05, statistically significant difference.
tebral muscles and ligaments and removal the facet joints and lamina, which may cause spinal instability and require additional fusion and internal fixation. Additional fixation surgeries significantly aggravate the extent of damage to the paravertebral muscles and ligaments, which is not necessary for tumor resection and fixation instruments, greatly increasing medical costs. In addition, patients have been reported to recover slowly, suffer from chronic low back pain, and have limited lumbar movement after open surgery. We have previously performed intraspinal subdural schwannoma and thoracic dumbbell tumor resections using the microtubular technique, and we have also attempted lumbar dumbbell tumor resection under spinal endoscopy.

For Eden type III-IV lumbar tumors with a single segment and a maximum diameter of < 5 cm, both PTET and PAMT achieved 1-stage total resection. In PTET approach, the tumor resection procedure extends from the paravertebral tumor to the intraspinal canal tumor. Therefore, we chose to reach the paravertebral tumor directly after intracapsular resection of the tumor, using the intervertebral foramens bony channel to enter the spinal canal and remove the tumor in the spinal canal, which can reduce the damage to the bony structure and paravertebral muscles of the spine. Puncture site, puncture path, and modified foraminoplasty are key to the success of PTET. PTET differs from the lumbar disc herniated endoscopic transforaminal approach (PTED) in terms of the puncture technique and foraminoplasty; the design of the puncture path made the working sheath easier to pass the intervertebral foramens and remove the tumor tissue in the spinal canal after paravertebral tumor resection. Since the dorsal root ganglion was mostly located in the intervertebral foramens, lumbar dumbbell-shaped tumors compressed the exiting nerve roots or dorsal root ganglion, causing low back and leg pain and movement disorders. Another effect of modified foraminoplasty was that the exiting nerve and dorsal root ganglion were adequately decompressed to relieve the symptoms of low back and leg pain.

During PTET surgical tumor resection, when the paravertebral tumor diameter was > 3 cm, endoscopic tumor resection spent more time; for schwannomas, the bearing-tumor nerve often accompanied the tumor supply blood vessels, which helped to find blood vessels, and under the “navigation” of the tumor-bearing nerve (exiting nerve), the endoscope can more easily enter the intervertebral foramens and remove tumor tissue in the spinal canal. Furthermore, under the influence of the lavage water pressure of the endoscope, it is often difficult to distinguish between the blood vessels supplying the tumor and the internal foraminal venous plexus. Alternately closing and opening saline can compare the morphological characteristics of blood vessels and help distinguish different blood vessels and nerve root branches. Tumors with rich blood supplies were prone to bleeding, which made it difficult to identify the tissue under the endoscope and increased the risk of surgery. Therefore, endoscopic tumor resection still has a relatively long learning curve, even for experienced spinal surgeons.

Tubular spine surgery involves the application of expandable tubules or nonexpandable tubule using tubular retractors of different diameters (14–28 mm) to treat various spinal diseases. This technique is safe and effective and does not increase the risk of nerve damage after resolving spinal diseases. In the PAMT approach, we achieved resection of intraspinal, foraminal, and paravertebral tumors by adjusting the position and angle of the paravertebral muscle path under the nonexpandable tubule (diameter, 14/16 mm). For larger Eden type III tumors, it is necessary to establish 2 paravertebral muscle tubular paths (dual-tubular paths) to remove intraspinal and paravertebral tumors, which can protect the facet joints and isthmus, avoid excessive traction and separation of muscles, and reduce the risk factors for spinal instability. However, for tumors with diameters > 5 cm or vascularized tumors, we still recommend open surgery or mini-open surgery.

For Eden III-IV lumbar dumbbell-shaped tumors, the EBL in the PAMT group was higher than that in the PTET group, but there was no significant difference in the operation time, JOA or VAS scores, or PHS. When subgroup analysis was performed according to different Eden types, it was found that for Eden type III tumors, the PTET group was significantly lower than the PAMT group’s JOA score at 6 months after surgery, but the EBL was lower than that of the PAMT group. The reason for the difference in EBL between the 2 groups may be that PTET was performed under saline perfusion pressure, which helped to reduce the bleeding of the venous plexus in the intervertebral foramina, but the number of cases in the 2 groups was small. Furthermore, the PAMT group included patients with spinal canal metastases and other pathological types of tumors. Therefore, it is difficult to ascertain whether there was a difference in EBL between the 2 procedures. The JOA score of the PAMT group was higher than that of the PTET group at 6 months after the operation, indicating that the early postoperative efficacy of the PAMT group may be better than that of the PTET group. However, there was no difference in the JOA scores at other follow-up periods and the last follow-up, indicating that the efficacy of the 2 groups was not significantly different. For
Eden type IV, there were no significant differences in the operative time, EBL, PHS, VAS, and JOA scores between the PAMT and PTET groups. Therefore, for single-segment lumbar dumbbell-shaped tumors (Eden types III and IV) with a maximum diameter of < 5 cm, we believe that both PAMT and PTET are alternative, effective, and minimally invasive treatment options.

This study analyzed the clinical results of PAMT and PTET in the treatment of single-segment lumbar dumbbell-shaped tumors (Eden types III and IV), but there are still several limitations. This research was a retrospective study with a low level of evidence. The number of cases collected in this study was small, and the follow-up time in some cases was < 2 years. Both PTET and PAMT are not suitable for all lumbar spine dumbbell tumor surgeries. For example, in cases of large paravertebral tumors (diameter, > 5 cm), such as tumors invading multiple intervertebral foramina, tumors with abundant blood supply, and scoliosis deformity, combined surgery or mini-open surgery is recommended for tumor removal. Although no tumor recurrence occurred during the follow-up period, it is undeniable that there is the possibility of tumor recurrence for PTET because the tumor is resected in pieces. PTET may result in residual tumor tissue for tumors that are too large, irregularly shaped, or incompletely enveloped. Finally, physicians cannot determine the pathological type of the tumor before surgery. If the pathological type of the tumor is a non-neurogenic tumor, physicians may be difficult to distinguish the tumor tissue from the normal tissue under spinal endoscopy, and intraoperative pathological analysis is often used to identify the tumor tissue. In the future, more cases and longer follow-up times are needed to verify the advantages and disadvantages of the 2 tubular spinal surgical methods.

**CONCLUSION**

PTET and PAMT are safe and effective surgical methods for Eden type III and IV lumbar dumbbell-shaped tumors, that can achieve 1-stage total tumor resection, reduce facet joint damage, and do not require fusion and internal fixation surgery. Furthermore, PAMT and PTET are alternative, effective, and minimally invasive treatments for dumbbell-shaped lumbar tumors.

**NOTES**

**Supplementary Material:** Supplementary material can be found via https://doi.org/10.14245/ns.2244152.076.

**Conflict of Interest:** The authors have nothing to disclose.


Comparison Between 3-Dimensional-Printed Titanium and Polyetheretherketone Cages: 1-Year Outcome After Minimally Invasive Transforaminal Interbody Fusion

Do-Yeon Kim¹, O-Hyuk Kwon², Jeong-Yoon Park²

¹Department of Neurosurgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea
²Department of Neurosurgery, Spine and Spinal Cord Institute, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Objective: Three-dimensional (3D)-printed titanium implants have been developed recently, but the utility is not yet proven. The aim of this study was to compare 3D-printed titanium and polyetheretherketone (PEEK) implants after minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF).

Methods: Between October 2018 and September 2021, we retrospectively analyzed 83 patients who underwent single-level MIS-TLIF (3D-printed titanium, 40; PEEK, 43). Radiologic parameters were assessed with x-ray and computed tomography (CT) at postoperative 1 week, 6 months, and 1 year. Clinical status was evaluated using Oswestry Disability Index, visual analogue scale score, and Bridwell fusion grading was assessed on 6-month and 1-year postoperative CT.

Results: There were no differences between the 2 groups in demographics and clinical outcomes. At 1-year of follow-up, the reported 3D-printed titanium fusion grades were grade I: 77.5% (31 patients), grade II: 17.5% (7 patients), and grade III: 5% (2 patients). The PEEK fusion grades were grade I: 51.2% (22 patients), grade II: 41.9% (18 patients), and grade III: 7.0% (3 patients). For overall fusion rate (grade I + II), there was no difference between the 2 cages (95.0% vs. 93.0%, p = 0.705), but grade I was reported at a higher incidence in 3D-printed titanium than PEEK (77.5% vs. 51.2%, p = 0.013). There was no difference between cages based on subsidence and complications.

Conclusion: There were no significant differences in the overall fusion rate for MIS-TLIF surgery between 3D-printed titanium and PEEK, but the fusion grade was better in 3D-printed titanium than in PEEK. Long-term follow-up is required to verify the effectiveness.

Keywords: Minimally invasive transforaminal lumbar interbody fusion, 3-dimensional-printed titanium, Polyetheretherketone, Fusion rate

INTRODUCTION

Due to the increase in life expectancy, lumbar spine degenerative disease is increasing in the elderly population.¹ Consequentially, there have been advances in surgical methods for lumbar degenerative disease, and interbody cages have been widely and frequently used for lumbar fusion surgery.²³ Minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) is a more recently developed technique that is widely performed in lumbar degenerative diseases and has a high fusion rate.⁴⁷ Many kinds of cages have been used for lumbar interbody fusion, and the 2 most popular cages are titanium and polyetheretherketone-
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Interbody cages. These interbody cages have been routinely used in fusion surgery and have been reported to have positive results. However, there are some disadvantages to these traditional solid titanium and PEEK cages. Solid titanium cages have a good fusion rate, but subsidence is frequent due to the high elastic modulus, and there are disadvantages for radiopaque. The PEEK cage complements the titanium shortcomings because it has radiolucency, and elastic modulus is similar to human cortical bone. However, the titanium cage promotes cell adhesion and is advantageous for bone fusion due to better osseous-integration and biocompatibility than the PEEK cage.

With developments in 3D-printing technology, many spine implants using 3D-printing technology have been released. The 3D-printer could produce a tailored cage to each patient and a desired shape or a complex shape. Therefore, recently produced 3D-printed titanium cages can be generated to reduce elastic modulus; they are produced with a rough surface and structure and an ideal porosity. These structures have similar properties to cancellous tissue and facilitate osteoblast cell regrowth. Therefore, we compared the fusion rate and quality of fusion for 3D-printed titanium and PEEK cages.

MATERIALS AND METHODS

1. Patient Population
Between October 2018 and September 2021, we retrospectively analyzed 83 patients who underwent single-level MIS-TLIF. The patients with follow-up more than 1-year were included in this study, and perioperative, clinical and radiologic date were collected. A total of 40 patients underwent MIS-TLIF with a 3D-printed titanium cage (PANTHER, Mantiz, Daegu, Korea), and 43 patients with a PEEK cage (CAPSTONE, Medtronic, Memphis, TN, USA). All patients had persistent low back pain and radiating pain in the lower extremities despite 3 months of conservative treatment. These patients had spinal stenosis (central or foraminal stenosis), recurrent herniated disc, spondylolisthesis, or instability. The patients were not diagnosed with osteoporosis and were not treated with antosteoporosis agents. The Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine approved this study (No. 2020-0971-001).

2. Preparation of 3D-Printed Titanium Cage
We used a 3D-printed titanium cage based on patient disc size (PANTHER, Mantiz, Daegu, Korea) (Fig. 1). This 3D model was produced using metal power bed fusion technology, which is also known as a Selective Laser Melting 3D printer (EP-M250, Shining 3D Tech., Hangzhou, China). This 3D-printed titanium cage has a mean pore size range of 630 μm to 730 μm and a mean porosity range of 70% to 80%. A straight bullet type was used for both the PEEK and the 3D-printed titanium cage. The height and length were measured and applied according to the patient’s anatomical characteristics. This 3D-printed titanium cage was a standard-made, and height and length of the cage did not differ with PEEK cage.

3. Surgical Technique
The MIS-TLIF was performed as previously described, and the MIS-TLIF surgery was performed from the symptomatic side of the patient. The surgical level was confirmed under C-arm guidance. A 3-cm incision was applied at lateral pedicle line on disc space, and a working channel was created with a tubular retractor (METRx, Medtronic, Memphis, TN, USA). Total facetectomy, partial laminectomy, and ligamentum flav...
vum removal were performed using a high-speed drill, osteotome, Kerrison punch, and pituitary rongeur. Contralateral side decompression was performed in all patients, and discectomy and preparation of disc space for fusion were conducted. Autologous local bone was inserted in the empty disc space. Both 3D-printed titanium and PEEK cage were filled with a mixture of demineralized bone matrix and small autologous local bone, and the fusion material in both cages were the same except for the cage. During this process, we placed the cage at as much of a transverse angle as possible (Fig. 2). Finally, the percutaneous pedicle screw was inserted into the appropriate position under fluoroscopic guidance. All pedicle screws were the same (ZE-NIUS, Medyssey, Jecheon, Korea). All procedures were performed by one neurosurgeon, who had sufficient MIS-TLIF experience (more than 1,000 cases).

4. Clinical Assessment

Collected patient information was demographics, medical comorbidities, surgical level, and surgical indications. Each patient was evaluated on an outpatient basis within 1 week and at about 1 year after surgery for Oswestry Disability Index (ODI), visual analogue scale (VAS) score, bone mineral density (BMD), and body mass index (BMI) (Table 1).

5. Radiologic Examination

The x-ray and CT scans were performed at approximately 6 months and 1 year postoperative. The Bridwell fusion grades were as follows: grade I, fused with trabecular bone formation; grade II, graft was intact but not completely remodeled, and there was no luency in the upper and lower parts of the graft; grade III, graft was intact, but there was luency above and below the graft; grade IV, fusion was absent with collapse or resorption of graft (Fig. 3). The calculated fusion rate was the sum of grades I and II.

Measurement of subsidence is inconsistently defined in the literature because of use of relative and absolute measurements, and the most frequently used measurement method for defining subsidence was based on a threshold of 2 mm. Therefore, we defined “subsidence” as segmental vertebral body height decrease by 2 mm or more at the last follow-up compared with 1 week after surgery. Segmental vertebral body height was measured from the midpoint of the cranial endplate of the upper vertebra to the caudal endplate of the lower vertebra (Fig. 4). The evaluation of the radiologic parameters was independently measured by 2 physicians not related to the surgery, and the average value was calculated.

6. Statistical Analysis

Chi-square test, Student t-test, and Mann-Whitney U-test were used for statistical analysis using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA). Data are expressed as mean and standard deviation. A p-value lower than 0.05 was considered statistically significant.
Table 1. Demographics and clinical data

<table>
<thead>
<tr>
<th>Variable</th>
<th>3D-printed titanium (n = 40)</th>
<th>PEEK (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.739</td>
</tr>
<tr>
<td>Male</td>
<td>21 (52.5)</td>
<td>21 (48.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (47.5)</td>
<td>22 (51.2)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.17 ± 11.70</td>
<td>58.53 ± 12.46</td>
<td>0.810</td>
</tr>
<tr>
<td>Specific fusion level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3/4</td>
<td>4 (10.0)</td>
<td>6 (14.0)</td>
<td>0.740</td>
</tr>
<tr>
<td>L4/5</td>
<td>28 (70.0)</td>
<td>30 (69.8)</td>
<td>0.982</td>
</tr>
<tr>
<td>L5/S1</td>
<td>8 (20.0)</td>
<td>7 (16.3)</td>
<td>0.778</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Spinal stenosis</td>
<td>17 (42.5)</td>
<td>16 (37.2)</td>
<td>0.659</td>
</tr>
<tr>
<td>Spondylolisthesis/instability</td>
<td>19 (47.5)</td>
<td>25 (58.1)</td>
<td>0.383</td>
</tr>
<tr>
<td>Recurrent herniated disc</td>
<td>4 (10.0)</td>
<td>2 (4.7)</td>
<td>0.422</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>-1.62 ± 1.08</td>
<td>-1.49 ± 0.81</td>
<td>0.748</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.22 ± 3.52</td>
<td>24.52 ± 2.78</td>
<td>0.444</td>
</tr>
<tr>
<td>Clinical results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop ODI (%)</td>
<td>50.80 ± 24.64</td>
<td>45.58 ± 13.31</td>
<td>0.522</td>
</tr>
<tr>
<td>Postop ODI (%)</td>
<td>38.42 ± 14.36</td>
<td>36.96 ± 9.77</td>
<td>0.684</td>
</tr>
<tr>
<td>Preop VAS (back pain)</td>
<td>4.4 ± 1.46</td>
<td>2.02 ± 0.91</td>
<td>0.476</td>
</tr>
<tr>
<td>Postop VAS (back pain)</td>
<td>2.02 ± 0.91</td>
<td>2.30 ± 1.16</td>
<td>0.235</td>
</tr>
<tr>
<td>Preop VAS (leg pain)</td>
<td>6.27 ± 1.86</td>
<td>6.05 ± 2.83</td>
<td>0.942</td>
</tr>
<tr>
<td>Postop VAS (leg pain)</td>
<td>2.92 ± 2.22</td>
<td>3.00 ± 1.88</td>
<td>0.826</td>
</tr>
<tr>
<td>Complication</td>
<td>0</td>
<td>1*</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. 3D, 3-dimensional; PEEK, polyetheretherketone; BMD, bone mineral density; BMI, body mass index; ODI, Oswestry Disability Index; VAS, visual analogue scale. Chi-square test, Student t-test, and Mann-Whitney U-test were used for statistical analysis. *One-case complication was screw loosening, and do not need reoperation.

RESULTS

We retrospectively analyzed the data of 83 patients who underwent single-level MIS-TLIF surgery for degenerative lumbar disease. Of the total 83 patients, 40 were in the 3D-printed titanium group and 43 were in the PEEK cage group. There were no statistically significant differences in sex and age between the 2 groups (Table 1). A fusion level of L4/5 was the most frequent site for specific surgery in both groups (70% vs. 69.8%) (Table 1). There was no statistically significant difference in BMD, BMI, and clinical results (ODI or VAS) (Table 1).

Successful fusion according to the Bridwell fusion grading system was observed in 33 patients (82.5%) in the 3D-printed titanium cage and 34 patients (79.1%) in the PEEK cage at 6-month follow-up and was observed 38 patients (95%) in the 3D-printed titanium and 42 patients (93%) in the PEEK cage at 1-year follow-up. This difference was not significant at 6 months and 1 year after surgery (82.5% vs. 79.1%, p = 0.692, 95.0% vs. 93.0%, p = 0.705, respectively). However, there was a difference in detailed fusion grade between the 2 cages. In the 3D-printed titanium cage, grade I was 37.5%, grade II was 45.0%, and grade III was 17.5% at 6-month follow-up. At 1-year follow-up of 3D-printed titanium cage, grade I was 77.5%, grade II was 17.5%, and grade III was 5%. Meanwhile, in the PEEK, grade I was 16.3%, grade II was 62.4%, grade III was 20.9% at 6-month follow-up. At 1-year follow-up of PEEK, grade I was 51.2%, grade II was 41.9%, grade III was 7%. There was no grade IV in either group (Table 2). Based on these results, only grade I was statistically significantly higher in 3D-printed titanium than PEEK cage at 6-month and 1-year follow-up. (37.5% vs. 16.3% at 6-months, p = 0.029, 77.5% vs. 51.2% at 1-year, p = 0.013) (Table 2).

Among patients who underwent surgery at L4/5, there were
28 patients in the 3D-printed titanium and 30 patients in the PEEK cage. The fusion rate was not significant at 6 month and 1 year after surgery (82.1% vs. 76.7%, p = 0.462, 96.4% vs. 96.7%, p = 0.737, respectively). In L4/5, there was also a difference in detailed fusion grade between the 2 cages. In the 3D-printed titanium cage, grade I was 35.7%, grade II was 46.4%, and grade III was 17.9% at 6-month follow-up. In addition, at 1-year follow-up of 3D-printed titanium cage, grade I was 78.6%, grade II was 17.9%, and grade III was 3.6%. Meanwhile, in the PEEK, grade I was 13.3%, grade II was 63.3%, grade III was 23.3%. In addition, at 1-year follow-up of PEEK, grade I was 53.3%, grade II was 43.3%, grade III was 3.3% (Table 3).

No significant differences were found between groups in segmental vertebral body height at preoperative, immediate postoperative, and final follow-up. In addition, subsidence occurred in 15 patients (37.5%) in the 3D-printed titanium cage and 18 patients (41.9%) in the PEEK cage. There was no difference between the 2 cages in incidence rate of subsidence (37.5% vs. 41.9%, p = 0.685) or difference in segmental vertebral body height (segmental vertebral body height difference between immediate postoperative and final follow-up x-ray) (4.07 mm vs. 3.56 mm, p = 0.520) (Table 2). In addition, when the patients who underwent surgery at L4/5 level were selected, There was no difference between the 2 cages in incidence rate of subsidence (35.7% vs. 43.3%, p = 0.373) or difference in segmental vertebral body height (segmental vertebral body height difference between immediate postoperative and final follow-up x-ray) (4.38 mm vs. 3.11 mm, p = 0.224) (Table 3).

DISCUSSION

Previous studies have shown that MIS-TLIF was effective surgical treatment in degenerative lumbar spine disease, and the aim of TLIF is to stabilize the unstable movement of the spine by fusion. PEEK has been associated with weaker imaging disturbance in CT and x-ray, because of radiolucency. In addition, PEEK has been reported less mechanical complications, because of lower elastic modulus. Despite these advantages, due to the inherent characteristics of PEEK, integration of osteoblast is low. Olivares-Navarrete et al. reported that fibrous tissues grow around PEEK implants because osteoblastic differentiation of progenitor cells decreases and inflammatory reactions increase due to apoptosis and necrosis. In addition, McGilvray et al. found through histopathology that PEEK implants had poorly vascularized fibrous connective tissue and increased inflammatory response, consisting of lymphocytes and macrophages, in an in vivo ovine lumbar fusion model.

In comparison, titanium is advantageous for bone remodel-
Table 2. Radiologic parameter

<table>
<thead>
<tr>
<th>Variable</th>
<th>3D-printed titanium (n = 40)</th>
<th>PEEK (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion Grade (Bridwell fusion grade) at 6-month follow-up</td>
<td>3.11 ± 2.94</td>
<td>7 (16.3)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Grade I</td>
<td>15 (37.5)</td>
<td>7 (16.3)</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>18 (45.0)</td>
<td>27 (62.8)</td>
<td>0.104</td>
</tr>
<tr>
<td>Grade III</td>
<td>7 (17.5)</td>
<td>9 (20.9)</td>
<td>0.692</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Fusion rate (grade I+grade II)</td>
<td>42 (93.0)</td>
<td>34 (79.1)</td>
<td>0.692</td>
</tr>
</tbody>
</table>

Table 3. Radiologic parameter (L4/5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>3D-printed titanium (n = 28)</th>
<th>PEEK (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion grade (Bridwell fusion grade) at 6-month follow-up</td>
<td>76.32 ± 10.39</td>
<td>7 (17.5)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Grade I</td>
<td>23 (82.1)</td>
<td>23 (76.7)</td>
<td>0.462</td>
</tr>
<tr>
<td>Grade II</td>
<td>5 (17.9)</td>
<td>7 (23.3)</td>
<td>0.034*</td>
</tr>
<tr>
<td>Grade III</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Fusion rate (grade I+grade II)</td>
<td>32 (93.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Subsidence

<table>
<thead>
<tr>
<th>Variable</th>
<th>3D-printed titanium (n = 40)</th>
<th>PEEK (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental vertebral body height</td>
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<tr>
<td>Preoperative (mm)</td>
<td>69.88 ± 6.56 (n = 40)</td>
<td>72.53 ± 9.58</td>
<td>0.180</td>
</tr>
<tr>
<td>Immediate operative (mm)</td>
<td>73.76 ± 6.04 (n = 39)</td>
<td>75.03 ± 9.62</td>
<td>0.813</td>
</tr>
<tr>
<td>Last follow-up (mm)</td>
<td>69.68 ± 5.84 (n = 39)</td>
<td>71.33 ± 8.97</td>
<td>0.325</td>
</tr>
<tr>
<td>Gap of segmental vertebral body height (mm)†</td>
<td>4.07 ± 3.46 (n = 39)</td>
<td>3.56 ± 3.34</td>
<td>0.520</td>
</tr>
<tr>
<td>Subsidence†</td>
<td>15 (37.5)</td>
<td>18 (41.9)</td>
<td>0.685</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation. *p < 0.05, statistically significant difference. †Gap of height was measured by segmental vertebral body height difference between immediate postoperative and last follow-up x-ray. Subsidence is defined segmental vertebral body height decreased by more than 2 mm at last follow-up after surgery than at immediate postoperative x-ray. Chi-square test, Student’s t-test, and Mann-Whitney U-test were used for statistical analysis.

3D-Printed Titanium vs. PEEK Cages

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In our study, there was no difference in early-stage fusion rate between 3D-printed titanium and PEEK cages (82.5% vs. 79.1% at 6 months, 95.0% vs. 93.0% at 1 year). However, previous comparison between titanium and PEEK cages has been performed with a solid titanium cage instead of a 3D-printed titanium cage. The 3D-printed titanium cage has a finer structure than solid titanium cage, which can increase the porosity and decrease the elastic modulus. Titanium has been used for a long time as a major material for fracture and fusion surgery due to its high biocompatibility with bone. Solid titanium cage has also been used for interbody fusion for a long time, but due to its high elastic modulus and subsidence rate, it has been replaced by PEEK cage. The 3D-printed titanium cage was developed to overcome the elastic modulus problem of solid titanium and maintain the advantage of biocompatibility.

In our study, there was no difference in early-stage fusion rate between 3D-printed titanium and PEEK cages (82.5% vs. 79.1% at 6 months, 95.0% vs. 93.0% at 1 year). However, when com-
paring patients of fusion grade I, the quality was better in the 3D-printed titanium than in PEEK cage (37.5% vs. 16.3% at 6 months, 77.5% vs. 51.2% at 1 year) (Table 2). In order to exclude biomechanical effects according to each fusion level, there was no difference from the previous results when the fusion grade was measured for patients who had undergone at L4/5 (35.7% vs. 13.3% at 6 months, 78.6% vs. 53.3% at 1 year) (Table 3). This is the first study to evaluate early-stage fusion rate and to compare 3D-printed titanium and PEEK cages. We hypothesize that there will be no difference in fusion rate between 3D-printed titanium and PEEK cages in long-term follow-up, though 3D-printed titanium may be more advantageous in the early stage. This difference could be attributable to the more porous structure in the titanium cage due to application of 3D-printing technology and to the structural similarity to physiological cancellous bone.\textsuperscript{13,35} These structures showed good biocompatibility and induced osseous-integration.\textsuperscript{1,4,34,35}

Previous studies have indicated that solid titanium has a high elastic modulus, so subsidence incidence is high.\textsuperscript{11,12,36} Several studies have shown differences in subsidence between solid titanium and PEEK cages, with subsidence ratio ranging from 16% to 35% in solid titanium and from 0% to 28% in PEEK cages.\textsuperscript{11,12,26,37-39} Our study is the first comparative study to evaluate the subsidence between 3D-printed titanium and PEEK cages, and the results indicate no significant difference between the 2 cages in incidence of subsidence. Differences could be attributable to the unique porous 3D-printed titanium cage structure, and the elastic modulus could be adjusted by changing the size of the porosity. Therefore, it was possible to maintain an elastic modulus similar to the physiological level, resulting in no difference in fusion rate or incidence of subsidence with PEEK cage.\textsuperscript{1,4,34,35} In this study, subsidence was relatively high (3D-printed titanium, 37.5%; PEEK, 41.9%), but there were no significant differences in preoperative segmental vertebral body height or final follow-up metrics (3D-printed titanium, 69.88 to 69.68 mm; PEEK, 72.53 to 71.33 mm). This indicates that clinically meaningful subsidence was not high (Table 2).

This study had several limitations. First, it was difficult to determine final fusion because the 3D-printed titanium cage is relatively new, and the long-term fusion rate cannot be measured. Second, due to the radiologic interference of titanium, it may be difficult to distinguish fusion grade. Third, since the occurrence of subsidence was based only on radiographic and morphologic results, it is difficult to determine whether clinical subsidence occurred. This limitation seemed to have occurred due to the short follow-up period, therefore, all cases in this study will be followed for more than 2 years to report the final results. Despite the limitations described, this study is the first to clinically compare the fusion rates of 3D-printed titanium and PEEK cage. In addition, we observed that the 3D-printed titanium showed better fusion quality than PEEK cage in early preliminary outcomes after MIS-TLIF, which is likely because of the difference in porous structure and biocompatibility of 3D-printed titanium. With development of recent 3D-printing technology, it is possible to overcome the limitations of PEEK and solid titanium implants, and we are confident that 3D-printed titanium cage will be used increasingly for spine fusion.

**CONCLUSION**

The overall fusion rate of MIS-TLIF surgery showed no significant difference between 3D-printed titanium and PEEK cages. In addition, there was no difference between the 2 groups in incidence of subsidence. However, fusion grade was better in the 3D-printed titanium than PEEK cage. With development of recent 3D-printing technology, it is possible to overcome the limitations of previous spine implants, and we are confident that 3D-printed titanium technology will contribute to improvements in spine fusion surgery.

**NOTES**

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**Author Contribution:** Conceptualization: JP; Data curation: DK, OK; Formal analysis: DK, OK; Funding acquisition: DK; Methodology: DK, OK; Project administration: JP; Writing - original draft: DK; Writing - review & editing: JP.

**ORCID**

Do-Yeon Kim: 0000-0002-2898-078X
O-Hyuk Kwon: 0000-0002-9065-1055
Jeong-Yoon Park: 0000-0002-3728-7784

**REFERENCES**


ing polyetheretherketone cages or titanium cages with transpedicular instrumentation. Eur Spine J 2014;23:2150-5.
Higher American Society of Anesthesiologists Classification Does Not Limit Safety or Improvement Following Minimally Invasive Transforaminal Lumbar Interbody Fusion

Conor P. Lynch, Elliot D.K. Cha, Cara E. Geoghegan, Caroline N. Jadczak, Shruthi Mohan, Kern Singh

Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

Objective: The American Society of Anesthesiologists (ASA) physical status classification has been used to risk stratify surgical candidates. Our study compares outcomes of minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) procedures based on preoperative ASA physical status classification.

Methods: A surgical registry was reviewed for primary, single-level MIS TLIF patients. Patients were categorized by preoperative ASA physical status classification: ASA I, ASA II, ASA III+. Perioperative complications were compared among groups. Patient-reported outcome measures (PROMs) for back pain, leg pain, physical function, and disability were recorded preoperatively and at 6-week, 12-week, 6-month, 1-year, and 2-year postoperative timepoints. PROM improvement from baseline (ΔPROM) and minimum clinically important difference (MCID) achievement was calculated for each timepoint and compared among groups. MCID achievement was determined as ΔPROMs that surpassed previously established MCID values.

Results: Of the 487 patients, 64 had an ASA classification of I, whereas 336 had an ASA of II, and 87 had an ASA of III or greater. Rates of complications were not associated with ASA classification (all p > 0.050). Neither mean PROM scores nor ΔPROM scores were significantly associated with ASA classification at any timepoint (all p > 0.050). MCID achievement was significantly associated with ASA classification for back pain at 1 year only (p = 0.041). Overall MCID achievement was not significantly associated with ASA classification for any PROM (p > 0.050).

Conclusion: While ASA classification has been commonly used to risk stratify surgical candidates for spinal procedures, patients with an ASA of III or greater may be able to achieve similar long-term outcomes following MIS TLIF given proper selection criteria.

Keywords: Anesthesiologist, Patient-reported outcomes, Minimally invasive surgery, Transforaminal lumbar interbody fusion

INTRODUCTION

Minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) has proven to be an efficacious treatment option for those experiencing degenerative spine pathologies such as central stenosis and spondylolisthesis while minimizing soft tissue trauma and disruption of posterior musculature.1 As with many surgical procedures, evidence-based patient selection cri-
While the classification itself only accounts for the physical health of the patient, several past studies have demonstrated a correlation between ASA classification and operative outcomes such as postoperative complications, intraoperative blood loss, and overall morbidity and mortality. Within the spine population, studies have reported a high ASA classification to be a significant risk factor for outcomes such as reoperation and readmission rates, postoperative complications, and greater direct costs. However, some evidence suggests that these risks may be lower for minimally invasive spinal procedures. In light of these conflicting findings, it is necessary to comprehensively address ASA classification in the context of various perioperative characteristics to better understand outcomes following MIS TLIF procedures specifically.

In addition to the more traditional objective assessment of operative outcomes, patient-reported outcome measures (PROMs) are self-reported questionnaires that allow clinicians to understand postoperative pain, disability and physical function from the patient’s perspective. By quantifying PROM scores in terms of the minimum clinically important difference (MCID), a value that represents the minimum change in score a patient perceives as beneficial, clinicians can identify changes that are clinically significant to the patient. While a significant number of studies have investigated ASA classification and perioperative outcomes in the spine population, there is limited literature focusing on ASA in the context of PROMs. The few studies that have addressed this topic have generally been overly broad to draw direct conclusions about ASA classification for specific populations, or were limited in their reporting of long-term outcome improvement. This relative dearth of patient-centered data highlights the need to investigate the relationship between ASA classification and PROMs in the context of specific spine procedures.

ASA has been previously used as selection criteria to assess whether a patient is fit for surgery, but beyond this safety profile, there is limited literature to indicate whether the score can successfully predict a patient’s course of recovery. We aim to clarify this relationship and determine the value of ASA classification as a patient selection criterion for minimally invasive spine surgery, which may have important implications for clinical practice. Investigating ASA classification and PROMs, in addition to other perioperative characteristics, will improve the understanding of this scoring system’s effect on longitudinal, clinically significant outcomes.

MATERIALS AND METHODS

1. Patient Population

This study was approved by the Institutional Review Board of Rush University Medical Center (ORA #14051301) and written informed consent were obtained from patient prior to subject enrollment and data collection. Prospectively collected data was retrospectively reviewed via a private surgical database for minimally invasive lumbar fusion patients from January 2014 to February 2020. Inclusion criteria were patients undergoing primary, elective, single-level MIS TLIF procedures for degenerative spinal pathology. Exclusion criteria were patients missing a preoperative ASA classification or whose procedures were indicated for traumatic, infectious, or malignant etiologies. Additionally, to mitigate the confounding effects on outcomes following MIS TLIF, multilevel procedures were also excluded from the study. All procedures were performed by a single attending spine surgeon.

2. Data Collection

Patient demographic data was collected, including age, gender, body mass index (BMI), smoking status, and workers’ compensation status. Prevalence of various preoperative medical diagnoses were recorded for diabetes mellitus, acute immune deficiency syndrome (AIDS), history of myocardial infarction, neurological disease, arthritis, congestive heart failure, peripheral vascular disease, metastasis, liver disease, renal failure, chronic lung disease, and gastrointestinal bleeding. Prevalence of pre-existing spinal pathology was assessed for recurrent herniated nucleus pulposus, degenerative spondylolisthesis, and ischemic spondylolisthesis. Perioperative characteristics including operative duration (from skin incision to skin closure), estimated blood loss (EBL), and postoperative length of stay were recorded. Incidences of postoperative complications such as aspiration requiring reintubation, urinary retention, urinary tract infection, epidural hematoma, acute renal failure, postoperative anemia, altered mental status, venous thromboembolism, pulmonary embolism, pneumothorax, arrhythmia, ileus, pneumonia, atelectasis, pleural effusion, fever, or pancreatitis were recorded.
corded and confirmed via direct review of the electronic medical record. Specific circumstances and outcomes regarding confirmed complications were then reviewed and described.

PROMs were administered preoperatively and at 6-week, 12-week, 6-month, 1-year, and 2-year postoperative timepoints via a secure online portal and completed by patients either in the clinic using a provided electronic tablet prior to the appointment or at home using personal devices. Administered PROMs included the visual analogue scale (VAS) back, VAS leg, Oswestry Disability Index (ODI), 12-Item Short Form health survey physical composite score (SF-12 PCS), and Patient-Reported Outcomes Measurement Information System physical function (PROMIS PF).

### 3. Surgical Technique

Following localization of the appropriate spinal level via lateral fluoroscopy, an incision was made lateral to the midline and sequential dilators were used to gain exposure. A central laminectomy and bilateral partial facetectomy were performed. Following preparation of the endplates, an interbody cage along

### Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 487)</th>
<th>ASA PS classification</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (n = 64)</td>
<td>II (n = 336)</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>52.1 ± 11.7</td>
<td>42.1 ± 10.2</td>
<td>52.4 ± 11.1</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>209 (42.9)</td>
<td>21 (32.8)</td>
<td>155 (46.1)</td>
</tr>
<tr>
<td>Male</td>
<td>278 (57.1)</td>
<td>43 (67.2)</td>
<td>181 (53.9)</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>260 (53.4)</td>
<td>45 (70.3)</td>
<td>189 (56.3)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>227 (46.6)</td>
<td>19 (29.7)</td>
<td>147 (43.8)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>404 (83)</td>
<td>54 (84.4)</td>
<td>280 (83.3)</td>
</tr>
<tr>
<td>Smoker</td>
<td>83 (17)</td>
<td>10 (15.6)</td>
<td>56 (16.7)</td>
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<tr>
<td><strong>Insurance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-WC</td>
<td>311 (63.9)</td>
<td>29 (45.3)</td>
<td>227 (67.6)</td>
</tr>
<tr>
<td>WC</td>
<td>176 (36.1)</td>
<td>35 (54.7)</td>
<td>109 (32.4)</td>
</tr>
<tr>
<td><strong>Medical diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>58 (11.9)</td>
<td>0 (0)</td>
<td>30 (8.9)</td>
</tr>
<tr>
<td>AIDS</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>177 (36.4)</td>
<td>4 (6.3)</td>
<td>113 (33.7)</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>9 (1.9)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>87 (17.9)</td>
<td>1 (1.6)</td>
<td>63 (18.8)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5 (1)</td>
<td>1 (1.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>PVD</td>
<td>9 (1.9)</td>
<td>0 (0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>5 (1.5)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (0.8)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>32 (6.6)</td>
<td>0 (0)</td>
<td>24 (7.2)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1 (0.21)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

ASA PS, American Society of Anesthesiologists physical status; WC, workers’ compensation; AIDS, acute immune deficiency syndrome; PVD, peripheral vascular disease; GI, gastrointestinal.

*p < 0.05, statistically significant differences. 'p-values calculated using 1-way analysis of variance (continuous) or chi-square analysis (categorical).
with bone graft was subsequently positioned in the interbody space. Bilateral pedicle screws were then placed above and below the level of interest and rods were attached to achieve compression.

4. Statistical Analysis

Patients were grouped according to their preoperative ASA classification based on a score of I, II, or III+. Demographic characteristics, preoperative medical and spinal pathology, and perioperative characteristics were compared between groups using chi-square or 1-way analysis of variance (ANOVA) for categorical and continuous variables, respectively. Rates of individual and total postoperative complications were compared between groups using Fisher exact test.

\[ \Delta \text{PROM} \]

scores were calculated as the difference between preoperative values and each postoperative timepoint. Mean PROM scores and \( \Delta \)PROM scores were compared among groups for each measure at each timepoint using 1-way ANOVA. Achievement of an MCID was determined by comparing \( \Delta \)PROM score to previously established threshold values: 2.2 (VAS back), 5.0 (VAS leg), 8.2 (ODI), 2.5 (SF-12 PCS), and 4.5 (PROM-IS PF). Rates of MCID achievement for each measure were

Table 2. Perioperative characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 487)</th>
<th>ASA PS classification</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (n = 64)</td>
<td>II (n = 336)</td>
</tr>
<tr>
<td>Spinal pathology</td>
<td></td>
<td>I (n = 64)</td>
<td>II (n = 336)</td>
</tr>
<tr>
<td>Recurrent HNP</td>
<td>31 (6.4)</td>
<td>5 (7.8)</td>
<td>20 (6.0)</td>
</tr>
<tr>
<td>Degenerative spondylolisthesis</td>
<td>263 (65.8)</td>
<td>27 (58.7)</td>
<td>188 (67.6)</td>
</tr>
<tr>
<td>Isthmic spondylolisthesis</td>
<td>127 (31.8)</td>
<td>19 (40.4)</td>
<td>843 (0.3)</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>127.9 ± 35.8</td>
<td>122.9 ± 32.2</td>
<td>126.3 ± 35.3</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>68.6 ± 69.5</td>
<td>62.8 ± 44.4</td>
<td>69.3 ± 74.9</td>
</tr>
<tr>
<td>Length of stay (hr)</td>
<td>50.5 ± 38.1</td>
<td>46.2 ± 30.0</td>
<td>49.3 ± 37.8</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± standard deviation.
ASA PS, American Society of Anesthesiologists physical status; HNP, herniated nucleus pulposus.
* \( p < 0.05 \), statistically significant differences. † \( p \)-values calculated using 1-way analysis of variance (continuous) or chi-square analysis (categorical).

Table 3. Postoperative complications

<table>
<thead>
<tr>
<th>Complication⁹</th>
<th>Total (n = 487)</th>
<th>ASA PS classification</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (n = 64)</td>
<td>II (n = 336)</td>
</tr>
<tr>
<td>Aspiration/reintubation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>5 (1)</td>
<td>0 (0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>UTI</td>
<td>3 (0.6)</td>
<td>0 (0)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Postoperative anemia</td>
<td>3 (0.6)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ileus</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>1 (0.2)</td>
<td>1 (1.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>19 (3.9)</td>
<td>1 (1.6)</td>
<td>14 (4.2)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
ASA PS, American Society of Anesthesiologists physical status; UTI, urinary tract infection.
* \( p \)-value calculated using Fisher exact test. ⁹ Patients did not have complications associated with a venous thromboembolism, pulmonary embolism, pneumonia, pleural effusion, or fever of unknown origin.
compared among groups at each postoperative timepoint and overall using simple logistic regression.

RESULTS

A total of 487 MIS TLIF patients were included with an average age of 52.1 years. Of these, 64 patients had an ASA classification of I, whereas 336 had an ASA classification of II, and 87 had an ASA classification ≥ III. A majority of patients were male (57.1%), nonobese (BMI < 30 kg/m²), and nonsmokers (83.0%) (Table 1). ASA groups significantly differed on the basis of age (p < 0.001), BMI (p < 0.001), and workers’ compensation status (p = 0.003). Prevalence of diabetes (p < 0.001), AIDS (p = 0.001), myocardial infarction (p < 0.001), hypertension (p < 0.001), neurological disease (p < 0.001), arthritis (p < 0.001), congestive heart failure (p = 0.031), and peripheral vascular disease (p = 0.010) were significantly associated with ASA groups. Preoperative spinal pathology did not significantly vary between ASA groups (all p > 0.05). Operative duration was significantly associated with ASA groups (p = 0.013), while EBL (p = 0.792) and postoperative length of stay (p = 0.089) were not (Table 2). A total of 5 patients experienced urinary retention, 3 urinary tract infection, 2 epidural hematoma, 1 acute renal failure, 3 postoperative anemia, 1 altered mental status, 1 arrhythmia, 1 ileus, 1 atelectasis, and 1 pancreatitis. No individual complication type nor total complication rates were significantly associated with ASA groups (all p > 0.05) (Table 3). Circumstances and outcomes of individual complications are detailed in Table 4.

Neither mean PROM scores nor APROM scores significantly differed based on ASA group at any timepoint for any measure (all p > 0.05) (Tables 5, 6). MCID achievement significantly varied among ASA groups for VAS back at 1 year only (p = 0.041), but did not vary for any other individual timepoints nor overall (all p > 0.05) (Table 7).

DISCUSSION

ASA classification has been viewed as a concise way of conveying a patients’ general physical health status and thereby, their risk of undergoing general anesthesia. While higher ASA scores have been used by many spine surgeons as a key part of their patient selection criteria, literature supporting the utility of this measure is somewhat limited in the field of spine surgery. Furthermore, beyond the immediate perioperative period, the impact of ASA classification on more long-term patient-reported outcomes is relatively unreported. While ASA classification was clearly associated with increased medical comorbidity in our cohort, differences in perioperative outcomes were relatively minor and impact on long-term clinical improvement was negligible.

### Table 4. Individual incidences of complications and associated outcomes

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary retention</td>
<td>5 Patients with significantly elevated PVR required a foley catheter upon discharge but discontinued use by first follow-up appointment.</td>
</tr>
<tr>
<td>UTI</td>
<td>3 Patients developed a urinary tract infection and were discharged on antibiotics</td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>2 Patients developed epidural hematomas, underwent evacuation, and were discharged in stable condition</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 Patient had acute tubular necrosis on POD1 with a Cr increased 2-fold from baseline on POD4. Monitored in medical ICU until Cr dropped to 2.2 and was discharged safely to a rehab facility.</td>
</tr>
<tr>
<td>Postoperative anemia</td>
<td>2 Patients required transfusion with 1 unit of PRBC, 1 patient with 2 units. All patients were discharged in stable condition.</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>1 Patient experienced recurrent staring episodes on POD1. CT scan was concerning for subarachnoid hemorrhage and was transferred to neuro ICU with a negative workup. Mental status returned to baseline on POD6 and was transferred to a rehab facility for concerns of alcohol withdrawal</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 Patient had atrial fibrillation with RVR on POD1, underwent TTE and cardioversion. Discharged in stable condition and followed up with PCP and cardiology.</td>
</tr>
<tr>
<td>Ileus</td>
<td>1 Patient experienced abdominal distention on POD3. Gastroenterology consulted. Rectal tube was placed to decompress the large bowel. Patient was tolerating a regular diet by discharge.</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Linear opacities were identified on chest x-ray with low lung volumes consistent with atelectasis; patient was discharged in stable condition to follow up with sleep study.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 Patient had elevated lipase and was thought to be suffering from mild pancreatitis. Lipase significantly decreased by discharge and instructed to follow up with gastroenterology.</td>
</tr>
</tbody>
</table>

PVR, postvoid residual volume; UTI, urinary tract infection; POD, postoperative day; Cr, creatinine; ICU, intensive care unit; PRBC, packed red blood cells; CT, computed tomography; RVR, rapid ventricular response; TTE, transthoracic echocardiogram; PCP, primary care physician.
### Table 5. Patient-reported outcomes

<table>
<thead>
<tr>
<th>PROM</th>
<th>ASA PS classification</th>
<th>I</th>
<th>II</th>
<th>III+</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAS back</strong></td>
<td></td>
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<tr>
<td>Preoperative</td>
<td>6.7 ± 1.5</td>
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<td>1 Year</td>
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<td>2 Years</td>
<td>3.8 ± 3.1</td>
<td>3.4 ± 2.9</td>
<td>4.7 ± 3.3</td>
<td>0.367</td>
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<td><strong>VAS leg</strong></td>
<td></td>
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<tr>
<td>Preoperative</td>
<td>4.5 ± 3.2</td>
<td>5.6 ± 2.9</td>
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<td>6 Weeks</td>
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<td>12 Weeks</td>
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<td>6 Months</td>
<td>2.1 ± 3.2</td>
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<td>2.9 ± 2.9</td>
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<td>1 Year</td>
<td>1.3 ± 1.7</td>
<td>2.7 ± 2.9</td>
<td>2.1 ± 2.8</td>
<td>0.274</td>
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<tr>
<td>2 Years</td>
<td>1.9 ± 2.7</td>
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<td>4.0 ± 3.6</td>
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<td><strong>ODI</strong></td>
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<tr>
<td>Preoperative</td>
<td>38.5 ± 17.4</td>
<td>40.9 ± 16.3</td>
<td>44.2 ± 14.5</td>
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<tr>
<td>6 Weeks</td>
<td>33.9 ± 23.0</td>
<td>35.4 ± 18.7</td>
<td>40.4 ± 17.7</td>
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<td>12 Weeks</td>
<td>27.6 ± 20.4</td>
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<td>36.0 ± 18.6</td>
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<td>6 Months</td>
<td>21.9 ± 21.8</td>
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<td>1 Year</td>
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<td>2 Years</td>
<td>21.7 ± 17.6</td>
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<td>33.9 ± 30.0</td>
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<tr>
<td><strong>SF-12 PCS</strong></td>
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<tr>
<td>Preoperative</td>
<td>33.3 ± 7.5</td>
<td>31.5 ± 9.0</td>
<td>29.0 ± 10.1</td>
<td>0.149</td>
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<td>6 Weeks</td>
<td>33.4 ± 9.2</td>
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<td>28.1 ± 8.5</td>
<td>0.074</td>
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<td>12 Weeks</td>
<td>38.5 ± 9.8</td>
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<td>6 Months</td>
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<td>1 Year</td>
<td>42.0 ± 10.3</td>
<td>40.7 ± 12.3</td>
<td>37.2 ± 10.1</td>
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<td>2 Years</td>
<td>46.0 ± 7.8</td>
<td>41.1 ± 11.5</td>
<td>33.4 ± 11.5</td>
<td>0.087</td>
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<td><strong>PROMIS PF</strong></td>
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</tr>
<tr>
<td>Preoperative</td>
<td>37.1 ± 6.4</td>
<td>35.7 ± 6.2</td>
<td>34.5 ± 5.3</td>
<td>0.387</td>
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<td>6 Weeks</td>
<td>40.2 ± 7.0</td>
<td>38.0 ± 7.1</td>
<td>34.9 ± 6.6</td>
<td>0.103</td>
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<td>12 Weeks</td>
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<td>41.0 ± 7.5</td>
<td>0.397</td>
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<td>6 Months</td>
<td>47.0 ± 5.7</td>
<td>44.3 ± 7.1</td>
<td>40.5 ± 7.5</td>
<td>0.066</td>
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<tr>
<td>1 Year</td>
<td>47.4 ± 11.3</td>
<td>46.1 ± 9.3</td>
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<td>0.126</td>
<td></td>
</tr>
<tr>
<td>2 Years</td>
<td>48.6 ± 4.1</td>
<td>44.7 ± 9.5</td>
<td>36.7 ± 8.2</td>
<td>0.088</td>
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</tbody>
</table>

Values are presented as mean ± standard deviation.

PROM, patient-reported outcome measure; ASA PS, American Society of Anesthesiologists physical status; VAS, visual analogue scale; ODI, Oswestry Disability Index; SF-12 PCS, 12-item Short Form health survey physical composite score; PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function.

<sup>†</sup>p-values calculated using 1-way analysis of variance.
<table>
<thead>
<tr>
<th>PROM</th>
<th>ASA PS classification</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>∆VAS back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>2.9±2.1</td>
<td>2.8±2.8</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>3.0±2.4</td>
<td>3.1±2.8</td>
</tr>
<tr>
<td>6 Months</td>
<td>2.9±2.6</td>
<td>3.1±3.0</td>
</tr>
<tr>
<td>1 Year</td>
<td>4.5±2.8</td>
<td>3.3±3.1</td>
</tr>
<tr>
<td>2 Years</td>
<td>3.2±3.3</td>
<td>3.3±3.2</td>
</tr>
<tr>
<td>∆VAS leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>1.9±3.2</td>
<td>2.6±3.3</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>2.3±3.0</td>
<td>3.0±3.1</td>
</tr>
<tr>
<td>6 Months</td>
<td>1.8±2.7</td>
<td>2.9±3.3</td>
</tr>
<tr>
<td>1 Year</td>
<td>2.5±2.4</td>
<td>3.2±3.1</td>
</tr>
<tr>
<td>2 Years</td>
<td>2.4±2.5</td>
<td>3.6±2.7</td>
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<tr>
<td>∆ODI</td>
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<td>6 Weeks</td>
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<td>7.2±18.6</td>
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<tr>
<td>12 Weeks</td>
<td>10.3±13.8</td>
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<td>6 Months</td>
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<td>17.1±18.3</td>
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<tr>
<td>1 Year</td>
<td>18.2±15.7</td>
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<td>2 Years</td>
<td>17.6±19.8</td>
<td>17.6±17.3</td>
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<tr>
<td>∆SF-12 PCS</td>
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<tr>
<td>6 Weeks</td>
<td>2.0±11.6</td>
<td>1.3±8.3</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>7.0±10.9</td>
<td>4.9±9.5</td>
</tr>
<tr>
<td>6 Months</td>
<td>11.8±5.9</td>
<td>8.7±11.4</td>
</tr>
<tr>
<td>1 Year</td>
<td>13.5±9.6</td>
<td>10.8±10.4</td>
</tr>
<tr>
<td>2 Years</td>
<td>8.1±7.1</td>
<td>9.2±10.5</td>
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<tr>
<td>∆PROMIS PF</td>
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<tr>
<td>6 Weeks</td>
<td>2.3±5.8</td>
<td>2.3±6.6</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>4.9±5.7</td>
<td>5.7±7.3</td>
</tr>
<tr>
<td>6 Months</td>
<td>8.2±5.5</td>
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<tr>
<td>1 Year</td>
<td>8.7±6.4</td>
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<tr>
<td>2 Years</td>
<td>8.7±6.3</td>
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</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

PROM, patient-reported outcome measure; ASA PS, American Society of Anesthesiologists physical status; VAS, visual analogue scale; ODI, Oswestry Disability Index; SF-12 PCS, 12-item Short Form health survey physical composite score; PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function.

* p-values calculated using 1-way analysis of variance.

Our cohort demonstrated clear associations between a number of demographic factors, as well as several significant medical comorbidities. Age was significantly associated with ASA classification, with each progressive ASA group demonstrating older mean ages than the group below. While a majority of the overall cohort demonstrated increases, those with the highest ASA classification demonstrated significant worse outcomes.

### Table 7. MCID achievement

<table>
<thead>
<tr>
<th>PROM</th>
<th>ASA PS classification</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>VAS back</td>
<td></td>
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</tr>
<tr>
<td>6 Weeks</td>
<td>31 (60.8)</td>
<td>155 (56.2)</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>25 (55.6)</td>
<td>150 (57.9)</td>
</tr>
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<td>6 Months</td>
<td>24 (54.6)</td>
<td>151 (59.9)</td>
</tr>
<tr>
<td>1 Year</td>
<td>6 (66.7)</td>
<td>52 (63.4)</td>
</tr>
<tr>
<td>2 Years</td>
<td>3 (42.9)</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td>Overall</td>
<td>39 (72.2)</td>
<td>227 (76.4)</td>
</tr>
<tr>
<td>ODI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Weeks</td>
<td>4 (19.1)</td>
<td>38 (27)</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>3 (17.7)</td>
<td>41 (29.9)</td>
</tr>
<tr>
<td>6 Months</td>
<td>2 (12.5)</td>
<td>38 (27.3)</td>
</tr>
<tr>
<td>1 Year</td>
<td>2 (22.2)</td>
<td>26 (31.3)</td>
</tr>
<tr>
<td>2 Years</td>
<td>1 (20.0)</td>
<td>15 (31.3)</td>
</tr>
<tr>
<td>Overall</td>
<td>7 (29.2)</td>
<td>71 (44.1)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

ASA PS, American Society of Anesthesiologists physical status; MCID, minimum clinically important difference; PROM, patient-reported outcome measure; ASA PS, American Society of Anesthesiologists physical status; VAS, visual analogue scale; ODI, Oswestry Disability Index; SF-12 PCS, 12-item Short Form health survey physical composite score; PROMIS PF, Patient-Reported Outcomes Measurement Information System physical function.

* p < 0.05, statistically significant differences. 'p-values calculated using simple logistic regression.
all cohort had a BMI < 30 kg/m², over 70% of the ASA III+ group was obese. Interestingly, workers’ compensation patients made up the majority of the ASA I group only. To some degree, this is an expected distribution as those individuals who are able to claim workers’ compensation are typically of age or physical ability to participate in the workforce. Past comparative studies have also noted this significant difference, whereby patients categorized as workers’ compensation were significantly younger and had a lower comorbidity burden; both potential signs of reduced systemic disease burden. It would be more surprising to see a larger proportion of patients with an ASA of II or III+ who, by definition of the scoring system, would be dealing with mild to severe systemic disease, but nonetheless remain in the workforce. Unsurprisingly, both relatively severe cardiovascular pathology and more common diagnoses such as arthritis and hypertension were associated with increasing ASA classification. These strong statistical relationships between ASA classification and medical comorbidity are consistent with the measures’ intended purpose and can be seen as confirmation that the appropriate classification was assigned.

ASA physical status classification has been suggested as a tool for preoperative risk stratification in spine surgery by a number of previous studies, although it should be noted that this was not the measure’s originally intended purpose. Rather, the ASA classification was designed to be used as a concise way of conveying a patient’s health status, primarily for statistical analysis and interprovider communication. Nonetheless, a host of researchers have reported greater rates of complications, extended postoperative stay, and readmissions among spine patients with an ASA classification > II. Specific to the posterior approach, prior studies looking at 30-day readmissions and complication rates noted that patients with an ASA > III who underwent either a posterior lumbar interbody fusion or TLIF were at increased risk (odds ratio, 1.411; p < 0.001; 95% confidence interval, 1.177–1.692). Additionally, Ondeeck et al. analyzed approximately 16,500 posterior lumbar fusion patients and was able to demonstrate that ASA was particularly meaningful as a predictor of severe postoperative adverse events and extended length of stay, which was further supported by a multivariate analysis of posterior lumbar fusion patients. However, this may be a reflection of inherent differences between the 2 types of posterior fusion procedures, whereby MIS TLIF is associated with lower complication rate (8.7% vs. 17.0%) and odds ratio (OR, 0.47; 95% CI, 0.28–0.81; p = 0.006).

Our analysis among MIS TLIF patients failed to replicate this predictive value of ASA for perioperative morbidity. Interestingly, operative duration was significantly greater for patients with the highest ASA classifications; however, EBL and length of stay, which might be more expected to correlate with increasing ASA, did not demonstrate significant associations with this measure. Overall, complications were quite rare amongst our cohort, which may be attributable to a combination of careful patient selection, minimally invasive surgical techniques, and the expertise of an experienced surgeon that regularly performs a high volume of MIS TLIF procedures. Nonetheless, the few complications that were observed were distributed relatively evenly among the 3 groups and demonstrated no significant associations with ASA classification. Given previous reports of increased surgical morbidity among patients with an ASA classification > II, some surgeons may view this threshold as an attractive criterion for patient selection, particularly for outpatient/ambulatory orthopaedic surgery. However, our results demonstrate that this practice may be too conservative and exclude patients who would otherwise safely benefit from minimally invasive spinal procedures. The current study is not alone in these findings; in fact, Narain et al. similarly reported that an ASA classification > II was not significantly associated with greater rates of medical or surgical complications following minimally invasive lumbar fusion procedures.

While a relatively substantial body of literature exists regarding the relationship between ASA classification and propensity for perioperative complications and adverse outcomes, research regarding the impact of ASA classification on patient-reported outcomes is much more limited. McGirt et al. conducted one of the few studies to assess the relationship of ASA classification with PROM scores. These authors used a large national database to create predictive models for outcomes among all elective lumbar procedures and determined that, among a variety of other factors, higher ASA classification was associated with worse 12-month outcomes in disability, pain, and quality of life following elective lumbar spinal surgery. While McGirt et al. did include improvement in PROM scores and achievement of MCID as outcomes in their relatively complex predictive model - detailed via 2 “hypothetical patients,” they only reported direct analysis of the effects of ASA on mean PROM scores at preoperative and 12-month postoperative timepoints. This methodological/reporting choice, along with the significant heterogeneity of their population (single and multilevel, primary and revision, as well as a variety of procedure types) precludes meaningful conclusions about the direct relationship of ASA classification with postoperative improvement in patient-reported outcomes. Yoo et al. performed a more focused analysis of the
impact of ASA classification on PROMS for TLIF procedures in particular, and determined that ASA classification was associated with improvement in VAS back, but not VAS leg, ODI, or SF-12 PCS. However, this analysis was also limited to 6-month outcomes and did not include quantification of MCID achievement.

Given the conflicting results and methodological limitations of these previous studies, it is important to directly and longitudinally assess the impact of ASA classification on patients’ ability to achieve meaningful clinical improvement following minimally invasive lumbar fusion. Despite our use of a relatively large cohort to facilitate well-powered statistical analysis, we were unable to demonstrate any significant differences between ASA groups either in mean PROM scores or ΔPROM improvement at any of the assessed timepoints. Furthermore, analysis of MCID achievement showed no significant impacts of ASA for any of the assessed PROMs either overall or at individual timepoints through 2-years postoperatively, with the exception of VAS back at 1 year. These results allow for a more pertinent assessment of the relevance (or lack thereof) of ASA classification for this specific population because of our focused selection of only patients undergoing primary, single-level MIS TLIF procedures and our collection longitudinal PROM data throughout the full 2-year postoperative period.

One major potential shortcoming of the ASA classification is its relatively subjective assignment criteria. Several previous studies have demonstrated questionable interrater reliability in ASA classification assignment. Among 97 anesthesiologists in Hong Kong asked to classify 10 hypothetical patients, overall agreement on classification was below 60% for all but 1 patient (for whom agreement was 67%), and was as low as 36% for one patient. An overall Cohen’s Kappa of 0.34 was reported, indicating only fair reliability of rating between observers. These findings were consistent with those previously reported by an older, United States-based study by Owens et al. This potential for inconsistency, coupled with the lack of significant effects either in terms of safety profiles or patient-reported outcomes may be cause to question the utility of ASA classification for some populations. Specifically, limiting selection criteria for MIS TLIF procedures to patients with an ASA classification ≤ II may exclude some patients that could otherwise stand to safely and significantly benefit from outpatient MIS TLIF. Physicians that are sufficiently experienced in minimally invasive surgical techniques may consider removing ASA classification as part of their patient selection criteria for outpatient surgical procedures.

The present study represents one of the most comprehensive assessments of the association of ASA classification with surgical outcomes specifically for MIS TLIF patients. However, our findings should be considered in the context of several limitations. First, while a moderately large sample was included, the single-surgeon, single-institution nature of this analysis may limit generalizability to other providers and populations. Additionally, previous studies have demonstrated variability in the assignment of ASA classification between different institutions and different regions. Furthermore, while this study included patients with a range of ASA classifications from minimal to severe disease, patients were carefully vetted and selected by an experienced minimally invasive spine surgeon, which may play an important role in the favorable outcomes demonstrated in patients with higher ASA classification.

CONCLUSION

Increasing ASA classification was significantly associated with greater prevalence of a variety of medical comorbidities. However, while operative duration was significantly longer for patients with higher ASA classification, other perioperative outcomes were similar for all patients and rates of complications were favorable regardless of ASA classification. Similarly, patient-reported outcomes in pain, disability, and physical function including mean scores, absolute improvement, and achievement of MCID did not significantly vary based on preoperative ASA. Therefore, we recommend that ASA classification > II should not necessarily preclude otherwise appropriate patients from undergoing MIS TLIF procedures, even in the outpatient setting.

NOTES

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ORCID
Conor P. Lynch: 0000-0002-9554-2878
REFERENCES


Indirect Decompression Using Oblique Lumbar Interbody Fusion Revision Surgery Following Previous Posterior Decompression: Comparison of Clinical and Radiologic Outcomes Between Direct and Indirect Decompression Revision Surgery

Sang-Jin Park¹, Jong-Moon Hwang², Dae-Chul Cho³, Subum Lee⁴, Chi Heon Kim⁵,⁶, Inbo Han⁷, Dae-Won Park⁸, Heum-Dai Kwon⁹, Kyoung-Tae Kim³

¹Department of Neurosurgery, Charmjoeun Spine and Joint Hospital, Daegu, Korea
²Department of Rehabilitation Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea
³Department of Neurosurgery, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu, Korea
⁴Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea
⁵Department of Neurosurgery and Medical Device Development, Seoul National University College of Medicine, Seoul, Korea
⁶Department of Neurosurgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea
⁷Department of Neurosurgery, Good Moonhwa Hospital, Busan, Korea
⁸Department of Neurosurgery, Pohang Stroke and Spine Hospital, Pohang, Korea

Objective: This study compared the radiological and clinical outcomes with transforaminal lumbar interbody fusion (TLIF) to evaluate the effect of indirect decompression through oblique lumbar interbody fusion (OLIF) as revision surgery.

Methods: We enrolled patients who underwent single-level fusion with revision surgery at the same level as the previous decompression level. We retrospectively reviewed 25 patients who underwent OLIF from 2017 to 2018 and 25 who received TLIF from 2014 to 2018. Radiologic and clinical outcomes were evaluated by cross-sectional area (CSA) of the spinal canal, thickness and area of the ligamentum flavum (LF), subsidence, disc height, fusion rate, Oswestry Disability Index (ODI), and visual analogue scale (VAS).

Results: Compared with OLIF, the thickness and area of the LF after surgery were significantly less in TLIF, and the resulting CSA extension was also significantly higher. However, both groups showed improvement in ODI and VAS after surgery, and there was no difference between the groups. Complications related to the posterior approach in TLIF were 4 cases, and in OLIF, there were 2 cases that underwent additional posterior decompression surgery and 6 cases of transient paresthesia.

Conclusion: Since complications associated with the posterior approach can be avoided, OLIF is a safer and useful minimally invasive surgery. Therefore, appropriate indications are applied, OLIF is a good alternative to TLIF when revision surgery is considered.

Keywords: Oblique lumbar interbody fusion, Transforaminal lumbar interbody fusion, Indirect decompression, Direct decompression, Revision surgery
INTRODUCTION

Lumbar spinal stenosis (LSS) with or without low-grade spondylolisthesis in degenerative spinal disease is found in a large portion of the elderly population and is a major cause of chronic low back pain, neurogenic claudication, and radiculopathy. It has already been reported that surgical posterior decompression is more effective and superior to conservative treatment in LSS, and it is performed as the primary surgical method when conservative treatment is no longer effective.\(^{1-3}\)

Postoperative progressive spondylolisthesis, recurrent stenosis, and recurrent herniated nucleus pulposus are the main indications for reoperation, which has been reported to have a rate of 9.5% at 4 years postoperatively and up to 19% at 11 years postoperatively.\(^ {4,5}\) Reoperation at the same level as the previous decompression is preferably treated with fusion because laminectomy had been performed previously and the remaining facet joint is smaller.\(^ {6}\) Fusion is therefore often performed in consideration of mechanical back pain and destabilization occurring postlaminectomy good results have been reported in long-term outcomes.\(^ {6}\)

The posterior lumbar interbody fusion (PLIF) or transforminal lumbar interbody fusion (TLIF) is a direct decompression method that removes the facet and ligamentum flavum (LF). However, performing PLIF or TLIF as revision surgery is challenging for surgeons. Anatomical landmarks are obscured due to previous surgery, and the risk of complications such as incidental durotomy, neural injury, and surgical site infection may be increased due to epidural adhesions.\(^ {7-10}\)

Oblique lumbar interbody fusion (OLIF) is a minimally invasive surgical technique using an oblique retroperitoneal approach which differs from PLIF and TLIF.\(^ {11}\) OLIF uses a relatively large cage compared to PLIF and TLIF cages, so it is advantageous when forming solid intervertebral stability. The taller cage used with OLIF also reduces disc bulging and increases the LF to induce indirect decompression.\(^ {12-14}\) Additionally, compared to PLIF and TLIF, the surgical time is shorter, blood loss is less, and paravertebral muscles are preserved.\(^ {15,16}\)

When revision surgery is considered, OLIF takes an oblique retroperitoneal approach rather than using the previous surgical site, so dural adhesions or altered anatomical landmarks are not obstacles which reduces the risk of related complications. When OLIF is performed at the same level as the previous surgery, insufficient information exists on how adhesions caused by previous decompression surgery affect indirect decompression, and on whether indirect decompression revision surgery is sufficient compared to traditional direct decompression. This study compares the radiological and clinical outcomes of TLIF and OLIF as revision surgery in recurrent stenosis that occurred at the same level after previous posterior decompression surgery and will help resolve these concerns about this technique.

MATERIALS AND METHODS

1. Patient Demographics

All patients were provided with written informed consent and the relevant Institutional Review Board of the Kyungpook National University Hospital approved this study (KNUH 2022-02-010). Patients were enrolled who had undergone previous posterior lumbar decompression surgery (decompression laminectomy, hemilaminectomy and discectomy, and a unilateral approach with bilateral decompression) and who underwent revision fusion surgery at the same level. Previous posterior decompression surgery was performed for spinal stenosis or herniated nucleus pulposus (HNP) without improvement in symptoms despite conservative treatment. Revision fusion surgery was performed if recurrent or new-onset neurological symptoms and/or leg pain were present during follow-up and spondylolisthesis with segmental instability, recurrent stenosis, and recurrent HNP were diagnosed at the same level. The decision criteria for TLIF and OLIF in revision fusion surgery were the same. After explaining the pros and cons of each surgical procedure, the surgeon decided on the surgical procedure according to the patient’s request and the surgeon’s discretion.

OLIF was introduced in 2016 in this institution with TLIF being the primary technique prior to that. Cases in which TLIF was performed as revision surgery were therefore selected from 2014 to 2018, and cases in which OLIF was performed were selected from 2017 to 2018 to minimize the effects of the learning curve. All surgeries were performed by 2 spine surgeons with more than 10 years of experience.

For revision surgery, cases that received single-level fusion from L3 to S1 were grouped into 2 groups and compared: TLIF, 25 cases and OLIF, 25 cases. High-grade spondylolisthesis, combined sequestrated disc herniation, infection, trauma, and tumor cases were all excluded.

Age, sex, symptom duration, diagnosis prior to revision surgery, surgical level, bone mineral density (BMD), subsidence, and additional posterior decompression surgery were investigated in all of the 50 enrolled patients. BMD was defined using a T-score as follows: greater than -1.0, normal; greater than -2.5 but less than -1.0, osteopenia; and less than -2.5, osteoporosis.
2. Surgical Technique

Patients who underwent TLIF, had the procedure through a midline skin incision in the prone position after induction of general anesthesia, and bilateral subperiosteal dissection to expose the facet joint while preserving the posterior midline structures. After bilateral facetectomy, disectomy, and endplate preparation, 2 cages were inserted, one from each side, and autograft was used as a fusion material, followed by pedicle screw placement.

For OLIF, it performed through a left side retroperitoneal approach in the right lateral decubitus position. At the L3–4 and L4–5, levels the cage was inserted through the corridor between the psoas muscle and the aorta, and at the L5–S1 level, it was inserted through the corridor between the right iliac artery and the left iliac vein. In all OLIF cases, the OLIF system (Medtronic, Memphis, TN, USA) was used, allograft (Grafton, Medtronic) was used for the cage as a fusion material, and percutaneous pedicle screw placement (longitude system, Medtronic) was performed. Cage height was determined by preoperative computed tomography (CT) in all patients: if intervertebral disc height was greater than 6 mm, a cage 4 mm higher than the intervertebral disc height was used and if the intervertebral disc height was less than 6 mm, a 10-mm cage was inserted. Additional posterior decompression surgery was performed if the patient’s symptoms did not improve after surgery, or if the improvement was insufficient. In our series, 2 patients underwent the additional posterior decompression at 6 and 8 days after OLIF, respectively.

3. Radiological and Clinical Evaluation

Magnetic resonance imaging (MRI) was taken using a 1.5-T EXCITE whole-body imaging system (General Electric, Milwaukee, WI, USA). The axial localizing sequence was taken from the surgical site to identify the disc space gap, and 4 slices were obtained with 4.0-mm slice thickness and 1.0 mm spacing between slices per level. Images were displayed and analyzed through PiView (INFINITT, Seoul, South Korea) digital image viewing software. The cross-sectional area (CSA) of the spinal canal and LF measured at the surgical site was measured using a graphic cursor to measure the outline of the spinal canal. The thickness of the LF was defined as the average of the longest thicknesses of both ligaments (Fig. 1A). Spinal canal area and LF thickness were evaluated by MRI scans performed immediately before and after surgery, and at 12 months after surgery. Intervertebral disc height was defined as the distance between the superior and inferior endplates, vertically connected from the center of the anteroposterior diameter of the inferior vertebral body (Fig. 1B). Subsidence was classified according to postoperative disc height loss as follows: none, <10%; mild, 10%–24%; moderate, 25%–49%; and severe, 50%–100% (Fig. 1C). Fusion rate was evaluated by radiography and CT scan. Solid fusion was determined when there was continuous trabecular bone in the cage and/or bone union of the facet joint was observed without screw loosening (Fig. 2).

Fig. 1. (A) The cross-sectional area (CSA) of the spinal canal (red arrow and text) and the thickness (yellow arrow and text) and area (green arrow and text) of the ligamentum flavum (LF) were measured at the mid-disc level of the axial sequence using T2-weighted magnetic resonance imaging. (B) Intervertebral disc height (DH) was measured in lateral radiography as the length of the line from the midpoint of the inferior endplate to the superior endplate vertically. (C) Subsidence was measured by the degree of cage subsidence into the vertebral endplates on lateral radiography.
Clinical outcomes were evaluated preoperatively, 6 months, 12 months, and 24 months postoperatively using the Oswestry Disability Index (ODI) and the visual analogue scale (VAS) for both back and dominant leg pain.

4. Statistical Analysis

Variables between the TLIF and OLIF surgery groups were compared using Mann-Whitney U-tests. A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS ver. 18.0 (IBM Corp., Armonk, New York, USA).

RESULTS

1. Demographic Variables

The ages of the TLIF and OLIF surgery groups were similar. There were 13 males and 12 females in the TLIF surgery group, and 9 males and 16 females in the OLIF surgery group. Symptom duration was 7.6 ± 6.9 months in the TLIF surgery group and 7.6 ± 2.6 months in the OLIF surgery group, and as such, there was no difference between the 2 groups. The mean follow-up durations of the TLIF and OLIF groups were 32.4 ± 8.5 months (range, 24–58) and 28.9 ± 5.8 months (range, 24–43), respectively, and there was no statistical difference between the 2 groups (p = 0.094). In the TLIF surgery group, there were 10 cases of spondylolisthesis, 8 cases of recurrent stenosis, and 7 cases of recurrent HNP. In the OLIF surgery group, there were 13 cases of spondylolisthesis, 10 cases of recurrent stenosis, and 2 cases of recurrent HNP. As for the operation level, 3 cases were at L3–4, 20 were at L4–5, and 2 were at L5–S1 in the TLIF surgery group, and 2 cases were at L3–4, 20 cases were at L4–5, and 3 were at L5–S1 in the OLIF surgery group. Regarding bone mineral density (BMD), there were 15 cases of normal, 7 cases of osteopenia (T-score < -2.5), and 3 cases of osteoporosis (T-score ≤ -2.5) in the TLIF surgery group, and 8 cases of normal, 12 cases of osteopenia (T-score < -2.5), and 5 cases of osteoporosis (T-score ≤ -2.5) in the OLIF surgery group. The rate of subidence was 8% in the TLIF surgery group and 4% in the OLIF surgery group. In addition, there were 2 cases of additional posterior decompression surgery in the OLIF group.

Table 1. Demographics of the enrolled patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>TLIF surgery group (n = 25)</th>
<th>OLIF surgery group (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.6 ± 9.9</td>
<td>66.6 ± 8.65</td>
<td>0.254</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>13:12</td>
<td>9:16</td>
<td>0.393</td>
</tr>
<tr>
<td>Symptom duration (mo)</td>
<td>7.6 ± 6.9</td>
<td>7.6 ± 2.6</td>
<td>0.978</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>32.4 ± 8.5 (24–58)</td>
<td>28.9 ± 5.8 (24–43)</td>
<td>0.094</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>0.183</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Recurrent stenosis</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Recurrent HNP</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Operation level</td>
<td></td>
<td></td>
<td>0.819</td>
</tr>
<tr>
<td>L3–4</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>L4–5</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>L5–S1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Osteopenia (T-score &lt; -1.0)</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (T-score ≤ -2.5)</td>
<td>3</td>
<td>5</td>
<td>0.139</td>
</tr>
<tr>
<td>Subsidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3</td>
<td>0</td>
<td>0.047*</td>
</tr>
<tr>
<td>Additional posterior</td>
<td>0 (0)</td>
<td>2 (4.0)</td>
<td>0.490</td>
</tr>
<tr>
<td>decompression surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation (range) or number (%).

TLIF, transforaminal lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; HNP, herniated nucleus pulposus; BMD, bone mineral density.

*p < 0.05, statistically significant difference.
and 3 cases were at L5–S1, in the OLIF surgery group. There was no significant difference in BMD between the TLIF surgery group and the OLIF surgery group, however, there was a significant difference in subsidence (p = 0.047) (Table 1). In the OLIF surgery group, 2 cases did not show sufficient symptom improvement, so additional posterior decompression surgery was subsequently performed.

2. Clinical Outcomes

Clinical outcomes between the TLIF and OLIF surgery groups were compared except for the 2 cases who underwent additional posterior decompression surgery. In the TLIF surgery group, the ODI score improved from 28.0 ± 7.7 preoperatively to 16.0 ± 7.3 at 12 months postoperatively and 17.1 ± 6.3 at 24 months postoperatively. VAS for leg and back pain also improved from 7.3 ± 1.7 and 5.0 ± 2.5 preoperatively to 2.9 ± 2.2 and 2.5 ± 2.0 at 12 months postoperatively and 3.1 ± 1.9 and 2.7 ± 1.7 at 24 months postoperatively.

In the OLIF surgery group, the ODI score improved from 25.6 ± 5.9 preoperatively to 12.6 ± 4.5 at 12 months postoperatively and 13.1 ± 4.4 at 24 months postoperatively. VAS for leg pain improved from 6.4 ± 1.4 preoperatively to 3.4 ± 1.2 at 12 months postoperatively and 3.3 ± 1.0 at 24 months postoperatively, and VAS for back pain improved from 5.8 ± 1.2 preoperatively to 2.9 ± 1.1 at 12 months postoperatively and 2.8 ± 1.4 at 24 months postoperatively.

There were no significant differences in ODI score, VAS for leg and back pain between the 2 groups before, 6 months, 12 months, and 24 months after surgery (Table 2).

3. Radiological Outcomes

The preoperative CSA of the spinal canal was 108.9 ± 54.3 mm² in the TLIF surgery group and 99.1 ± 45.2 mm² in the OLIF surgery group. At 12 months after surgery, the CSA of the spinal canal was 173.5 ± 38.6 mm² and 125.6 ± 46.7 mm² in TLIF surgery and OLIF surgery, respectively. The increase was higher in the TLIF surgery group than in the OLIF surgery group, and there was a statistically significant difference between the 2 groups (p = 0.023 and p < 0.001). There were no significant differences in LF thickness between the 2 groups, with the TLIF surgery group at 4.54 ± 1.75 mm and the OLIF surgery group at 3.53 ± 1.4 mm before surgery. At 12 months postoperatively, the LF thickness was significantly decreased in the TLIF surgery group compared to the OLIF surgery group to 1.76 ± 0.68 mm and 2.5 ± 1.0 mm, respectively (p < 0.001 and p < 0.001). There were no significant differences in LF areas between the 2 groups preoperatively, 78.4 ± 46.6 mm² for TLIF surgery and 75.8 ± 44.6 mm² for OLIF surgery. At 12 months postoperatively, LF areas were significantly decreased to 20.6 ± 10.7 mm² in the TLIF surgery group and less so in the OLIF surgery group which decreased to 53.9 ± 29.9 mm² (p < 0.001 and p < 0.001) (Table 3). Subsidence was compared by evaluating the decrease in disc height after surgery between the 2 groups. In the TLIF surgery group, mild (32.0%), moderate (24.0%), and severe (12.0%) subsidence was observed, and in the OLIF surgery group, mild and moderate subsidence was present at 13.0% and 21.7%. There was no significant difference in disc height between the 2 groups before surgery, but after surgery, the disc height of the OLIF surgery group was 12.7 ± 2.0 mm and that of the TLIF surgery group was 10.7 ± 2.2 mm, showing a more significant increase than that of the TLIF surgery group (p < 0.006 and p < 0.001). There were no significant differences in the fusion rates between the 2 groups at 1 year and 1.5 years after surgery. The fusion rates at 1.5 years in the TLIF and OLIF surgery groups were 80% (20 of 25) and 87% (20 of 23), respectively (Table 4).

Table 2. Comparison of clinical outcome between TLIF and OLIF surgery group (exclusion of additional posterior decompression surgery)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TLIF surgery group (n = 25)</th>
<th>OLIF surgery group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODI</td>
<td>Preoperative</td>
<td>28.0 ± 7.7</td>
<td>25.6 ± 5.9</td>
</tr>
<tr>
<td></td>
<td>6 Months after surgery</td>
<td>16.8 ± 6.5</td>
<td>14.8 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>12 Months after surgery</td>
<td>16.0 ± 7.3</td>
<td>12.6 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>24 Months after surgery</td>
<td>17.1 ± 6.3</td>
<td>13.1 ± 4.4</td>
</tr>
<tr>
<td>VAS-leg</td>
<td>Preoperative</td>
<td>7.3 ± 1.7</td>
<td>6.4 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>6 Months after surgery</td>
<td>3.0 ± 1.6</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>12 Months after surgery</td>
<td>2.9 ± 2.2</td>
<td>3.4 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>24 Months after surgery</td>
<td>3.1 ± 1.9</td>
<td>3.3 ± 1.0</td>
</tr>
<tr>
<td>VAS-back</td>
<td>Preoperative</td>
<td>5.0 ± 2.5</td>
<td>5.8 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>6 Months after surgery</td>
<td>2.6 ± 1.5</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>12 Months after surgery</td>
<td>2.5 ± 2.0</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>24 Months after surgery</td>
<td>2.7 ± 1.7</td>
<td>2.8 ± 1.4</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. TLIF, transforaminal lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; ODI, Oswestry Disability Index; VAS, visual analogue scale.
4. Complications

The TLIF surgery group had 4 cases of posterior approach-related complications, 2 cases of wound dehiscence, 3 cases of cerebrospinal fluid (CSF) leakage, and 1 case of nerve damage. Two of the CSF leakage cases were accompanied by wound dehiscence and nerve damage, respectively. The OLIF surgery group had 6 cases of transient paresthesia on the approach side, which was significantly different from that in the TLIF surgery group (p = 0.022) (Table 5). There was no ureteral injury, vascular injury, sympathetic trunk injury, or superior hypogastric plexus injury in the OLIF surgery group. Although it is not a surgery-related complication, 2 cases in the OLIF surgery group underwent additional posterior decompression surgery because

### Table 3. Comparison of radiologic outcome between TLIF and OLIF surgery group (exclusion of additional posterior decompression surgery)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TLIF surgery group (n = 25)</th>
<th>OLIF surgery group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional area of spinal canal (mm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>108.9 ± 54.3</td>
<td>99.1 ± 45.2</td>
<td>0.502</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>173.5 ± 38.6</td>
<td>125.62 ± 46.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Increasing percentage [(12 months – preop)/preop × 100]</td>
<td>90.9 ± 87.6</td>
<td>41.7 ± 50.3</td>
<td>0.023*</td>
</tr>
<tr>
<td>Increasing value (mm²) (12 months – preop)</td>
<td>64.6 ± 45.4</td>
<td>26.5 ± 14.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LF thickness (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>4.54 ± 1.75</td>
<td>3.53 ± 1.4</td>
<td>0.033</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>1.76 ± 0.68</td>
<td>2.5 ± 1.0</td>
<td>0.003*</td>
</tr>
<tr>
<td>Decreasing percentage [(preop – 12 months)/preop × 100]</td>
<td>57.8 ± 19.4</td>
<td>26.5 ± 17.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Decreasing value (mm) (preop – 12 months)</td>
<td>2.77 ± 1.47</td>
<td>1.0 ± 0.82</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LF area (mm²)</td>
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<tr>
<td>Preoperative</td>
<td>78.4 ± 46.6</td>
<td>75.8 ± 44.6</td>
<td>0.847</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>20.6 ± 10.7</td>
<td>53.9 ± 29.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Decreasing percentage [(preop – 12 months)/preop × 100]</td>
<td>70.7 ± 12.8</td>
<td>24.6 ± 17.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Decreasing value (mm²) (preop – 12 months)</td>
<td>57.7 ± 38.5</td>
<td>21.9 ± 21.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Subsidence</td>
<td></td>
<td></td>
<td>0.186</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>15</td>
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<tr>
<td>Mild</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
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<td>5</td>
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<tr>
<td>Severe</td>
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<td>0</td>
<td></td>
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<tr>
<td>Disc height (mm)</td>
<td></td>
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<tr>
<td>Preoperative</td>
<td>9.0 ± 2.3</td>
<td>8.1 ± 1.9</td>
<td>0.134</td>
</tr>
<tr>
<td>12 Months after surgery</td>
<td>10.7 ± 2.2</td>
<td>12.7 ± 2.0</td>
<td>0.002*</td>
</tr>
<tr>
<td>Increasing percentage [(12 months – preop)/preop × 100]</td>
<td>28.5 ± 46.4</td>
<td>63.3 ± 35.9</td>
<td>0.006*</td>
</tr>
<tr>
<td>Increasing value (mm) (12 months – preop)</td>
<td>1.7 ± 3.2</td>
<td>4.6 ± 2.0</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

TLIF, transforaminal lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; preop, preoperative; LF, ligament flavum.

*p < 0.05, statistically significant difference.

### Table 4. Comparison of radiologic fusion rate between TLIF and OLIF surgery group (exclusion of additional posterior decompression surgery)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TLIF surgery group (n = 25)</th>
<th>OLIF surgery group (n = 23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusion at 1 year after surgery</td>
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<td></td>
<td>0.687</td>
</tr>
<tr>
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<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>13</td>
<td></td>
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<tr>
<td>Fusion at 1.5 year after surgery</td>
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<td>0.661</td>
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<tr>
<td>Yes</td>
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<tr>
<td>No</td>
<td>5</td>
<td>3</td>
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</table>

TLIF, transforaminal lumbar interbody fusion; OLIF, oblique lumbar interbody fusion.
Comparison of Outcomes Between Direct and Indirect Decompression Revision Surgery

Park SJ, et al.

In this study, the OLIF surgery group showed,

Similarly, the overall outcomes, including ODI, VAS for leg, and VAS for back. Our results suggest that even in revision, the CSA extension necessary for clinical improvement can be sufficiently obtained by indirect decompression.

In this study, both the number and grade of subsidence showed

Table 5. Complication related with surgical approach between TLIF and OLIF surgery group

<table>
<thead>
<tr>
<th>Variable</th>
<th>TLIF surgery group (n = 25)</th>
<th>OLIF surgery group (n = 25)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Posterior approach-related complication</td>
<td>4 Cases†</td>
<td>0 Case</td>
<td>0.117</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>2 Cases</td>
<td>0 Case</td>
<td>0.490</td>
</tr>
<tr>
<td>CSF leakage</td>
<td>3 Cases</td>
<td>0 Case</td>
<td>0.235</td>
</tr>
<tr>
<td>Nerve damage</td>
<td>1 Case</td>
<td>0 Case</td>
<td>1.000</td>
</tr>
<tr>
<td>Transient paresthesia (approach side)</td>
<td>0 Case</td>
<td>6 Cases</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

TLIF, transforaminal lumbar interbody fusion; OLIF, oblique lumbar interbody fusion; CSF, cerebrospinal fluid.

*p < 0.05, statistically significant difference. †Two CSF leakage cases had wound dehiscence and nerve damage, respectively.

the symptoms did not improve sufficiently after surgery.

DISCUSSION

This study compares the radiological and clinical outcomes between 2 surgical groups: direct decompression with TLIF and indirect decompression with OLIF; for revision surgery at the same level as previous posterior decompression. Traditional posterior approach revision surgery, such as PLIF and TLIF, is a burden on the surgeon because of the high risk of incidental durotomy and nerve root injury due to scar tissue and dural adhesions from previous surgeries.

In the literature comparing primary surgery and revision surgery in open TLIF, it was reported that the risk of inadvertent dural tears increased by 3.2 times when one or more previous lumbar decompressions were performed. Similarly, the overall complication rate of the group that underwent primary TLIF surgery and the group that underwent revision TLIF surgery was 59 of 287 (20.6%) and 76 of 244 (31.1%), respectively (odds ratio [OR], 1.75; p < 0.01), incidental durotomy was 32 of 287 (11.1%) and 44 of 244 (18%), respectively (OR, 1.75; p = 0.03). In a study that performed PLIF in 50 patients as revision surgery, neurologic complications (leg pain or motor loss) occurred in 32% and permanent cases occurred in 8%. Similar results were reported in studies on primary and revision surgery of minimally invasive (MIS) TLIF. According to Kang et al., 4% of dural tears occur during primary surgery and 19% occur during revisional surgeries, Selznick et al. reported that CSF leakage per level was 5.9% in primary surgery and 21.4% in revision.

In a meta-analysis study comparing OLIF and MIS TLIF, there was no significant difference in overall complication rates between the 2 groups (13.8% in MIS TLIF; 16.3% in OLIF; p = 0.45). In approach-related complications, dural tear and root injury occurred in 4 cases (1.7%) of 232 patients in the MIS TLIF group, and none in 240 patients in the OLIF group. Symptomatic chain injury occurred in 3 cases (1.3%) in the OLIF group and none in the MIS TLIF group. In the OLIF and MIS TLIF groups, different complications may occur depending on the approach, so it is difficult to determine which surgical procedure is better.

As revision surgery, OLIF surgery is a retroperitoneal oblique approach rather than an approach to the previous surgical site, so altered anatomical landmarks and dural adhesions do not interfere during surgery. In our study, there were 4 cases of posterior approach-related complications in the TLIF surgery group, whereas none occurred in the OLIF surgery group. In the OLIF surgery group, there were 6 cases of transient paresthesia and the incidence was significantly higher than that of the TLIF surgery group, but all symptoms resolved within a few weeks after surgery. Therefore, in terms of complications, OLIF can be a safer alternative surgical technique compared to TLIF.

In this study, the preoperative CSA of spinal canal in the TLIF and OLIF surgery groups was 108.9 ± 54.3 mm² and 99.1 ± 45.2 mm², respectively. Considering that the symptomatic LSS of the CSA of spinal canal from previous studies is ≤ 77.5 mm², it is considered that the preoperative CSA of spinal canal in both groups is larger than 77.5 mm² because our subjects underwent previous posterior decompression (Figs. 3A, 4A). In another report, 3 weeks after OLIF surgery, the median CSA extension ratio was confirmed to be 30.2%, and all subjects showed clinical improvement. In this study, the OLIF surgery group showed a CSA extension of 41.7% ± 50.3%, and the TLIF surgery showed a CSA extension of 90.9% ± 87.6%. The reason CSA extension showed greater results in the TLIF surgery group is thought to be due to posterior direct decompression (Figs. 3C, 4C). This is supported by our results that the TLIF surgery group showed a greater reduction in LF thickness (57.8% ± 19.4% in TLIF, 26.5% ± 17.2% in OLIF) and LF area (70.7% ± 12.8% in TLIF, 24.6% ± 17.3% in OLIF) before and 12 months after surgery than the OLIF surgery group. Although the CSA extension was greater in the TLIF surgery group than in the OLIF surgery group, there were no significant differences between the 2 groups in clinical outcomes, including ODI, VAS for leg, and VAS for back. Our results suggest that even in revision, the CSA extension necessary for clinical improvement can be sufficiently obtained by indirect decompression.

In this study, both the number and grade of subsidence showed
worse outcomes in the TLIF surgery group than in the OLIF surgery group. Subsidence was observed in 17 cases in the TLIF surgery group, among which 8 cases were mild, 6 cases were moderate, and 3 cases were severe. On the other hand, in the OLIF surgery group, 3 cases were mild, 5 cases were moderate, and there were no severe cases. This is thought to be advantageous for subsidence because the OLIF cage can use a longer length than the TLIF cage, and the cage can be placed on the cortical rim of the vertebral body to support it. Although there was no statistical significance, VAS of leg preoperatively was higher in the TLIF surgery group than in the OLIF surgery group (7.3 ± 1.7 in TLIF, 6.4 ± 1.4 in OLIF, p = 0.075), and at 6 months postoperatively, the TLIF surgery group was lower than the OLIF surgery group (3.0 ± 1.6 in TLIF, 3.8 ± 1.0 in OLIF, p = 0.056). This suggests that although the TLIF surgery group may be at a disadvantage compared to the OLIF surgery group in terms of subsidence, the TLIF surgery group was better in terms of nerve root decompression. In a study evaluating radiographic outcomes according to cage type in TLIF reported that the increase in foraminal height obtained through TLIF was small, but that the more important key was direct decompression. In this study, we provide evidence to support our claim.

In a recent report on revision OLIF surgery performed on 34 patients at the same level after previous lumbar decompression, the CSA extension increased from 136.4 ± 57.9 mm² to 194.1 ± 58.6 mm² before and after surgery, the clinical improvement rate was 59.0%, and fusion rates of 93.0% were reported. These results suggest that indirect decompression is sufficient in revision surgery when performed with OLIF and that OLIF can be a good alternative for revision surgery. However, this study is different from our study in that the L5–S1 level, which has a relatively high frequency of LSS, was excluded from the study.
Comparison of Outcomes Between Direct and Indirect Decompression Revision Surgery

Prior to this study, we compared the clinical and radiological outcomes of primary OLIF surgery and revision OLIF surgery. In previous studies, OLIF as revision surgery showed acceptable clinical outcomes, but the effect of indirect decompression was less than that of primary OLIF, which is thought to be due to perineural adhesions and scar formation from previous surgery. In this study, the clinical and radiological outcomes of TLIF and OLIF performed as revision surgery were compared, and there were no differences in clinical outcomes between the 2 groups. These results suggest that perineural adhesion and scar formation caused by previous surgery may have slightly less improvement in clinical outcomes during revision surgery compared to primary surgery, but this suggests that there is no difference in the effects of perineural adhesion and scar formation on both direct decompression and indirect decompression.

The disadvantage of indirect decompression through OLIF compared to TLIF is that if symptoms do not improve after surgery, additional posterior decompression surgery may be required. In our study, 2 cases in the OLIF surgery group underwent additional posterior decompression surgery. They did not show any improvement in symptoms after surgery, and both patients complained of dominant radiculopathy on the same side as the previous decompression side. They underwent additional posterior decompression surgery within 2 weeks after OLIF surgery, and their symptoms improved after the subsequent surgery. These results are the basis for supporting the content of our previous study that, as revision surgery, OLIF reduced the effects of indirect decompression due to perineural adhesion and scar formation in the same side as the previous decompression compared to the virgin side.

If symptoms persist or residual symptoms remain on the same side as the previous decompression side, additional posterior decompression surgery may be required after OLIF, which is a limitation of OLIF. On the other hand, good outcomes can be expected when revision OLIF is considered as a symptom of the virgin side. Therefore, if appropriate indications are applied, OLIF can be a good alternative to TLIF in revision surgery. However, to support our claim, a comparative study on the risks of additional posterior decompression surgery within 2 weeks after OLIF surgery, and their symptoms improved after the subsequent surgery. These results are the basis for supporting the content of our previous study that, as revision surgery, OLIF reduced the effects of indirect decompression due to perineural adhesion and scar formation in the same side as the previous decompression compared to the virgin side.

Conclusions:

1. Since complications associated with the posterior approach can be avoided, OLIF is a safer and useful minimally invasive surgery. Transient paresthesia after OLIF surgery may occasionally occur, but is acceptable as it usually improves. However, due to perineural adhesions or scar formation, there may not be sufficient symptom improvement, and in some cases, additional posterior decompression surgery may be required, which is a limitation of OLIF. Therefore, appropriate indications are applied, OLIF is a good alternative to TLIF when revision surgery is considered.

Notices:

Conflict of Interest: The authors have nothing to disclose.
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**ORCID**

Sang-Jin Park: 0000-0003-1712-1848
Jong-Moon Hwang: 0000-0002-9807-8783
Dae-Chul Cho: 0000-0002-2899-8015
Subum Lee: 0000-0003-4732-8137
Dae-Won Park: 0000-0003-1103-2908
Chi Heon Kim: 0000-0003-0497-1130
Inbo Han: 0000-0002-0834-9325
Heum-Dai Kwon: 0000-0003-1657-6234
Kyoung-Tae Kim: 0000-0003-1657-6234

**REFERENCES**


Comparative Analysis of Transforaminal Endoscopic Thoracic Discectomy and Microscopic Discectomy for Symptomatic Thoracic Disc Herniation

Junseok Bae¹, Jisang Kim¹, Sang-Ho Lee¹, Jin-Sung Kim²

¹Department of Neurosurgery, Wooridul Spine Hospital, Seoul, Korea
²Department of Neurosurgery, Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Objective: To evaluate the clinical outcomes of transforaminal endoscopic thoracic discectomy (TETD) and microscopic discectomy (MD) for the treatment of symptomatic thoracic disc herniation (TDH).

Methods: Seventy-seven patients (mean, 55.9 years; follow-up, 11.2 months) with symptomatic TDH were retrospectively reviewed (39 TETD and 38 MD). Radiological factors and perioperative outcomes were reviewed. Visual analogue scale (VAS), Oswestry Disability Index (ODI), and American Spinal Injury Association impairment scale were used to evaluate clinical and functional outcomes. Patient satisfaction was evaluated using modified MacNab criteria.

Results: The levels of surgery and the location of hernia were evenly distributed in the both groups. The operative time (70.6 minutes vs. 175.7 minutes), estimated blood loss (3.8 mL vs. 357.4 mL), and length of hospital stay (7.0 days vs. 13.0 days) were significantly different between the TETD and MD groups (p < 0.05). VAS scores for dorsal back pain and ODI scores were significantly improved in both groups (p < 0.05). Patients who underwent TETD tended to be more satisfied with the outcome in terms of the modified MacNab criteria (89.7% vs. 73.0%, p = 0.059). Two patients in the MD group underwent revision surgery, whereas one patient in the TETD group underwent MD because of incomplete decompression.

Conclusion: TETD for the symptomatic TDH is a feasible and safe procedure that could be used for a wider range of surgical levels with a shorter operative time and hospital stay and less blood loss. While achieving similar outcomes, TETD achieved better patient satisfaction because of the use of local anesthesia and its minimal invasiveness.

Keywords: Thoracic disc herniation, Transforaminal endoscopic thoracic discectomy, Microscopic discectomy

INTRODUCTION

Symptomatic thoracic disc herniation (TDH) is a relatively uncommon condition, accounting for less than 1% of all disc herniations.¹,² If appropriate conservative treatment, such as epidural steroid injection, physical therapy, and medication, fails to improve patients’ symptoms, surgical treatment is indicated. Progressive myelopathy with a significant neurologic deficit is an absolute surgical indication for TDH. Surgical treatment for TDH has been widely applied according to the location and characteristic of the hernia, clinical presentation, and surgeon’s experience with approaches ranging from the posteri-
or approach (laminectomy) to posterolateral (transpedicular, transfacet), lateral (costotransversectomy, lateral extracavitary), ventrolateral (transthoracic, mini-thoracotomy, thoracoscopy), and ventral (transsternal) approaches. The choice of thoracic disc resection is largely determined by the location and nature of the hernia, the clinical picture, the surgeon’s training, clinical experience, and personal preference. Because excessive surgical morbidity can be counterproductive, it is even more important to choose the least morbid surgical approach for thoracic disc resection. The surgical approach to the thoracic spine is often accompanied by approach-related complications that cause instability and neurological deterioration because of the unique susceptibility of the thoracic spinal cord to retraction injury. Clinical symptoms of TDH are often presented as various types of severe, incapacitating pain and any surgical access will cause. This makes the selection of a minimally pathological surgical approach for thoracic disc resection even more important.

The treatment of degenerative spinal disease is continuously evolving because of the progression of minimally invasive spinal surgery. The minimally invasive surgeries for TDH include video-assisted thoracoscopic discectomy, microscopic discectomy (MD), and transforaminal endoscopic thoracic discectomy (TETD). Currently, TETD has been described as a safe procedure with favorable outcomes for TDH. In the case of paramedian or foraminal disc herniation, a posterolateral approach or posterior approach is appropriate. MD has consisted with both posterior andposterolateral approach. Lam inection is mainly attempted to decompress spinal canal stenosis but has limitation of ventral decompression due to spinal cord retraction. Posterolateral approach such as transpedicular or transfacetal approach has been reported with good clinical outcomes in resecting herniated disc without complications. To the best of our knowledge, no study has compared TETD and MD for TDH. In this study, we compared the clinical outcomes of TETD and MD in patients with symptomatic TDH.

MATERIALS AND METHODS

1. Study Design and Patient Population

After receiving approval from the Institutional Review Board of Wooridul Spine Hospital (WRD1RB-2020-02-006), 84 patients with symptomatic TDH who underwent either TETD or MD between January 2016 and August 2019 at Wooridul Spine Hospital were retrospectively reviewed. Inclusion criteria were (1) diagnosis of paramedian or foraminal soft TDH confirmed by magnetic resonance imaging (MRI) findings corresponding to the patient’s clinical symptoms, (2) dorsal back pain with or without radiating pain, or mild myelopathy (American Spinal Injury Association [ASIA] grade C, D) associated with TDH, and (3) failure of appropriate conservative treatments including medication, physical therapy, and epidural steroid injection. The exclusion criteria were (1) extensive calcified or hard disc herniation, (2) concomitant ossification of the posterior longitudinal ligament (OPLL), (3) central extruded herniation, (4) spinal fracture or instability, (5) infection, and (6) tumor.

2. Assessment of Perioperative Outcomes

Perioperative data were assessed using clinical charts and operative records. Before and after surgery, dorsal back or leg pain was measured using the 10-point visual analogue scale (VAS) (score range 0–10), and function was assessed using the Oswestry Disability Index (ODI) (score range 0–100). To evaluate the neurological level of impairment, we recorded the preoperative and postoperative American Spinal Injury Association impairment scale score. Patient satisfaction was assessed using modified MacNab criteria (excellent, good, fair, or poor). Grades of excellent and good were regarded as satisfying results, whereas grades of fair and poor as nonsatisfying results. All postoperative outcomes were obtained at the last follow-up.

Radiological factors such as the location of the herniation, presence of disc calcification, and combined ossification of the ligamentum flavum (OLF) were evaluated with MRI and computed tomography scans. Axial locations of disc herniation were categorized as paramedian or foraminal.

The levels of surgery were categorized into 3 subgroups: upper (T1–2 to T4–5), middle (T5–6 to T8–9), and lower (T9–10 to T12–L1) thorax. The operative time, estimated blood loss (EBL), hospital stay, and rate of complications were evaluated to assess the outcomes of the surgeries.

3. Operative Procedure

In TETD, surgery was performed using local anesthesia and intravenous sedation with the patient in the prone position. The skin entry point was commonly located approximately 5–6 cm from the midline. After infiltration of local anesthetics, an 18G needle is advanced along the planned trajectory under lateral fluoroscopic view to the lateral aspect of the superior facet. A guidewire was inserted through the needle. Discography was performed by injecting a mixture of radiopaque dye and indigo carmine. Foraminoplasty was performed using a round reamer or bone drill. The 3.1-mm endoscope (TESSYS thx, Joimax GmbH, Karlsruhe, Germany) was introduced through a 5.8-
mm outer diameter working cannula. Under the direct visualization, a blue-stained annular surface and herniated disc fragment could be identified. By removing the annulus of the outer layer and the internal layer of the posterior longitudinal ligament (PLL) with a side-firing laser, the blue-stained herniated fragment was released from anchoring. Then the fragment was removed using microforceps. The Ho:YAG laser was used to resect the PLL, thickened annulus, and partially calcified hernia. After adequate decompression, the skin was closed, and a sterile dressing was applied (Fig. 1A-H).

In MD, the patient was placed on a Wilson frame in the prone position under general anesthesia. The surgical level was localized utilizing C-arm fluoroscopic guidance. After making a midline incision, subperiosteal dissection was performed to expose the interlaminar space. Using a high-speed drill and a curette, partial hemilaminectomy, medial facetectomy, and flavectomy were performed under microscopic visualization. In case of dural sac is extended laterally, facetectomy is extended or partial pediculotomy was done to avoid dural retraction. Annulotomy was performed with a carbon dioxide (CO\textsubscript{2}) laser followed by gentle fragmentectomy with a microscopic instrument. We did not retract the dura mater but dissected the ventral epidural space to squeeze the fragment and pull it out of the annulotomy site with a right-angled dissector. After thorough decompression of the neural structure was achieved, closure was performed in a conventional way (Fig. 2A-G).

4. Statistical Analysis

Descriptive statistics for continuous variables are presented as means with standard deviations, and dichotomous variables are presented as frequencies with percentages in parentheses. Collected variables were compared to assess the statistical significance of any differences after the respective operative method (group A vs. group B). We used, where appropriate, Mann-Whitney U-test and t-test for continuous variables, and Pearson chi-square test and Fisher exact test for dichotomous variables, without missing data imputation. All statistical tests were performed using 2-sided tests, and p-values < 0.05 were considered statistically significant. All analyses were performed using the statistical software package SAS 9.4 (SAS Institute, Cary, NC, USA).

![Fig. 1. Case presentation of a 50-year-old male patient presenting with thoracic back pain and radiating pain in the left chest. Preoperative sagittal (A) and axial (B) magnetic resonance imaging (MRI) scans show paramedian thoracic disc herniation at the T7–8 on the left side. The transforaminal approach is used for endoscopic discectomy. (C, D) The intraoperative fluoroscopic view shows the placement of the working channel. Endoscopic view showing removal of blue-stained disc fragment with endoscopic forceps (E) and full decompressed dural sac (F). (G, H) Postoperative MRI scans show decompression of the spinal cord after discectomy.](https://doi.org/10.14245/ns.2244294.147)
RESULTS

Among 84 patients, 77 patients (mean age, 55.9 ± 16.6 years, 49 men; mean follow-up, 11.2 ± 5.2 months) met the inclusion criteria. TETD was performed in 39 patients (mean age, 49.5 ± 14.7 years), and MD was conducted in 38 patients (mean age, 62.6 ± 16.2 years). The levels of surgery were relatively evenly distributed in the TETD group (15% upper thorax, 51.2% mid thorax, and 33.3% lower thorax) and MD group (7.8% upper thorax, 26.3% mid thorax, and 65.7% lower thorax). Concomitant OLF was more common in the MD group than in the TETD group (34.2% vs. 2.6%, p < 0.001). The axial location of disc herniation and calcification of the disc did not have a between-group difference (p = 0.622 and p = 0.861, respectively). Patient demographics are summarized in Table 1.

Preoperatively, the VAS score was significantly lower in the TETD group (7.5 ± 0.6) than in the MD group (7.9 ± 0.8) (p = 0.014). No significant difference in the preoperative ODI score was observed between the groups (p = 0.095). The distribution of the preoperative ASIA impairment scale score was significantly different between the groups (p = 0.009). The MD group had a higher percentage of neurologically impaired patients than the TETD group. There were no significant differences in postoperative outcome measurements, including VAS, ODI, and ASIA impairment scale scores between the groups (p = 0.082, p = 0.121, and p = 0.080, respectively). Patients who underwent TETD tended to be more satisfied with the outcome in terms of MacNab criteria than those who underwent MD (89% vs. 71%, p = 0.059). The mean operative time, EBL, and hospital stay were significantly different between the groups. The TETD
group had a significantly shorter operative time (70.6 ± 25.4 minutes vs. 175.7 ± 54.8 minutes, p = 0.002), less EBL (3.8 ± 17.7 mL vs. 357.4 ± 239.8 mL, p < 0.001), and shorter hospital stay (7.0 ± 8.6 days vs. 13.0 ± 7.5 days, p = 0.002) than the MD group. One patient in the TETD group underwent MD because of incomplete decompression. Two patients in the MD group underwent revision surgery because of incomplete decompression and the presence of a postoperative hematoma on the next day after surgery (Table 2).

**DISCUSSION**

The management of TDH is evolving continuously because of the progression of minimally invasive spinal surgery. Mack et al. and Horowitz et al. were among the first to describe minimally invasive endoscopic approaches to the thoracic spine by the technique of video-assisted thoracic surgery. Advances in minimally invasive spinal surgery have allowed for the endoscopic removal of TDH. Jho described the technique of endoscopic transpedicular thoracic discectomy with 0° and 70° 4-mm endoscopes that requires a relatively small 2-cm incision and minimal tissue dissection. This approach avoids the need for a separate skin incision in the chest wall, which is required for thoracoscopic approaches, and the need for postoperative chest drainage. Several publications on outcomes of endoscopic thoracic discectomy have confirmed the efficacy and safety of the procedure. Cho et al. reported oblique paraspinal approach which made skin incision on 5–6 cm lateral from midline to place tubular retractor on the facet joint then drilling it to expose exiting root and lateral portion of dural sac. As a modification of transfacetal approach, it avoids necessity of dural retraction as well as provides good microscopic visualization on the ventral dural space. In the present study, authors’ MD technique included partial facet resection with or without pediclectomy, which is also modification of transfacetal or transpedicular approach. With the usage of CO₂ laser, a safe and delicate resection of hernia was possible without aggressive facet or pedicle resection.

The present study showed that TETD and MD are effective treatments for symptomatic TDH. In terms of demographics, there were significant difference in terms of age and presence of OLF between the groups. MD group was older (49.5 years vs. 62.6 years, p < 0.001), and there were more patients in the MD group with OLF (13 (34.2%) vs. 1 (2.6%), p < 0.001). The MD group had a significantly shorter operative time (175.7 ± 54.8 minutes vs. 70.6 ± 25.4 minutes, p = 0.002), less EBL (357.4 ± 239.9 mL vs. 3.8 ± 17.7 mL, p < 0.001), and shorter hospital stay (13.0 ± 7.5 days vs. 7.0 ± 8.7 days, p = 0.002). Two patients in the MD group underwent revision surgery because of incomplete decompression and the presence of a postoperative hematoma on the next day after surgery (Table 2).

**Table 1. Demographic data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TETD (n = 39)</th>
<th>MD (n = 38)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.5 ± 14.7</td>
<td>62.6 ± 16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.132</td>
</tr>
<tr>
<td>Male</td>
<td>28 (71.8)</td>
<td>21 (55.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (28.2)</td>
<td>17 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
<td>0.277</td>
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<tr>
<td>(mo)</td>
<td>4.8 ± 4.6</td>
<td>6.2 ± 5.6</td>
<td></td>
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<tr>
<td>Disc location</td>
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<tr>
<td>Paramedian</td>
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<td>35 (92.1)</td>
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<tr>
<td>Foraminal</td>
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<td>3 (7.9)</td>
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<tr>
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<td>6 (15.4)</td>
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<tr>
<td>Middle</td>
<td>20 (51.3)</td>
<td>9 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>13 (33.0)</td>
<td>20 (52.6)</td>
<td></td>
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<tr>
<td>Multiple</td>
<td>0 (0)</td>
<td>6 (15.8)</td>
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<tr>
<td>Calcification (partial)</td>
<td>12 (30.8)</td>
<td>11 (28.9)</td>
<td>0.861</td>
</tr>
<tr>
<td>OLF</td>
<td>1 (2.6)</td>
<td>13 (34.2)</td>
<td>&lt;0.001</td>
</tr>
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</table>

Values are presented as mean ± standard deviation or number (%). TETD, transforaminal endoscopic thoracic discectomy; MD, microscopic discectomy; OLF, ossification of ligamentum flavum.

**Table 2. Perioperative outcomes**

<table>
<thead>
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<th>MD</th>
<th>p-value</th>
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<td>Preoperative VAS</td>
<td>7.5 ± 0.6</td>
<td>7.9 ± 0.8</td>
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<td>Postoperative VAS</td>
<td>2.5 ± 0.6</td>
<td>2.8 ± 0.5</td>
<td>0.082</td>
</tr>
<tr>
<td>Preoperative ODI</td>
<td>47.6 ± 18.8</td>
<td>43.2 ± 20.1</td>
<td>0.095</td>
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<tr>
<td>Postoperative ODI</td>
<td>13.7 ± 4.3</td>
<td>14.7 ± 5.7</td>
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<td>Preoperative ASIA</td>
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<td>0.009</td>
</tr>
<tr>
<td>C</td>
<td>1 (2.6)</td>
<td>8 (21.1)</td>
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</tr>
<tr>
<td>D</td>
<td>20 (51.3)</td>
<td>22 (57.9)</td>
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<td>E</td>
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<td>E</td>
<td>18 (46.2)</td>
<td>10 (26.3)</td>
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<td>Modified MacNab criteria</td>
<td></td>
<td></td>
<td>0.059</td>
</tr>
<tr>
<td>Satisfying (excellent, good)</td>
<td>35 (89.7)</td>
<td>27 (73.0)</td>
<td></td>
</tr>
<tr>
<td>Nonsatisfying (fair, poor)</td>
<td>4 (10.3)</td>
<td>10 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>70.6 ± 25.4</td>
<td>175.7 ± 54.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Estimated blood loss</td>
<td>3.8 ± 17.7</td>
<td>357.4 ± 239.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>7.0 ± 8.7</td>
<td>13.0 ± 7.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Revision surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete decompression</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Postoperative hematoma</td>
<td>-</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). TETD, transforaminal endoscopic discectomy; MD, microscopic discectomy; ODI, Oswestry Disability Index; VAS, visual analogue scale; ASIA, American Spinal Injury Association.
62.6 years) and concomitant OLF (2.6% vs. 34.2%). High prevalence of OLF is reason of older patient population in MD. Due to high prevalence of OLF in the lower thoracic level, MD groups tended to have more lower thoracic level surgery. However, this difference did not affect the clinical and functional outcomes between groups. This implies importance of preferred indication of each surgical approach according to concomitant degenerative pathology at the index level. Patients from both groups reported lower postoperative ODI and VAS scores than preoperative scores, with satisfaction. There were no significant differences in the clinical outcome measures, such as the postoperative VAS, ODI, and ASIA impairment scale scores, between the groups. TETD had a significant advantage in terms of awake anesthsia, less blood loss, and short operative time and hospital stay. For these reasons, patients who underwent TETD tended to be more satisfied with the outcome in terms of modified MacNab criteria than those who underwent MD. This result is concordant with recent systemic review that reported as excellent or good outcomes were achieved for full endoscopic procedures in a mean of 81% of patients (range, 46%–100%) with a complication rate of 8% (range, 0%–15%), comparing favorably with rates reported after open discectomy (anterior, posterolateral, and thoracoscopic) or by endoscopic tubular assisted approaches.

In addition to less EBL and a short operative time and hospital stay, TETD has more benefits. Endoscopic discectomies generally do not require laminectomy or facetectomy, which induces postoperative spinal instability. Less traction on the neural structure can reduce nerve edema, and minimal neural tissue exposure reduces postoperative neural adhesion and prevents scar tissue formation, which can help improve surgical outcomes. Besides, TETD is associated with less possibility of postoperative morbidity due to local anesthesia, less blood loss, and short operative time and hospital stay, which makes both surgeons and patients comfortable with the selection. Moreover, the technique is associated with less approach-related muscle damage than conventional open surgeries, which carry a higher possibility of postoperative back pain. From this aspect, TETD may be more applicable to patients with intractable chronic dorsal back pain rather than motor weakness. Although one patient in our study had undergone MD because of incomplete decompression after TETD, there was no morbidity related to the revision surgery. Considering everything, TETD may be a primary surgical option for paramedian soft TDH with dominant dorsal back pain.

Although calcified herniation is considered to be challenging, partially calcified discs can be resected with a special endoscopic instrument, such as a high-speed drill and side-firing Ho:YAG laser. In the present study, we treated 12 patients with partial calcification of the disc. Only one of them did not improve and was not satisfied postoperatively, so this patient underwent MD for wide decompression. The other 12 patients with calcified lesions had a relatively favorable outcome. Paolini et al. reported 2 cases of successful resection of calcified TDH using an endoscope-assisted posterior approach. Under experienced surgeons, calcified herniation can be treated with a careful surgical approach and proper patient selection. It is necessary to consider open surgery for patients with concomitant OLF, OPLL, and hard disc. Favorable surgical outcomes using the CO2 laser in microscopic surgery for calcified lesions have been reported.

It is important to select an appropriate patient for TETD to avoid reoperation, conversion to open surgery, and surgical complications. Regarding multilevel TDH, MD may be more applicable than TETD because the operation time including the preparation is long and the radiation exposure to the patient and the surgeon becomes higher. In our cases, the TETD group had no multilevel TDH, whereas the MD group had multilevel TDHs in 5.3% of cases. Moreover, patients with severe neurologic deficits are not yet appropriate candidates for TETD. If a patient with TDH has a progressive motor weakness, MD with wide decompression or the transthoracic approach should be considered. Concomitant OLF compressing the spinal cord in addition to TDH causing myelopathy is another important factor in deciding the surgical approach. MD is superior in simultaneous 360° decompression of OLF and TDH causing severe myelopathy. In addition to microscopic decompression, posterior stabilization can be performed according to postoperative instability.

Despite some advantages of TETD, it still has many limitations as a standard treatment for TDH. TETD has a steeper learning curve. The specific endoscopic instrumentation, 2-dimensional endoscopic images, and operation through a small opening to reach the spine at a longer distance and greater angle are unique to endoscopy, and may not be intuitive to surgeons who are accustomed to only open procedures. This unfamiliarity may inevitably be related to postoperative complications or incomplete decompression. TETD should be performed by a spinal surgeon who is not only experienced in open surgery but also familiar with endoscopic spinal procedures, with a thorough surgical plan.

Despite the strength that the present study is the first to compare the clinical outcomes of TETD and MD, it has some limi-
tations. First, this retrospective review relied on existing medical records for the collection of clinical and operative data. Second, our study had selection bias. The differences in patient characteristics may have affected the results. Patients in the MD group were significantly older, neurologically impaired, and had more combined OLF than those in the TETD group. However, this difference reveals different indications of TETD and MD in treating symptomatic TDH. Prospective, randomized trials are necessary to provide conclusive results.

CONCLUSION

TETD for the symptomatic thoracic spine is a feasible and safe procedure that could be used for a wider range of surgical levels with a shorter operative time and hospital stay and less blood loss. Although TETD and MD achieve similar clinical and functional outcomes, TETD achieved better patient satisfaction than MD because of the use of local anesthesia and its minimally invasive approach. In case the patient’s pain and neurological status is similar, MD is more applicable to patients with severe neurologic deficits and combined OLF.

NOTES

Conflict of Interest: JB is a consultant for Joimax GmbH. SHL is a consultant for Joimax GmbH. JSK is a consultant of Richard Wolf, GmbH, and Elliquence, LLC. Except for that, no potential conflict of interest relevant to this article was reported.

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Author Contribution: Conceptualization: JB, SL, JK; Data curation: JK; Project administration: JB, JK; Writing - original draft: JB, JK; Writing - review & editing: JB.

ORCID

Junseok Bae: 0000-0003-0042-7242
Sang-Ho Lee: 0000-0002-8526-0260
Jin-Sung Kim: 0000-0001-5086-0875

REFERENCES

Assessing the Learning Process of Transforaminal Endoscopic Discectomy for Sciatica

Pravesh Shankar Gadjradj1, Pieter Schutte2, Arnold Vreeling3, Paul Depauw1, Biswadjiet S. Harhangi1

1Department of Neurosurgery, Park Medical Center, Rotterdam, The Netherlands
2Department of Neurosurgery, Alrijne Hospital, Leiderdorp, The Netherlands
3Department of Orthopedics, Rinstate Hospital, Arnhem, The Netherlands

Objective: Percutaneous transforaminal endoscopic discectomy (PTED) is gaining popularity by both surgeons and patients as a less invasive treatment option for sciatica. Concerns, however, exist for its learning curve. No previous study has assessed the learning process of PTED. Hereby we present the learning process of 3 surgeons learning PTED.

Methods: This analysis was conducted alongside a multicenter randomized controlled trial. After attending a cadaveric workshop, 3 spine-dedicated surgeons started performing PTED, initially under the supervision of a senior surgeon. After each 5 cases, and up to case 20, the learning process was evaluated using the validated questionnaires (objective structured assessment of technical skills [OSATS], global operative assessment of laparoscopic skills [GOALS]) and a 10-step checklist specifically developed for PTED.

Results: In total, 3 learning curve surgeons performed a total of 161 cases. Based on self-assessment, surgeons improved mostly in the domains “time and motion,” “respect for tissue,” and “knowledge and handling of instruments.” Learning curve surgeons were more able to detect differences in performances on the OSATS than the senior surgeon. Based on the GOALS, the biggest improvements could be seen in “depth-perception” and “autonomy.” Based on the 10-item specific checklist, all surgeons performed all 10 steps by case 10, while only 1 surgeon performed all steps adequately by case 15.

Conclusion: Based on these study results, PTED appears to be successfully adopted stepwise by 3 spine-dedicated surgeons. From 15 cases on, most steps are performed adequately. However, more cases might be necessary to achieve good clinical results. Validated tools are needed to determine the cutoff when a surgeon should be able to perform PTED independently.

Keywords: Lumbar disc herniation, Endoscopic discectomy, Sciatica, Randomized controlled trial

INTRODUCTION

Full-endoscopic spine surgery is gaining interest as a less invasive alternative to treat sciatica caused by a lumbar disc herniation.1-7 Compared to microdiscectomy, which is regarded as the golden standard to treat sciatica, full-endoscopic procedures have a smaller incision, require less destruction of bony structures, and facilitate outpatient surgery.8-10 On the other hand, full-endoscopic procedures rely more on fluoroscopy and expose both patients and surgeons to more radiation.11 Another disadvantage of full-endoscopic procedures is the learning curve. The learning curve is often seen as a barrier by surgeons for offering full-endoscopic spine surgery.12,13 Especially more so for percutaneous transfomaminal endoscopic discectomy (PTED) which may be more difficult to perform compared to its interlaminar variant, because of the transfomaminal route that most surgeons are unfamiliar with.14

Recently, the results of a randomized controlled trial (RCT)
were published in which noninferiority of PTED in leg pain reduction was shown compared to microdiscectomy. In addition, PTED resulted in more favorable outcomes regarding functionality, quality of life, recovery, and opioid utilization. Furthermore, mainly due to less societal costs, PTED showed dominance in cost-effectiveness over microdiscectomy. These study results are an important foundation for the implementation of PTED for sciatica.

As PTED warrants implementation, studies assessing the surgical learning curve are needed. Most studies assessing the learning curve are focused on duration of surgery or patient-reported outcomes such as leg pain. Up to now, no studies have been conducted that evaluated the learning curve process from start systematically. In the set-up of the current study, 3 surgeons naive to PTED, were trained in PTED by a senior surgeon. Their learning process has been extensively measured using questionnaires. In the current manuscript, the results of this learning process are presented.

**MATERIALS AND METHODS**

**1. Trial Design**

A multicenter, noninferiority, RCT was conducted at 4 general hospitals in The Netherlands among patients with sciatica caused by lumbar disc herniation. Details of the protocol and study design have been published previously. The study was funded by ZonMw, The Netherlands Organization for Health Research and Development. The trial was initiated and performed without involvements of the industry. The research protocol was approved by the research ethics board of all participating hospitals. All patients provided written informed consent prior to enrollment. The trial was registered at ClinicalTrials.gov (NCT02602093).

**2. Enrollment and Randomization**

From February 2016 to April 2019 patients were screened and enrolled by spine surgeons. Patients were eligible for the PTED-study if they were between 18 to 70 years of age; had more than 6 weeks of excessive radiating pain and no tendency for any clinical improvement; had an indication for surgery; had magnetic resonance imaging demonstrating a disc herniation with nerve compression with or without concomitant spinal or lateral recess stenosis or sequestration, and; had sufficient knowledge of the Dutch language in order to complete forms and follow instructions independently. Exclusion criteria were previous surgery on the same or adjacent disc level; cauda equina syndrome; spondylolytic or degenerative spondylolisthesis; pregnancy; severe comorbid medical or psychiatric disorder (American Society of Anesthesiologists physical status classification > II); severe caudal or cranial sequestration of disc fragments; contraindication for surgery and moving abroad on short notice.

Patients were randomized in a 1:1 ratio to PTED or microdiscectomy using computer-generated variable block sizes (4, 6, or 8), stratified by enrolling center. Blinding of patients was not feasible because of the substantial differences between both procedures (e.g., PTED having an 8-mm incision lateral of the spine and microdiscectomy having an incision of 2–5 cm dorsal of the spine in the midline).

**3. Learning Curve Procedure**

All trial surgeons were spine-dedicated surgeons who had 8 to 11 years of experience in performing degenerative lumbar surgery. Before the trial, only one of the participating neurosurgeons was proficient in performing PTED in The Netherlands. During this study, 3 surgeons (one per center) were trained in performing PTED, alongside the senior surgeon in the fourth hospital. Each surgeon attended a hands-on cadaveric workshop on PTED. This workshop existed of presentations on indications, outcomes, and pearls and pitfalls of PTED. After these presentations, the surgeons could practice PTED multiple times on a cadaver. After this workshop they performed 10 to 20 procedures under the supervision of the senior surgeon. Afterwards, they would perform PTED independently. Based on an educated guess, we assumed that the learning curve would take 50 cases per surgeon.

**4. Percutaneous Transforaminal Endoscopic Discectomy**

The full procedure has been published previously. Local anesthesia was administered. After insertion of a guidewire in the neuroforamen, conical rods are introduced followed by a drill to enlarge the neuroforamen. Hereafter, an endoscope was introduced within the working channel using an 8-mm cannula. A forceps was used to remove the disc fragments. Patients were treated on an outpatient basis. All surgeons used the same instruments (MaxMoreSpine, Unterföhring, Germany).

**5. Outcome Measures and Statistical Analysis**

A complete overview of the patient-reported outcome measures (PROMs) measured during the PTED-study, along with the statistical analysis plan, has been published elsewhere. In brief, the PTED-study was a RCT which established the noninferiority of PTED in leg pain reduction compared to microdiscectomy.
ficiency of PTED in leg pain reduction compared to microdiscectomy. The sample size was set at 682 patients and included 150 learning curve cases which were matched with 150 microdiscectomy cases. The PTED learning curve cases were excluded for the primary analysis.

The following instruments were used during the study:

- The objective structured assessment of technical skills (OSATS)

The OSATS is often used by attending physicians to score technical skills of residents. The OSATS scores 8 different domains and an overall score on technical scales on a scale ranging from 4 to 10 (highest skills). These domains are: indication for surgery; respect for tissue; time and motion; knowledge & handling of instruments; use of assistants; flow of operation; knowledge of specific procedure; and perioperative management. The OSATS was assessed by both the learning curve surgeons themselves, and the senior surgeon.

- A 10-item checklist with 10 essential steps of PTED was created (Supplementary material 1)

After each 5 cases, the senior surgeon would score if the learning curve surgeons would have performed all of these 10 steps, and whether it was performed adequately.

- The global operative assessment of laparoscopic skills (GOALS)

This questionnaire was specifically validated to grade overall technological proficiency for laparoscopic skills. As it was estimated that its domains would also be applicable to endoscopic surgery (i.e., depth-perception, bimanual dexterity, efficiency, tissue handling, and autonomy), it was also used in the current study. The GOALS were scored by the senior surgeon on a 1 to 5 Likert scale.

Measurements were conducted before the cadaveric workshop and were then repeated after each 5 cases up to case 20. At baseline, demographics, and expectations of the learning curve, were collected. Then, after each 5 cases up to case 20, the OSATS, 10-item checklist and GOALS were collected. All analyses were conducted with IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

1. Study Procedures

From February 2016 to April 2019, 613 patients were randomized between microdiscectomy and PTED (Fig. 1). Of the 304 cases assigned to PTED, 161 were assigned to the 3 learning curve surgeons. Learning curve surgeons had tenures ranging from 8 to 11 years (Table 1). At baseline, the learning curve surgeons expected to have a learning curve of 20 to 25 cases. On a 0 to 10 scale, learning curve surgeons scored the (1) difficulty of PTED a 7.8, (2) need for theoretical training a 6.6; and (3) the need for practical training a 9.5.

2. Objective Structured Assessment of Technical Skills

Fig. 2 gives an overview of the scores on the OSATS after each 5 cases up to case 20, as scored by the learning curve surgeons themselves. All 8 domains and the overall scores showed im-

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**Fig. 1.** Flowchart with an overview of the enrollment and follow-up during the PTED-study. PTED, percutaneous transforaminal endoscopic discectomy; OM, open microdiscectomy.
Table 1. Demographics of the 3 spine surgeons naive to PTED and the senior surgeon proficient in PTED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experienced surgeon</th>
<th>LC surgeon 1</th>
<th>LC surgeon 2</th>
<th>LC surgeon 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenure (yr)</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Main specialty</td>
<td>Neurosurgery</td>
<td>Neurosurgery</td>
<td>Neurosurgery</td>
<td>Orthopedics</td>
</tr>
<tr>
<td>Amount of PTEDs performed (n)</td>
<td>&gt; 200</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Expected learning curve (n)</td>
<td>-</td>
<td>20</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Knowledge of procedural steps (0 to 10)</td>
<td>-</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Difficulty of performing PTED (0 to 10)</td>
<td>-</td>
<td>7</td>
<td>8</td>
<td>8.5</td>
</tr>
<tr>
<td>Requirement of theoretical training (0 to 10)</td>
<td>-</td>
<td>10</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Requirement of practical training (0 to 10)</td>
<td>-</td>
<td>10</td>
<td>9.5</td>
<td>9</td>
</tr>
</tbody>
</table>

PTED, percutaneous transforaminal endoscopic discectomy; LC, learning curve.

Fig. 2. Scores on the objective structured assessment of technical skills on performing percutaneous transforaminal endoscopic discectomy for the different surgeons as scored by themselves and by the experienced surgeon, are shown. LC, learning curve.

Improvements between the first 5 and last 5 cases (Table 2). Biggest improvements between the first 5 cases and the last 5 cases, were seen in the domains ‘time and motion’ by 2.0 points, ‘respect for tissue’ by 1.7 points, and ‘knowledge and handling of instruments’ by 1.7 points. Scores of the senior surgeon were less sensitive to detect the change in the OSATS domains. Differences in OSATS scores as assessed by the learning curve surgeons versus the senior surgeon, ranged from 0 to 1.3.
Table 2. Mean scores of the learning curve surgeons on the OSATS on the first and last assessed cases, divided between self-assessment versus proficient surgeon scoring

<table>
<thead>
<tr>
<th>OSATS</th>
<th>Self-assessment First</th>
<th>Self-assessment Last</th>
<th>Self vs. experienced assessment MD First</th>
<th>Self vs. experienced assessment MD Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for surgery</td>
<td>8.3</td>
<td>9.7</td>
<td>1.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Respect for tissue</td>
<td>6.7</td>
<td>8.3</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Time and motion</td>
<td>5.7</td>
<td>7.7</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Knowledge and handling of instruments</td>
<td>6.3</td>
<td>8.0</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Use of assistants</td>
<td>7.3</td>
<td>8.7</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Flow of operation</td>
<td>6.7</td>
<td>7.3</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Knowledge of specific procedure</td>
<td>7.0</td>
<td>8.0</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Perioperative management</td>
<td>7.3</td>
<td>8.3</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Overall</td>
<td>6.7</td>
<td>7.3</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

OSATS, objective structured assessment of technical skills; MD, mean difference.

Fig. 3. Number of items performed on the 10-task specific items list per surgeon.

3. 10-Item Specific List

The results of the 10-item specific checklist are shown in Fig. 3. By the fifth case, all 3 learning curve surgeons did not perform 2 steps of the PTED procedure, while 1 to 3 steps were performed inadequately. By case 10, all 3 learning curve surgeons performed all tasks but all 3 performed 3 to 4 cases inadequately. In case 15, one surgeon performed all 10 steps adequately. Of the remaining 2 surgeons, one performed 1 task inadequate and the other 2 tasks.

4. Global Operative Assessment of Laparoscopic Skills

Fig. 4 gives an overview of the results on the GOALS. In general, the GOALS did not detect big differences between the cases. The biggest improvements in scores were found in the domains “time and motion,” “respect for tissue,” and “knowledge and handling of instruments.” Learning curve surgeons were more able to detect differences in performances on the OSATS than the senior surgeon. Based on the GOALS, the biggest improvements could be seen in “depth-perception” and “autonomy.” Based on the 10-item specific checklist, all surgeons performed all 10 steps by case 10, while only one surgeon performed all steps adequately by case 15.

A remarkable finding of this study is that self-assessment of

DISCUSSION

The current study presents the prospective results of the learning process of 3 surgeons, who had never performed PTED before. Other studies prospectively evaluating the learning curve process are lacking.

In total, the 3 learning curve surgeons performed a total of 161 cases. Based on self-assessment, surgeons improved mostly in the domains “time and motion,” “respect for tissue,” and “knowledge and handling of instruments.” Learning curve surgeons were more able to detect differences in performances on the OSATS than the senior surgeon. Based on the GOALS, the biggest improvements could be seen in “depth-perception” and “autonomy.” Based on the 10-item specific checklist, all surgeons performed all 10 steps by case 10, while only one surgeon performed all steps adequately by case 15.

Fig. 4 gives an overview of the results on the GOALS. In general, the GOALS did not detect big differences between the cases. The biggest improvements in scores were found in the domains “time and motion,” “respect for tissue,” and “knowledge and handling of instruments.” Learning curve surgeons were more able to detect differences in performances on the OSATS than the senior surgeon. Based on the GOALS, the biggest improvements could be seen in “depth-perception” and “autonomy.” Based on the 10-item specific checklist, all surgeons performed all 10 steps by case 10, while only one surgeon performed all steps adequately by case 15.

A remarkable finding of this study is that self-assessment of
the learning curve surgeons was more responsive to change compared to OSATS scores given by the senior surgeon. An explanation for this might be that the senior surgeon scored multiple surgeons in a long-time span and more scored around the mean, while the learning curve surgeons themselves were only involved with their own learning process and therefore more adequately noticed improvements on various domains.

Another unexpected finding was that according to the GOALS, only surgeon 2 showed a decrease in scores between the 10th and the 15th case. An explanation for this is that during the trial enrollment, the operating room at the hospital of surgeon 2 was closed temporarily which has also resulted in a lower recruitment. Therefore, surgeon 2 performed 32 cases at the same time span other surgeons performed 43 to 147 cases. Perhaps, the closure of the operating room might have resulted in a temporary set-back in the learning process.

Some limitations have to be acknowledged. First is the absence of a valid instrument to assess the learning curve process. During this study, the OSATS and the GOALS were used. Both of these questionnaires had other goals than they were used for the current study. The OSATS was intended to be an instrument to objectively measure technical skills of surgical residents, while the GOALS was intended specifically to measure laparoscopic skills while performing a cholecystectomy in novice trainees. The latter may also explain why the GOALS failed to measure change in skills for cases as all 3 learning curve surgeons already had some experience holding an endoscope due to performing endoscopic pituitary surgery or arthroscopy. Therefore, the GOALS might have been less sensitive to detect improvements of endoscopic skills in this study popu-
lation. The 10-item specific checklist did prove to be useful during the training process, as it showed step-by-step mastering of the procedure. However, after 15 cases, it could not detect further improvements in surgical skills. Another limitation is the slow enrollment rate for some centers. For instance, learning curve surgeon 2 performed 32 cases while surgeon 1 performed 86 cases during the same time. This slow enrollment rate might also have had consequences for the learning curve of the surgeons as they would perform only one PTED case per month. Strengths of this study include the prospective nature, the inclusion of multiple surgeons with different training backgrounds, and the systematic assessment of the learning process.

**CONCLUSION**

Based on these study results, PTED appears to be successfully adopted stepwise by 3 spine-dedicated surgeons. From 15 cases on, most steps of PTED have performed adequately. Validated tools, however, are needed to determine the cutoff when a surgeon should be able to perform PTED on his own.

**NOTES**

Supplementary Material: It can be found via https://doi.org/10.14245/ns.2244334.167. Supplementary material 1. 10-item specific checklist.

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: PSG; Data curation: PSG, PS; Formal analysis: PSG, AV, PD; Funding acquisition: PSG, BH; Methodology: PSG; Project administration: PSG; Visualization: PSG; Writing - original draft: PSG; Writing - review & editing: PSG, PS, AV, PD, BSH.

ORCID

Pravesh Shankar Gadjradj: 0000-0001-9672-4238
Pieter Schutte: 0000-0002-4363-3743
Paul Depauw: 0000-0003-3618-7068
Biswaajit S. Harhangi: 0000-0001-6983-3164

REFERENCES


### Supplementary Material 1. 10-Item specific checklist.

<table>
<thead>
<tr>
<th>Task</th>
<th>Performed</th>
<th>Inadequately done</th>
<th>Not done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring the correct place for skin incision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Introduction of the needle: feeling fascia, anesthetizing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has good control of the guidewire, minimizes recoil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checks positioning with fluoroscopy (SAP reached safely)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checks vocal anesthesia sufficiently</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Places TomShidi needle through SAP (noticing sound difference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilates the neuroforamen sufficiently</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognizes the anatomy through the endoscope (HNP, fat, etc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removes disk material safely and sufficiently</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checks if the nerve has been decompressed sufficiently (MRI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Building a Successful Practice of Endoscopic Spine Surgery: Learning, Setting the Goal, and Expanding the Border

Junseok Bae¹, Jin-Sung Kim²

¹Department of Neurosurgery, Wooridul Spine Hospital, Seoul, Korea
²Department of Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Recently, we have been surprised to figure out that the dramatic change in the reputation of endoscopic spine surgery has been taking place rapidly, and also tons of articles are coming out, especially from China, Korea, and other countries. However, the unfamiliar equipment, not handy optics, the narrow surgical field afforded by endoscopic spinal surgery, and eventually, steep learning curves have deterred many surgeons from this endoscopic spine surgical field. Overcoming the learning curve is a major barrier to entry in endoscopic spinal surgery.¹,²

In particular, since the transforaminal endoscopic approach is a new treatment method having a different surgical trajectory compared to that of the traditional surgical method, any novice surgeon who starts this surgery for the first time needs a 3-dimensional understanding of the neural foramen related to Kambin triangle.

In general, it is mentioned that endoscopic surgery requires a steep learning curve. More heuristic learning is needed than that of conventional spine surgery. Many researchers studied the learning process of endoscopic surgery and made presentations on how much surgical experience is needed until the surgery has uniform outcomes according to each criterion and goal.³-⁸ As such, most of the existing studies have an explicit limitation in suggesting the cutoff values of the initial 20 cases through comparison between random groups dichotomized based on the operation time.

In this issue, Gadjradj et al.⁹ present a clear objective to evaluate the learning curve. The objective structured assessment of technical skill was proposed as a tool to evaluate surgical residents with 8 specific items.¹⁰ However, this study showed that it could also be used to evaluate the skills of endoscopic surgery. The interesting thing about this study is that 'time and motion' showed the most development, followed by 'Respect tissue' and 'Knowledge and handling of Instruments.' This means that the operation time will gradually decrease as experience is accumulated, and unfamiliar instruments and other types of surgical anatomy can also show a lot of progress through experience. As a more specific endoscopic surgery learning object, the 10-time specific list makes it possible to subdivide each stage of endoscopic surgery and check whether it is performed. It seems necessary to change depending on the surgical technique, but it will be useful to set a specific checklist and identify where the trainee is in the learning process by distinguishing between 'performed,' 'inadequately
done,’ and ‘not done.’ When viewed in this way, differences in the degree of completion of surgical techniques were also confirmed for each individual in the first 5, 10, and 15 cases. This study is important because it is more apparent than the evaluation based on the operation time or complications, and both the trainee and the supervisor can evaluate objectively. In another paper by the same authors, learning curve surgeons trained in the same way showed lower performance than expert surgeons in the first year of operation time and recurrence rate but reported results that were comparable in patient satisfaction and progress. This suggests that endoscopic surgery can achieve reproducible and stable results even for beginners when well-trained and educated.

Contrary to a study of the learning curve for beginners on transforminal endoscopic lumbar discectomy (TELD), Yuan et al. report a study on extended indications of TELD. Hard discs or calcified discs have generally been regarded as a relative contraindication, and posterior apophyseal ring fracture is similar. However, the authors reported successful surgical results through sophisticated dissection and removal of fractured bone fragments. Although the probability of complications is higher and the operation time is longer than that of general TELD, it is a meaningful study in terms of expanding the indications of TELD as a minimally invasive surgical method for rare but difficult-to-treat lesions.

A learning curve is not an achievement curve. Just because the surgical technique has settled on a plateau at the initial stage of starting surgery cannot be evaluated as a completed technique. Due to the nature of the surgical method that varies according to the various indications of the transforminal endoscopic approach, the learning curve has a different start. Therefore, in addition to the surgical technique in the learning curve, it will be necessary to comprehensively evaluate the difficulty of indications, acute recurrence after surgery, and readmission.

With endoscopic surgery receiving more and more attention, proper guidelines and goal setting for education and training are more important than ever. Based on the detailed checklist presented in this study, it is necessary to discuss creating a consensus between endoscopic academic societies and experts.

**Conflict of Interest:** The authors have nothing to disclose.

**REFERENCES**

Title: Three Musicians
Year: 1921
Artist: Pablo Picasso
© 2022 - Succession Pablo Picasso - SACK (Korea)
Augmented Reality to Improve Surgical Workflow in Minimally Invasive Transforaminal Lumbar Interbody Fusion – A Feasibility Study With Case Series

Fabian Sommer, Ibrahim Hussain, Sertac Kirnaz, Jacob L. Goldberg, Rodrigo Navarro-Ramirez, Lynn B. McGrath Jr, Franziska A. Schmidt, Branden Medary, Pravesh Shankar Gadjradj, Roger Härtl

Department of Neurological Surgery, Weill Cornell Medicine, New York Presbyterian Hospital/Och Spine, New York, NY, USA

Objective: Minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) is a highly reproducible procedure for the fusion of spinal segments. We recently introduced the concept of “total navigation” to improve workflow and eliminate fluoroscopy. Image-guided surgery incorporating augmented reality (AR) may further facilitate workflow. In this study, we developed and evaluated a protocol to integrate AR into the workflow of MIS-TLIF.

Methods: A case series of 10 patients was the basis for the evaluation of a protocol to facilitate tubular MIS-TLIF by the application of AR. Surgical TLIF landmarks were marked on a preoperative computed tomography (CT)-scan using dedicated software. This marked CT scan was fused intraoperatively with the low-dose navigation CT scan using elastic image fusion, and the markers were transferred to the intraoperative scan. Our experience with this workflow and the surgical outcomes were collected.

Results: Our AR protocol was safely implemented in all cases. The TLIF landmarks could be preoperatively planned and transferred to the intraoperative imaging. Of the 10 cases, 1 case had additionally a synovial cyst resection and in 2 cases an additional bony decompression was performed due to central stenosis. The average procedure time was 160.6 ± 31.9 minutes. The AR implementation added 1.72 ± 0.37 minutes to the overall procedure time. No complications occurred.

Conclusion: Our findings support the idea that total navigation with AR may further facilitate the workflow, especially in cases with more complex anatomy and for teaching and training purposes. More work is needed to simplify the software and make AR integration more user-friendly.

Keywords: Augmented reality, Transforaminal lumbar interbody fusion, Navigation, Workflow

INTRODUCTION

Transformalional lumbar interbody fusion (TLIF) is a well-established surgical technique for stabilizing and decompressing a spinal motion segment utilizing a unilateral facetectomy to access the disc space for implantation of a cage and/or bone graft. It has become a routine operation performed through traditional open or minimally-invasive techniques and is associated with excellent outcomes in appropriately selected patients. By now it is defined by many predetermined land-
marks that help surgeons through the procedure. Furthermore, image-guided spinal surgery (IGSS) leveraging 3-dimensional computer navigation has shown improvement in the accuracy of screw placement, especially in minimally-invasive surgeries (MIS) where traditional landmarks are not visualized.

Recently, IGSS has been supplemented by augmented reality (AR). AR is defined as an enhancement of the real world by computer-generated images projected onto the user’s field of view. In this regard, AR can highlight anatomical structures relevant to the operation and artificially superimpose these structures onto the surgeon’s field of view during an operation. This projection can either be generated onto AR display headsets or directly onto the surgical microscope via AR application software. This technology can help surgeons identify crucial landmarks faster and with greater accuracy, especially in patients with complex anatomy or in revision cases.

This technology may be helpful for experienced surgeons when operating cases with challenging anatomical conditions like severe degenerative changes. Additionally, this technique offers enormous educational potential for novice surgeons and trainees. For example, MIS performed through tubular retractors are well established for treating herniated discs, lumbar stenosis, and performing TLIFs. These approaches offer very limited visualization through ports and carry a challenging learning curve given the lack of adjacent structures to use for anatomical reference. AR mitigates these issues through the display of crucial landmarks which can be displayed and identified even before they are seen in the microscopic field of view.

Tubular MIS-TLIF is a procedure that could particularly benefit from the application of AR and is based on reproducing a consistent procedural workflow guided by a series of fixed anatomical landmarks that can be difficult to visualize through an MIS approach. The typical workflow steps for MIS-TLIF based on the AO Spine curriculum “Key steps in an MIS-TLIF procedure” are shown in Fig. 1.

Facilitating the identification of the crucial anatomy and increasing the functional field of view for surgeons allows for the generation of step-by-step directions that could improve the procedure by streamlining the workflow during the surgery, reducing operative time and complication rates.

Here we present a technical report and workflow for the integration of AR and 3-dimensional (3D) navigation with the MIS-TLIF procedure highlighting important pearls and pitfalls. Our report is, to our knowledge, the first procedural description of a protocol to use AR for the MIS-TLIF procedure.

While the insertion of screws with 3D navigation or even with AR has been well described before, the use of AR for the identification of sequential surgical landmarks relevant to the other portions of the procedure is new and potentially very useful application of navigation and AR that expands the concept of our previously described idea of “total navigation” for spine cases.
MATERIALS AND METHODS

To evaluate the applicability of the tubular MIS-TLIF with AR support protocol, we performed a prospective case series of 10 patients. Baseline demographic data including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status classification grade. Perioperative data including blood loss operative time (measured from skin incision to skin closure), hospital length of stay, and complications were recorded. Patient-reported outcomes in the form of back and bilateral leg visual analogue scale scores before and after surgery were collected.

Exclusion criteria included nonelective (urgent or emergent) indication for surgery, presence of underlying malignant disease, and patient refusal. To avoid selection bias, after screening for exclusion criteria, randomization was performed using the digital randomizer “randomizer.org” to determine whether the patient would undergo surgery with AR. Postoperatively, before hospital discharge, AP and lateral x-rays were performed. After each surgery, a subjective qualitative assessment was made by the surgeon whether the use of AR was helpful or not in this surgery and whether the surgeon subjectively believed that AR helped to shorten the surgery time.

1. Preoperative Planning
Planning was performed on a standard PC using Brainlab Elements software. The basis for the planning was the CT images available during the diagnostic work-up of the patient’s pathology and symptomology. No additional CT images were taken for the planning of the AR. The outlining was done using the “smart brush” function of the software, which, based on automatic algorithms, merges the structures outlined on 2-dimensional (2D) individual slides of the CT to create a 3D outline.

2. AR Integration With Intraoperative Imaging
Preoperatively, AR planning was performed on a preoperative computed tomography (CT) scan using dedicated AR software (Brainlab Elements Smart Brush, Brainlab AG, Munich, Germany) which included anatomic landmarks and screw trajectories for the posterior instrumentation. All CT scans were already performed for diagnostic reasons and were not performed additionally for AR purposes, as to avoid additional radiation exposure to the patient. The operating rooms (ORs) were setup in the same manner as recommended for navigated cases (Fig. 2).

The preoperative planning dataset was fused with the intraoperative navigation CT (AIRO, Brainlab AG, Munich, Germany) using elastic fusion software (Brainlab Curvature Correction). A digital correction was performed using this software to account for the difference in lumbar lordosis between the supine preoperative CT and the prone iCT.

The accuracy of the fusion was checked and approved before each use by an orthopedic surgeon who was not involved in the surgery. After approval of the fusion, the anatomical structures highlighted in the navigation software were projected into the surgical microscope (Zeiss Pentero, Carl Zeiss Meditec AG, Jena, Germany) via an AR module. Color and brightness were adjusted according to the preference of the surgeon.

The following structures were marked for the TLIF procedure (Figs. 3, 4): (1) Inferior medial edge of the ipsilateral lamina, (2) ipsilateral Pars interarticularis (Pars), (3) ipsilateral superficial facet joint space, (4) ipsilateral pedicle of the caudal vertebra (IP), (5) disc space, (6) contralateral pedicles.

The contralateral pedicles and the pedicle of the upper ipsilateral vertebra were highlighted to allow better spatial orientation through the MIS tubular approach. Additionally, the entry points and trajectories for the pedicle screws were planned pre-
To assess the accuracy of the navigation, the surgeon was asked to subjectively assess the precision of augmented reality, which was tested by probing structures marked by AR using a ball tip in the microscope. Potential deviation from the actual anatomical structure was verified in the microscope.

3. AR Integration With Microscopic Field of View

After placing a reference array on the patient’s iliac crest, an intraoperative navigation CT was performed. After confirmation of the image fusion by an orthopedic surgeon, the next step is the registration of the surgical microscope with the navigation software. A reference array is rigidly affixed to the surgical microscope and connected to the navigation system. After the navigation cameras detect the reference arrays on both the patient and the microscope, the scope is then calibrated to the patient (Fig. 5).

For this purpose, a reference array was attached to the surgical microscope at the standard mounting point and the microscope was connected to the navigation system using a cable. After successful detection of the reference arrays on the patient and on the microscope by the navigation cameras, the microscope was calibrated to the patient. After focusing the microscope on the patient’s reference array, the patient array is automatically detected by the system and had to be manually calibrated on the navigation device by adjusting the digital edges to match the actual position. After confirming the calibration, the elements marked for AR could be projected into the surgical microscope’s field of view.

<table>
<thead>
<tr>
<th>Procedure step</th>
<th>Anatomical landmark</th>
<th>Abbreviation</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inferior medial edge of the ipsilateral lamina</td>
<td>IMEL</td>
<td>Red</td>
</tr>
<tr>
<td>2</td>
<td>Ipsilateral pars interarticularis</td>
<td>Pars</td>
<td>Green</td>
</tr>
<tr>
<td>3</td>
<td>Ipsilateral facet joint space</td>
<td>FJS</td>
<td>Orange</td>
</tr>
<tr>
<td>4</td>
<td>Ipsilateral pedicle L5</td>
<td>IP L5</td>
<td>Blue</td>
</tr>
<tr>
<td>5</td>
<td>Ipsilateral “pedicle” S1</td>
<td>IP S1</td>
<td>Blue</td>
</tr>
<tr>
<td>6</td>
<td>Intervertebral disc space</td>
<td>Disc</td>
<td>Yellow</td>
</tr>
<tr>
<td>7</td>
<td>Contralateral “pedicle” S1</td>
<td>CP S1</td>
<td>Purple</td>
</tr>
</tbody>
</table>

Fig. 3. Landmarks for L5/S1 transforaminal lumbar interbody fusion via left sided surgical approach highlighted on a spine model (L4 - sacrum).

Fig. 4. Landmarks for a L5/S1 transforaminal lumbar interbody fusion via left sided surgical approach highlighted on a computed tomography 3-dimensional reconstruction posterior view (A, B) and left sided lateral view (C, D). L5 Inferior medial edge of lamina (blue). L5 Pars (green). L5/S1 superficial facet joint space (purple). S1 “pedicle” ipsilateral (light blue). L5 pedicle ipsilateral (light blue). L5/S1 posterior part disc space (orange). L5 and S1 pedicle contralateral (light green).
4. Surgical Procedure

The MIS-TLIF was performed in the usual fashion outlined in the AO publication “step-by-step guide: key steps in MIS-TLIF procedure.” The use of AR as an operative adjunct requires no changes to this procedure. In all cases, the procedure was performed in the prone position and under general anesthesia using our total navigation approach. Before skin incision, a star reference array was placed on the iliac crest and a low-dose navigational CT scan was performed (Brainlab Airo). After the scan, navigated planning of the surgical approach was performed. In parallel, the digital fusion of the preoperative planning dataset with the intraoperative navigational CT was performed by the OR-team.

The skin incision and approach were made based on navigation approximately 4–5 cm paravertebrally. Next, navigation-guided percutaneous pedicle screws (Depuy/Synthes Viper Prime, Raynham, MA, USA) were placed using the preoperatively planned entry points. This step is performed first as it is the most reliant on accurate navigation. An autologous bone graft for fusion was harvested from the iliac crest through the caudal

Fig. 5. Intraoperative calibration of microscope to patient reference array. Yellow arrows point at the virtual calibration frame. (A) microscope view pre calibration. The virtual frame is not matching the reference array. (B) microscope view after calibration. The virtual frame is matched to the array.

Fig. 6. Verification of the accuracy with navigated pointer on highlighted Pars interarticularis. (A) Microscope view with pointer on Pars. (B) Navigation screen with pointer on Pars. Highlighted landmarks and planned screws also visible. IMEL, inferior medial edge of lamina.
most incision using standard technique. The navigation pointer was then used to find the optimal site and trajectory for the placement of a 21-mm tubular retractor.

After the positioning of the retractor, the surgical microscope was brought in and calibrated to the patient’s reference array (Fig. 5).

With successful calibration, the AR now becomes visible to the surgeon. With AR landmarks in view, soft tissue is dissected to the facet joint. The joint capsule is then visualized. After opening the joint capsule, the medial inferior border of the lamina marked by AR, and the marked Pars were presented as anatomical landmarks for resection of the inferior facet and the accuracy of the AR was verified using a navigated pointer (Fig. 6).

Drilling was always started at the medial border of the inferior lamina since this allows safe and reproducible access into the spinal canal where the dura is generally covered by a thick layer of ligamentum flavum. From here drilling proceeds in a linear fashion cranially and laterally towards the Pars and a trough is prepared (Fig. 7).

More cranial portions of the bone are removed using a 2-mm Kerrison rongeur in order to avoid violating the dura with the drill bit (Midas Rex, Medtronic, Dublin, Ireland). Once the Pars

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**Fig. 7.** (A) Illustration of surgical step 2 “removal of the inferior articular process (IAP)” for left sided L5/S1 transforaminal lumbar interbody fusion. “inferior medial edge of lamina (IMEL) refers to the starting point for drilling. (B) Microscope view showing the exposed anatomy from the inferior medial edge of the L5 lamina (blue) towards the marked left Pars interarticularis (green).

**Fig. 8.** Left sided L5/S1 transforaminal lumbar interbody fusion. (A) Illustration of surgical step 2 “removal of the inferior articular process.” (B) Microscope view of the initial drilling from inferior medial edge of lamina (IMEL) to Pars of the inferior articular process (IAP) of the facet joint. (C) Same view after bone drilling between the anatomical landmarks IMEL and Pars interarticularis. Inferior articular process still in place. The drilled trough between IMEL and Pars is highlighted (dashed yellow line).
has been disconnected the inferior articular process is harvested (Fig. 8).

Next, attention is turned towards the upper margin of the ipsilateral pedicle of the inferior vertebra. The pedicle is also highlighted as a landmark and color-coded using AR. The orientation on the pedicle is then used to resect the superior articular process (SAP) of the facet joint by drilling a trough right above the pedicle from medial to lateral and to expose the ligamentum flavum (Fig. 9).

The next landmark shown by AR is the disc space. After resection of the ligamentum flavum, the disc space is exposed and opened (Fig. 10).

Sufficient space was then created by discectomy and the bony endplates were exposed to place an implant. Prior to cage implantation, the optimal trajectory is determined using navigation and autologous bone is placed into the discectomy space. In addition, the autologous bone material harvested from the iliac crest and from the resected facet joint was placed in the cage. The cage is then navigated into optimal position.

After the final placement of the implant, the remaining discectomy cavity was also filled with an autologous bone graft.

If additional decompression is indicated, MIS “over-the-top technique” is performed at this time. For this purpose, the contralateral pedicles of the 2 fused vertebrae are projected into the microscope using AR to facilitate orientation (Fig. 11).

This allowed a better estimation of how far to decompress on
the contralateral side avoiding unnecessary destabilization.20

After fluoroscopic confirmation of implant position, posterior rods are placed. After adequate hemostasis is obtained, closure occurs in a standard fashion.

Postoperatively, patients go to the recovery room followed by the floor following a standard enhanced recovery after surgery protocol.

RESULTS

In total, 10 patients underwent tubular MIS-TLIF with the AR protocol. The cohort included 4 women and 6 men with a mean age of 65.9 ± 9.8. The mean BMI was 28.8 ± 10.5 kg/m² and the mean ASA physical status classification grade was 2.5 ± 0.5. All cases were single level; 6 involved L4/L5, 2 involved L3/4, one involved L2/L3, and 1 involved L5/S1. In 2 cases (20%) the TLIF was connected to an already existing fusion. In 1 case a resection of a synovial cyst was performed additionally and in 2 cases a MIS laminectomy and decompression of an additional level was performed due to symptomatic central stenosis.

The procedure time from skin incision to closure was 160.6 ± 31.9 minutes on average, (including the procedure time to treat the additional pathology in the 2 cases described above). Operative times in each case is listed in Table 1. The average hospital stay was 2.6 ± 1.0 days. The calibration time of the microscope to the AR was 103 ± 22.2 seconds.

Preoperatively 4 patients reported numbness, 1 patient isolated weakness and 2 patients both. Postoperatively, the neurological exam and wound healing were both monitored at 14 days post operatively. Neurological symptoms improved in all patients. No cerebrospinal fluid leaks, infections, or returns to OR occurred. No patients were readmitted to the hospital for any reason within 90 days. Revision surgery was not necessary in the current follow-up period of 8.4 ± 2.4 months on average.

The evaluated version of the AR software allowed the preoperative planning only on the 2D CT scan slides and not on the

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Table 1. Distribution of cases according to procedures and procedure time

<table>
<thead>
<tr>
<th>Case No.</th>
<th>TLIF level</th>
<th>Additional pathology</th>
<th>Additional procedure</th>
<th>Procedure time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2/3</td>
<td>Fusion L3/L4/L5</td>
<td>Extension of fusion</td>
<td>188</td>
</tr>
<tr>
<td>1</td>
<td>L3/4</td>
<td>Spinal canal stenosis L4/5</td>
<td>L4/L5 ULBD</td>
<td>219</td>
</tr>
<tr>
<td>1</td>
<td>L3/L4</td>
<td>Existing fusion L4/L5/S1; synovial cyst</td>
<td>Extension of fusion and cyst resection</td>
<td>167</td>
</tr>
<tr>
<td>1</td>
<td>L4/5</td>
<td>L3/4 spinal canal stenosis</td>
<td>L3/4 ULBD</td>
<td>190</td>
</tr>
<tr>
<td>5</td>
<td>L4/5</td>
<td>N/A</td>
<td>N/A</td>
<td>144 (+/-17)</td>
</tr>
<tr>
<td>1</td>
<td>L5/S1</td>
<td>N/A</td>
<td>N/A</td>
<td>165</td>
</tr>
</tbody>
</table>

TLIF, transforaminal lumbar interbody fusion; ULBD, unilateral approach bilateral decompression; N/A, not available.
3D reconstructions. In our experience, this required a learning curve to translate the position of the landmarks from 2D to the 3D view through the microscope in the OR. Additionally, 4–5 cases were needed to get familiar with the functions of the AR software. Since this limit, the comparability in our case series, we did not measure the preoperative planning time. The preoperative planning can be done when reviewing the images prior to the surgery and might take a user who is familiar with the workflow and the software less than 10 minutes. In the future, the suggested landmarks may be identified automatically through digital rendering. This function was in the available AR planning software already for different anatomical structures and the automatized rendering of the pedicle outlines worked reliably in our case series. However, advanced degenerative changes (osteophytes, facet arthropathy, severely collapsed disc space) caused inaccuracy of the automatized rendering function and needed manual correction of the outline.

AR was available in all cases at the time of soft tissue preparation. Actual anatomical precision was dependent on the precision of preoperative planning and subsequently matched the precision of the navigation device. Alignment was performed regularly during surgery using exposed anatomic landmarks such as the spinous process. Subjective precision on the part of the surgeon was reported to be <2 mm. In all cases, the additional guidance by AR was perceived as helpful by the surgeon. A subjective time advantage was assessed as “insignificant” in all cases.

**DISCUSSION**

AR is a new technology that could improve the workflow of the MIS-TLIF procedure and offers many further potential applications.

AR is currently available in 2 main systems: either on a head-mounted display or through integration with the surgical microscope. The 2 systems have different implementations and can be used together. One of the main uses of head-mounted AR displays in spinal surgery are the placement of implants such as pedicle screws. Head-mounted AR displays are limited to procedures where no surgical microscope is utilized since current models do not allow significant magnification of the surgical field or seamless introduction of the surgical microscope. When a procedure requires microscopic magnification and illumination (such as in tubular MIS surgery), head-mounted displays are limited and therefore microscope-based AR displays are utilized.

Besides these points, this technology has potential for other applications. Examples include resection of tumors and the optimization of workflow for highly standardized procedures such as shown here with TLIF.

Thereby AR should not be seen as a way to replace the established 3D navigation, it should be considered as an add-on technique for the 3D navigation to improve the intraoperative workflow.

Intraoperatively, this technique could help to identify the correct anatomical landmarks by highlighting them. This could be particularly helpful in MIS techniques with a narrow field of view such as the MIS-TLIF or in patients with severe degenerative changes and difficult anatomical conditions. In a typical MIS-TLIF, a surgeon must verify the location of anatomical landmarks within the surgical field of view using a navigated pointer and 3D navigation. Each time a surgical landmark is verified, the procedure must be paused, and the workflow interrupted. AR could help to improve the workflow of the surgery by highlighting the anatomical structures displayed in the microscope during the procedure removing the need to interrupt the surgery to verify the actual anatomy using a navigated pointer and 3D navigation. Additionally, the increased ease of finding the anatomical landmarks could help in making the surgery less demanding and less fatiguing for the surgeon, thus increasing the comfort for the surgeon and at the same time helping to minimize fatigue-related errors.

AR has other potential applications in areas including surgical education and training. By selectively highlighting relevant structures, complex anatomical constellations could be displayed more clearly, which could facilitate learning and improve the performance of surgeons in training. In addition, critical structures such as nerves or blood vessels could also be highlighted, which enables less experienced surgeons avoid to errors or complications. One other application of AR in surgical training would also be to highlight the next surgical steps by marking the appropriate anatomical landmarks. This allows the surgeon to dedicate additional attention to the actual anatomy and preparation during training. Moreover, the risk of skipping a surgical step is minimized. This contemporary technique when used on anatomical training models, cadavers as well as in live surgery has the potential to facilitate the familiarization of a complex surgical procedure and improve the learning curve. In addition, the existing global digital network would allow this technology to be used in training independent of their physical location, increasing access, and opening up a whole new field of surgical education and training.
Considering our results and the discussion above, there are many arguments in favor of the use of AR and its integration in MIS-TLIF. The planning of the procedure can take place in advance as part of the regular preoperative review of radiological imaging and does not delay the duration of the procedure. In comparison to a TLIF with navigation, the use of AR requires 2 additional steps be integrated into the procedure, the fusion of the preoperative planning CT with the intraoperative navigation CT and the calibration of the microscope to the navigation system. The image fusion is performed directly on the Brainlab Curve, the same hardware used for navigation, eliminating the need for an additional device in the OR. In our evaluation, the duration of the image fusion between the planning CT scan and the intraoperative CT scan was around 5 min although the duration of the image fusion step depends on the data size of the scan and the version of the Brainlab hardware being used. Additionally, the image fusion and calculations involved are performed in a manner that does not interrupt the use of the navigation feature of the device and this led to practically no delay in the surgical procedure. The planning of the surgical approach for the implantation of pedicle screws could take place without limitation, and digital image fusion was performed during the time in which the surgical approach for pedicle screws was performed. The second additional step, and actually the only one to alter the workflow, is the calibration of the microscope to the patient's position. As described, this requires the microscope to be shortly focused on the patient array and the navigation system is calibrated to the microscope. This step took an average of 103 ± 22 seconds in our evaluation and was not a significant delay in terms of the total operation time. The overall procedure time of a tubular MIS-TLIF in the literature is reported between 138.3 ± 33.3 and 210.6 ± 11.93 minutes. Our case series demonstrated an average procedure time of 160.6 ± 31.9 minutes, suggesting that our AR-integrated workflow does not cause a relevant delay of the procedure. However, our current study model does not allow us to determine the impact the use of AR has on duration of MIS-TLIF. The purpose of the current study was to develop an effective protocol for the reproducible application of AR for the MIS-TLIF. A prospective randomized trial, ideally involving multiple surgical centers, needs to be conducted to assess the actual benefit.

When implementing the presented workflow in a new center, our experience estimates a learning curve of around 10 cases to become familiar with the technology, the planning software, and workflow steps, depending on the center's experience with intraoperative navigation. Since this is the first description of this procedural protocol, it has not been implemented yet in other sites. Teaching hospitals may especially benefit from our workflow for young surgeons in training, in order to better familiarize them with the anatomy given the limited visualization through the MIS approach.

We set out to identify an efficient workflow for MIS-TLIF with AR and assess its practicality and reproducibility. This first attempt was successful. The small size of our cohort limits the strength of our conclusions and their generalizability. While we observed encouraging results, larger, multicenter trials will be needed to draw strong conclusions. In addition, AR remains relatively new and is subject to a significant learning curve. The learning curve for AR involves both the planning of the structures on the preoperative CT and the actual use during surgery. In the future automatic identification of landmarks by artificial intelligence could help automatizing the procedure, but the technology not yet advanced enough to provide this capability. Since our results are the first cases operated using our protocol, we were presumably still within the learning curve. For this reason, our results should still be viewed with this limitation. MIS-TLIF also has a significant learning curve however our study surgeon is a highly experienced surgeon using MIS-TLIF technique. It is possible that the benefit of the system is particularly significant for surgeons who are not yet so experienced, since the orientation, which is particularly difficult at the beginning, is facilitated. In order to be able to discuss this in a more differentiated way, studies with a larger number of cases and separate evaluations of surgeons with different levels of experience are necessary; this exceeds the limits of our evaluation.

Another limitation of our study is that comparatively few cases of level L5/S1 were included. In the literature, levels L4/L5 and L5/S1 are reported as the most common levels for TLIF, which probably corresponds to the personal experience of most surgeons. In our case series, level L4/L5 is the most common, however, level L5/S1 is considerably less represented. Given that level L5/S1 is surgically comparatively challenging to operate on, this might have potentially biased the procedure-specific data. We believe this limitation occurred due to the comparatively small sample size of our study. This can facilitate overrepresentation or underrepresentation, as in our case for level L5/S1. However, we believe that the technique we describe could support the surgeon and facilitate orientation during MIS-TLIF cases, particularly for the more challenging level L5/S1. Whether this is actually the case has to be verified in further studies with a larger number of cases.

Additionally, it is technically difficult to evaluate the actual
advantage that is provided by AR support. The surgeon's subjective assessment if AR facilitates the procedure was evaluated by questionnaire after each procedure, but this assessment is only subjective and not objective data. To overcome this limitation various scoring systems were developed from other fields, such as aviation, that attempt to objectify the subjective parameter of workload and mental and physical demand. However, in order to use these scoring systems in a valid manner to quantify the actual advantage of AR, ideally a randomized prospective comparison study with a control group without AR support is should be performed. Additionally, the benefit of the implementation of our workflow for the subgroup of surgeons in training should be evaluated with an own study, since this group may particularly benefit from this technology.

CONCLUSION

AR is a new technology with many promising applications reaching far beyond implant placement in spine. The MIS-TLIF procedure is particularly suitable to be supported by AR, as it is a procedure that is highly reliant on accurately recognizing anatomic landmarks. Our AR protocol for MIS-TLIF shows a possible application of AR to facilitate the workflow. AR implementation can be accomplished in parallel without a delay of the procedure. In the future AI software may be able to automatically identify and mark the relevant landmarks for TLIF.

Additionally, AR offers a new approach for teaching and training of surgeons in spine models and also in live surgery. Since there is a movement towards facilitating teaching and training especially in MISS, AR could potentially gain importance in this field in the future. Future studies should focus on evaluating the efficiency of this technique.

NOTES

Conflict of Interest: Roger Härtl is a consultant for Ulrich, Brainlab, DePuy-Synthes and has royalties from Zimmer. Dr. Sommer received speaker fees from Baxter. All other authors have no relevant financial interests that relate to the research described in this paper.

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ORCID

Fabian Sommer: 0000-0002-6284-7042
Franziska A. Schmidt: 0000-0002-4237-0910
Pravesh Shankar Gadjradj: 0000-0001-9672-4238
Roger Härtl: 0000-0003-2442-8944

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Posterior Apophyseal Ring Fracture in Adult Lumbar Disc Herniation: An 8-Year Experience in Minimally Invasive Surgical Management of 48 Cases

Shuo Yuan*, Qichao Wu*, Lei Zang, Ning Fan, Peng Du, Aobo Wang, Tianyi Wang, Fangda Si, Jian Li, Xiaochuan Kong

Department of Orthopedics, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

Objective: Posterior apophyseal ring fracture (PARF) is an uncommon disorder that is usually accompanied by lumbar disc herniation (LDH). The aim of this study is to describe the 8-year experience of performing minimally invasive treatment of PARF, giving particular attention to surgical technique and clinical outcome.

Methods: We reviewed 1,324 consecutive patients with LDH seen in our department between 2013 and 2020. Forty-eight patients (3.63%) were enrolled who were diagnosed with PARF associated with LDH and underwent transforminal endoscopic lumbar discectomy (TELD). Mean duration of the final postoperative follow-up was 5.1 years. The control group was comprised of 50 patients diagnosed with LDH without PARF at the same facility. Data on clinical outcomes were analyzed.

Results: The mean operation time in the PARF group was 105.4 minutes, which was longer than the mean operation time of the control group (83.9 minutes) (p = 0.001). Surgical complications, including dural tears (6.3%) and surgical instrument rupture (4.2%) were more common in the PARF group (p = 0.025). However, there was no significant difference in the proportion of excellent and good results and recurrence rates between the LDH patients with and those without PARF, respectively.

Conclusion: TELD is a safe and effective minimally invasive approach for the treatment of PARF. However, minimally invasive techniques may require longer operation time and steeper learning curve for inexperienced surgeons. The separation and removal of bone fragments, a key step in the procedure, requires patience and care to prevent rupture, residual surgical instruments, and leakage of cerebrospinal fluid.

Keywords: Apophysis fracture, Disc herniation, Clinical outcome, Percutaneous endoscopic lumbar discectomy, Microsurgery

INTRODUCTION

Lumbar posterior apophyseal ring fracture (PARF) is an uncommon disorder first described by Meyenburg in 1946, that occurs predominantly in adolescents, especially young athletes. The lesion is characterized by the separation of the bony fragments at the posterior rim of the lumbar vertebral endplate, projecting into the spinal canal. In most cases, PARF is accompanied by lumbar disc herniation (LDH), resulting in low back pain and nerve compression symptoms. Due to the persistence of spinal canal compression, some authors support early surgical intervention after simple conservative treatment. Over the last 3 decades, the clinical outcome of conventional open surgery for PARF combined with LDH has been recognized. Meanwhile, some authors have reported a series of challenges encountered during open surgery, such as decisions regarding intervertebral disc removal without removal of bone fragments that have not caused symptoms, the need for fusion,
and the avoidance of dura injury.6,11,12

Recently, minimally invasive surgery has become popular and has advantages over conventional open surgery such as the preservation of the natural anatomy to the maximum extent and reduction of postoperative complications.13 Transforminal endoscopic lumbar discectomy (TELD) is an ultra-minimally invasive surgical technique, and its indications have been extended from purely inclusive disc herniation, to the removal of various types of LDH and prolapse, as well as in the expansion of foramina.14 This emerging minimally invasive surgical technique in the treatment of PARF combined with LDH encounters some of the same challenges as open surgery in these patients.6,7 Therefore, there is a learning curve for inexperienced surgeons. However, there is scant literature on the clinical outcomes and management experience of performing minimally invasive treatment for PARF patients.

The aim of this study was to compare the treatment and outcomes in patients with PARF combined with LDH and those with LDH without PARF. In a series of 1,324 consecutive LDHs seen in our department, 48 patients underwent TELD for PARF accompanied by LDH. The control group was comprised of 50 patients diagnosed with LDH without PARF at the same facility.

MATERIALS AND METHODS

1. Patient Population

The study was approved by the Ethics Committee of Beijing Chaoyang Hospital (registration number: 2021-KE-25) and the research was performed in accordance with the guidelines of the Declaration of Helsinki. Through medical records, we identified 48 patients with PARF associated with LDH who underwent TELD in our department of orthopedics between January 2013 and December 2019. These patients were considered as the PARF group. Between January and June 2015, we treated 50 consecutive LDH patients without PARF; these were considered as the control group. Before surgery, conservative treatment was recommended, including bed rest and cobamamide injections. All patients were older than 18 years, and patients with a history of spondylolysis, spinal infection, severe spinal stenosis, tumors, or systemic diseases that affect the bone or joint were excluded. Patients with PARF occurring simultaneously in the upper and lower endplates or multiple spinal segments were excluded.

2. Operative Technique

For the TELD procedure, the patient was placed prone, and the entry point of the assumed approach was 12 to 14 cm lateral to the vertebral body. The surgical procedure involved the following steps:

- **Intraoperative location and surgical procedure.** (A, B) Posteroanterior and lateral radiographs obtained to determine intraoperative positioning. (C) Exposed prominent fragment. (D, E) Fragments being extracted. (F) Sufficient decompression of the traversing nerve root was ensured. (G) Bone removed. (H) Nucleus pulposus removed.

Fig. 1. Intraoperative location and surgical procedure. (A, B) Posteroanterior and lateral radiographs obtained to determine intraoperative positioning. (C) Exposed prominent fragment. (D, E) Fragments being extracted. (F) Sufficient decompression of the traversing nerve root was ensured. (G) Bone removed. (H) Nucleus pulposus removed.
to the midline of the spine at the affected intervertebral level. A guidewire was docked onto the targeted segment. The paravertebral muscles were dissected using serial cannulated dilators, 5-g/L lidocaine was used for infiltration and anesthesia around the facet, and a tubular retractor with an outer diameter of 7.5 mm was placed (Fig. 1A, B). Next, if the intervertebral foramen did not provide adequate surgical access to the spinal canal, burrs were used to further enlarge the opening. Under direct vision, decompression was performed using constant irrigation. The herniated disc and bone fragments were completely resected using a rongeur (Fig. 1C–H), and the mobile fragment around the nerve root was removed using a curette. If necessary, the bone could be crushed using a rongeur and then removed. Bipolar electrocoagulation was applied to promote hemostasis during operation. In addition, hemostatic gauze and gelatin sponge can be used to stanch the bleeding by compressing oozing bony surfaces. A wound drain can be placed as necessary to prevent postoperative hematoma. After irrigation and hemostasis, the surgical wounds were sutured in an anatomical order. Representative cases are presented in Fig. 2.

3. Come Assessment
The following general parameters were recorded for both patient groups: sex, age, levels of disc herniation, symptoms, history of trauma, preoperative neurological deficit, and duration of symptoms. We reviewed the medical records for operation duration, first ambulation time, complications, and the rate of recurrent LDH. Clinical outcomes were defined as excellent, good, fair, and poor according to the modified MacNab criteria.15 Statistical evaluation of clinical outcomes at the last follow-up was performed.

4. Data Analysis
Statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Data are shown as mean ± standard deviation. Paired-samples t-tests were used for continuous variables, and the chi-square test and Fisher exact test were used for categorical variables. Statistical significance was set at p < 0.05.

RESULTS
The patient characteristics in the PARF group are summarized in Table 1. A total of 48 adult patients diagnosed with PARF associated with LDH who underwent TELD were included in this study (38 [79.2%] men, 10 [20.8%] women). Mean duration of the final postoperative follow-up was 5.1 years (range, 2.2–8.6 years). The average age was 38.7 years (range, 18–57 years). There
was a clear history of trauma in 7 patients (14.6%) attributed to weight lifting and falls. It should be noted that trauma that is not directly related to PARF, and sedentary fatigue is not included in the statistics.

The average duration of symptoms was 12.7 months (range, 0.5–38 months). The predominant symptom was leg pain in 42 patients (87.5%) and lower back pain in 6 patients (12.5%). There were 39 (81.3%) PARF patients without normal preoperative neurological examinations, 8 patients (16.7%) showed decreased muscle strength of the lower limbs and shallow hypoesthesia, 4 patients (8.3%) showed asymmetric tendon reflexes, and 1 patient (2.1%) had cauda equina syndrome.

Computed tomography (CT) images were reviewed to classify PARF into 4 types according to the Takata’ classification (Fig. 3).16 The most common category was type II (43.8%), followed by type I (33.3%), and type III (22.9%) (Table 2). Our department has not treated a patient with type IV PARF. The most frequently involved site of PARF disease was the lower endplate of the L5 vertebral body (39.6%). All apophyseal ring fractures were at the same level as disc herniations. Forty-two cases (87.5%)...
Table 3. Clinical outcome in patients with or without PARF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With PARF (n = 48)</th>
<th>Without PARF (n = 50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation duration (mins)</td>
<td>105.4 ± 28.8</td>
<td>83.9 ± 19.5</td>
<td>0.001</td>
</tr>
<tr>
<td>First ambulation time (hr)</td>
<td>18.6 ± 3.5</td>
<td>16.0 ± 4.7</td>
<td>0.152</td>
</tr>
<tr>
<td>Effect of op on back pain</td>
<td></td>
<td></td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Excellent</td>
<td>4 (66.7)</td>
<td>5 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1 (16.7)</td>
<td>2 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Effect of op on leg pain</td>
<td></td>
<td></td>
<td>0.422</td>
</tr>
<tr>
<td>Excellent</td>
<td>31 (73.8)</td>
<td>36 (83.7)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>5 (11.9)</td>
<td>2 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>6 (14.3)</td>
<td>5 (11.6)</td>
<td></td>
</tr>
<tr>
<td>Postop outcome</td>
<td></td>
<td></td>
<td>0.851</td>
</tr>
<tr>
<td>Excellent</td>
<td>33 (68.8)</td>
<td>38 (76.0)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>8 (16.7)</td>
<td>7 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>6 (12.5)</td>
<td>4 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1 (2.1)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>Dural tear</td>
<td>3 (6.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Surgical instrument rupture</td>
<td>2 (4.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Recurrent LDH</td>
<td>2 (4.2)</td>
<td>3 (6.0)</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%). PARF, posterior apophyseal ring fracture; LDH, lumbar disc herniation.

had herniated discs located on the lateral side, and 6 cases (12.5%) had a central disc herniation. The number of small PARF was 26 (54.2%) and the number of large PARF was 22 (45.8%) (small or large, defined by 50% width of spinal canal). Clinical outcomes are summarized in Table 3. Thirty-three patients (68.8%) had excellent results, 8 (16.7%) had good results, 6 (12.5%) had fair results, and 1 (2.1%) demonstrated poor results. Postoperative CT scans were performed in all 48 PARF patients, and the results showed that intact bone fragments were removed in 45 cases (93.8%). In the remaining 3 cases (6.2%), decompression around the nerve root was adequate, although complete bone fragments were not removed. The mean operation time in the PARF group was 105.4 minutes (range, 75–135 minutes), which was longer than the control group (83.9 minutes; range, 65–105 minutes) (p < 0.05). In 2 patients (4.2%), we experienced surgical instrument rupture during the operation, but there were no residual instruments. Three patients (6.3%) experienced dural tears during surgery, and one of them required intraoperative repair due to cerebrospinal fluid leakage.

Recurrence developed in 2 patients (4.2%); both required reoperation at the same level (at 5 months and 2 years, respectively).

**DISCUSSION**

PARF is an uncommon disorder that is usually accompanied by LDH. Conventional open surgery was frequently recommended for PARF over the past 3 decades, with excellent and good rates of 85% to 97%. However, open surgery can cause greater trauma and loss of lumbar mobility, which is not conducive to the young population in which PARF is most common. TELD is an ultra-minimally invasive surgical technique. We reviewed our experience of the last 7 years of using TELD for the treatment of PARF, and found a good or excellent outcome in 85.4% of 48 patients. In addition, we found an average first ambulation time of 18.6 hours, and 35 patients (72.9%) returned to work within 2 months postoperatively. Although minimally invasive surgery has proven to be more advantageous than conventional open surgery in terms of maximal preservation of natural anatomy, these advancements require a longer learning curve for inexperienced surgeons. There are several issues of concern, including indications, decisions regarding apophyseal fragment removal, surgical approach, and complications.

Surgical indications for PARF remain controversial. Most authors support the necessity for surgical intervention for PARF with neurological deficits. Most of the controversy concerns whether PARF without neurological deficits (only low back pain and/or leg pain) requires surgery. Asazuma et al. and Bae et al. found that conservative treatment is ineffective in many cases with the evolution of chronic low back pain, and recommended surgical treatment. However, Krishnan et al. reported that among 19 patients without neurological deficits, 12 responded well to conservative treatment, and only 7 cases required surgical treatment. Chang et al. reported that 3 of 12 patients without neurological deficits had poor outcomes during conservative treatment. We believe that the above literature highlights the need for surgery in the background of the widespread popularity of open surgery in past years. In such scenarios, some authors may have preferred conservative treatment in order to avoid the shortcomings of open surgery such as large trauma to the anatomy, slow recovery, and loss of lumbar mobility. The authors of the present study suggest that the bone fragment clearly participates in pathogenic factors, and the rapid recovery seen in minimally invasive surgery can be partially attributed to the prevention of recurring symptoms and prolonged chronic pain that may have resulted if pathogenic fac-
tors were not removed.

Of concern is whether minimally invasive TELD can be used to remove large bone fragments, and whether the size of bone fragments is a factor in choosing minimally invasive or open surgery. In our study, 22 cases (54.2%) of large PARF were included, and the excellent and good rates were not significantly different from those with small PARF. Moreover, Matsumoto et al. reported that microendoscopic discectomy, another minimally invasive technique, can also complete the resection of a large PARF. There are 2 reasons why minimally invasive surgery can remove a large PARF: (1) in minimally invasive surgical procedures, large bone fragments are usually gradually removed by rongeurs and blue forceps bit by bit and not necessarily to preserve the integrity of the bone fragment; (2) a report of CT axial scans of patients with PARF showed that the bones are usually in strips, and the left and right diameters are significantly larger than the anterior and posterior diameters. In view of this situation, if the bone block is found to be unstable during the operation, the block can be removed along the direction of the tubular retractor. Therefore, the authors believe that the size of PARF should not be used as a factor in selecting the appropriate surgical procedure. However, multi-segment PARF and severe spinal stenosis are indications for open surgery.

A related issue is the consideration of complete removal of the bone fragment. In our study, partial PARF resection was performed in 13 patients (27.1%) with an excellent and good rate of 92.3%, and total resection was performed in 35 patients (72.9%), with an excellent and good rate of 94.2%. In addition, in a randomized controlled study with a mean follow-up of 4.3 years, Shirado et al. found that bone fragment resection did not affect clinical outcomes. However, most authors advocate that bone fragments should be completely removed, and the clinical results of several studies were satisfactory. The authors of the present study believe that the size of the bone fragment should not be a factor in choosing the appropriate surgical procedure. However, multi-segment PARF and severe spinal stenosis are indications for open surgery.

The main complications of minimally invasive treatment of PARF include dural tear, nerve root injury, surgical instrument rupture, postoperative infection, and recurrence. In our study, 3 patients (6.3%) developed dural tear, 2 patients (4.2%) developed recurrent LDH, and surgical instrument rupture occurred in 2 patients (4.2%). In studies reporting the results of open surgery for PARF, dural tear occurred in 1.2% to 7.4% of patients, and recurrent LDH occurred in 4.6% to 12.7% of patients. The complication rates of these reports and our report are similar. However, in minimally invasive treatment of PARF, surgical instrument rupture and dural tears are more common than in the treatment of pure LDH. This is because the fine micro rongeurs are easy to rupture or even remain when the hard bones are clamped roughly. Therefore, it is important to try the hardness of the bone block during the first clamp. If the texture is found to be hard, then you need to bite off the bone block bit by bit patiently from the surrounding area. In addition, the path-
ological changes of PARF are complex and slow, the spinal dura mater and nerves are compressed for a long time, and local inflammation causes scar adhesion, which may be the main reason why PARF is more common than dural tears in pure LDH. Moreover, we recommend removing the herniated disc first, and then “biting off” the bone that compresses the nerve root. After the herniated disc is removed, the nerve tension is reduced, which can avoid the complications of nerve injury caused by excessive nerve traction. Thus, the separation and removal of bone fragments, which is a key step in the procedure, requires patience and care.

The current study had several limitations. First, although PARF is divided into 4 types, there is no authoritative region division based on the prominent position of the bone block, which is a very important consideration for the choice of surgical approach. Investigation of this concept requires the support of multicenter, large sample, and long-term follow-up outcome studies. Second, patients in our center with PARF at multiple levels underwent open surgery and were not included in this study; their treatment plan needs to be supported by further study outcomes. Finally, further studies are necessary to better understand the pathoanatomy and pathophysiology of this disease.

CONCLUSION

In summary, our findings show that TELD is a safe and effective minimally invasive approach for the treatment of PARF with LDH. Minimally invasive surgery may require a longer learning curve for inexperienced surgeons. The authors hope that this study will provide valuable insights into minimally invasive techniques for the treatment of PARF.

NOTES

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Author Contributions: Conceptualization: LZ; methodology: QW and SY; formal analysis and investigation: SY, NF and PD; writing—original draft preparation: QW and AW; writing—review and editing: TW, FS, JL and QW; funding acquisition: LZ; resources: LZ; supervision: JL and XK.

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Surgeons Learning Curve of Transforaminal Endoscopic Discectomy for Sciatica

Pravesh S. Gadjradj1,2, Arnold Vreeling3, Paul R. Depauw4, Pieter J. Schutte5, Biswadjiet S. Harhangi2,6; on behalf of the PTED-Study Group

1Department of Neurological Surgery, Weill Cornell Brain and Spine Center, New York, NY, USA
2Department of Neurosurgery, Park Medical Center, Rotterdam, The Netherlands
3Department of Orthopedic Surgery, Rijnstate Ziekenhuis, Arnhem, The Netherlands
4Department of Neurosurgery, Elisabeth-TweeSteden Ziekenhuis, Tilburg, The Netherlands
5Department of Neurosurgery, Alrijne Ziekenhuis, Leiderdorp, The Netherlands
6Department of Neurosurgery, Erasmus Medical Center, Rotterdam, The Netherlands

Objective: Full-endoscopic spine surgery is gaining interest as a less-invasive alternative to treat sciatica caused by a lumbar disc herniation. Concerns, however, exist with the learning curve as percutaneous transforaminal endoscopic discectomy (PTED) appears to be more difficult to be performed compared to other techniques. In this study, the clinical outcomes during and after the learning curve are presented of 3 surgeons naïve to PTED.

Methods: In the first phase of a randomized controlled, noninferiority trial comparing PTED with microdiscectomy, 3 surgeons were trained in the PTED-procedure by a senior surgeon. After performing up to 20 cases under supervision, they started performing PTED on their own. Results of the early cases were compared to the later cases (>20). Furthermore, complications and reoperations were compared. Finally, differences in clinical outcomes between surgeons were compared.

Results: At 12 months of follow-up, 87% of the patients had follow-up data available. In general, there were no significant differences in patient-reported outcomes between the early and later PTED cases. Furthermore, outcomes of the early PTED cases were comparable to the outcomes of microdiscectomy, while the later PTED cases had small, but more favorable outcomes compared to microdiscectomy. Two learning curve surgeons had substantially higher rates of reoperations within 1 year, compared to the senior surgeon or the microdiscectomy group. Duration of surgery was also longer for all learning curve surgeons. Finally, when comparing clinical outcomes of patients undergoing PTED versus microdiscectomy, there appears to be some statistically significant differences in outcomes compared between the senior and 3 learning curve surgeons.

Conclusion: PTED appears to be safe to be adopted by surgeons naïve to the procedure when they are initially supervised by an experienced senior surgeon. Duration of surgery and risk of repeated surgery are increased during the learning curve, but patient-reported outcomes of the early PTED cases are similar to the outcomes of later PTED cases, and similar to the outcomes of microdiscectomy cases. This study underlines the need for an experienced mentor for surgeons to safely adopt PTED.

Keywords: Lumbar disc herniation, Endoscopic discectomy, Sciatica, Randomized controlled trial

INTRODUCTION

Full-endoscopic spine surgery is gaining interest as a less-invasive alternative to treat sciatica caused by a lumbar disc herniation.1,4 An important limitation of these procedures is that they appear to be more difficult to learn than other techniques.5,7
Especially so for percutaneous transforaminal endoscopic discectomy (PTED) which is a full-endoscopic technique, which removes the disc herniation trough the neuroforamen. This procedure does not only require the surgeon to operate through an endoscopic, but also from a far lateral position which is an unfamiliar approach for most surgeons.

Recently, we published the results of a randomized controlled trial (RCT) showing noninferiority in leg pain reduction of PTED compared to microdiscectomy in treating sciatica. Furthermore, we showed that PTED appeared to be more cost-effective than microdiscectomy from societal perspective. As these results warrant implementation of PTED as a less-invasive treatment option for sciatica, studies exploring the safety and clinical outcomes of patients during the learning curve are needed. In the beginning phase of our RCT, 3 spine surgeons were trained in performing PTED. In this paper, we present the results of the learning curve analyses.

**MATERIALS AND METHODS**

1. **Trial Design**
   A multicenter, noninferiority, RCT was conducted at 4 general hospitals in the Netherlands among patients with sciatica caused by lumbar disc herniation. Details of the protocol and study design have been published previously. The study was funded by ZonMw, The Netherlands Organization for Health Research and Development. The trial was initiated and performed without involvements of the industry. The research protocol was approved by the research ethics board of all participating hospitals. All patients provided written informed consent prior to enrollment. The trial was registered at ClinicalTrials.gov (NCT02602093).

2. **Enrollment and Randomization**
   From February 2016 to April 2019 patients were screened and enrolled by spine surgeons. Patients were eligible for the PTED-study if they were between 18 to 70 years of age; had more than 6 weeks of excessive radiating pain and no tendency for any clinical improvement; had an indication for surgery; had no previous surgery on the same or adjacent disc level; cauda equina syndrome; spondyloytic or degenerative spondylolisthesis; pregnancy; severe comorbid medical or psychiatric disorder (American Society of Anesthesiologists physical status classification > II); severe caudal or cranial sequestration of disc fragments; contraindication for surgery and moving abroad on short notice.

   Patients were randomized in a 1:1 ratio to PTED or microdiscectomy using computer-generated variable block sizes (4, 6, or 8), stratified by enrolling center. Blinding of patients was not feasible because of the substantial differences between both procedures (e.g., PTED having an 8-mm incision lateral of the spine and microdiscectomy having an incision of 2–5 cm dorsal of the spine in the midline).

3. **Learning Curve Procedure**
   All trial surgeons were spine-dedicated surgeons who had 8 to 11 years of experience in performing degenerative lumbar surgery. Before the trial, only one of the participating spine surgeons was proficient in performing PTED in the Netherlands. During this study, 3 surgeons (one per center) were trained in performing PTED. Each surgeon attended a hands-on cadaveric workshop on PTED. Afterwards they performed 10 to 20 procedures under supervision of the senior surgeon. Afterwards, they would perform PTED on their own. Based on an educated guess, we assumed the learning curve would take 50 cases per surgeon.

4. **Interventions**
   1) **PTED**
      The full procedure has been published previously. Local anesthesia was administered. An incision was made just above the dorsolateral side of the pelvis, where a needle was set from the incision to the superior articular process of the lower involved vertebrae of the herniated disc. After the needle had reached the superior articular process, a guidewire was inserted. Subsequently conical rods were introduced followed by a drill to enlarge the neuroforamen. Hereafter, an endoscope was introduced within the working channel using an 8-mm cannula. A forceps was used to remove the disc fragments. Patients were treated on an outpatient basis.

   2) **Microdiscectomy**
      Microdiscectomy was conducted under general anesthesia. The use of loupe or microscope magnification was optional. A paramedian incision was performed. Following the identification of the lamina, the ligamentum flavum was removed to identify the nerve root and disc herniation. Laminotomy, as well as...
foraminotomy, was performed, if necessary. For foraminal herniated discs a partial medial facetectomy was performed while for extraforaminal herniated discs, a parafacetal approach was used. Patients were discharged as soon as medically responsible, which was usually one day after surgery.

5. Outcome Measures and Statistical Analysis

A complete overview of the patient-reported outcome measures (PROMs) measured during the PTED-study, along with the statistical analysis plan, have been published elsewhere.\textsuperscript{2,11} In brief, the PTED-study was a RCT which established the non-inferiority of PTED in leg pain reduction compared to microdiscectomy. The sample size was set at 682 patients and included 150 learning curve cases which were matched with 150 microdiscectomy cases. The PTED learning curve cases were excluded for the primary analysis.

The primary outcome was the visual analogue scale (VAS) for leg pain, measuring leg pain from a 0 to 100 scale.\textsuperscript{14} Other outcomes were the Oswestry Disability Index (ODI), the VAS for back pain, VAS for quality of life, the 36-item Short Form Health Survey and 7-point Likert scales on recovery and satisfaction.\textsuperscript{15,16} Means and standard deviations were used to present the PROMs, or percentages with odds ratios (ORs) when appropriate. Early cases (first 20) and later PTED cases ( > 20) were compared using linear or logistic regression analyses. The learning curve in terms of duration of surgery, was visualized by creating scatter plots and basic control charts. Finally, differences in PROMs between surgeons, were assessed using subgroup analyses. Differences were tested using interaction p-values. Differences were expressed in 95% confidence intervals (CIs). A p-value lower than 0.05 showed statistical significance, while for the exploratory subgroup analyses a p-value lower than 0.0125 was considered to be statistically significant. The basic control chart was created using Microsoft Excel, while all other analyses were conducted with IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).

Fig. 1. Flowchart with an overview of the enrollment and follow-up during the PTED-study. PTED, percutaneous transforaminal endoscopic discectomy; LDH, lumbar disc herniation.
RESULTS

1. Patients

A total of 711 patients were screened for eligibility between February 2016 and April 2019. Of these, 613 were randomized to either microdiscectomy (N = 309) or PTED (N = 304). At 12 months after surgery, 87% of the patients had outcome data available (Fig. 1). Of the patients assigned to PTED, 143 (47.0%) were assigned to the senior surgeon, 86 (28.3%) to LC surgeon 1, 32 (10.5%) to LC surgeon 2, and 43 (14.1%) to LC surgeon 3.

Table 1 gives an overview of surgeon characteristics and baseline demographics of the patients. In general, baseline demographics such as age, body mass index, duration of sciatica, paid employment, level of disc herniation and the PROMs were comparable between groups. Some differences between groups appear in gender, smoking status, and preference for PTED.

2. Surgical Outcomes

Fig. 2 gives an overview of the surgical learning curve per surgeon through scatter plots and basic control charts. LC surgeon 1 appears to have a stable duration of surgery throughout the cases with 2 clear outliers, both caused by cases during which

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Table 1. Baseline demographics of the patients and the surgeons performing PTED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTED</th>
<th>Microdiscectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Senior surgeon</td>
<td>LC surgeon 1</td>
</tr>
<tr>
<td>Tenure (yr)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Amount of PTEDs performed (n)</td>
<td>&gt; 200</td>
<td>0</td>
</tr>
<tr>
<td>Expected learning curve (n)</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>No. of patients</td>
<td>143</td>
<td>86</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45.5 ± 12.6</td>
<td>45.4 ± 11.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>76 (53.1)</td>
<td>50 (58.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>31 (21.7)</td>
<td>27 (31.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.4 ± 3.7</td>
<td>26.6 ± 4.7</td>
</tr>
<tr>
<td>Paid employment</td>
<td>118 (82.5)</td>
<td>73 (84.9)</td>
</tr>
<tr>
<td>Duration of sciatica (mo)</td>
<td>4.2 ± 3.0</td>
<td>4.4 ± 3.1</td>
</tr>
<tr>
<td>Radiating pain in the right leg</td>
<td>66 (46.2)</td>
<td>46 (53.5)</td>
</tr>
<tr>
<td>Level of disk herniation causing sciatica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L2–3</td>
<td>1 (0.7)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>L3–4</td>
<td>10 (7.0)</td>
<td>13 (15.1)</td>
</tr>
<tr>
<td>L4–5</td>
<td>55 (38.5)</td>
<td>37 (43.0)</td>
</tr>
<tr>
<td>L5–6</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>L5–S1</td>
<td>76 (53.1)</td>
<td>35 (40.7)</td>
</tr>
<tr>
<td>L6–S1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Score on the VSA of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg pain</td>
<td>68.7 ± 20.4</td>
<td>70.4 ± 22.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>50.5 ± 27.3</td>
<td>49.7 ± 30.4</td>
</tr>
<tr>
<td>Oswestry Disability Index</td>
<td>45.5 ± 16.7</td>
<td>45.0 ± 15.9</td>
</tr>
<tr>
<td>Score on the VSA of general health</td>
<td>45.9 ± 20.3</td>
<td>48.2 ± 21.6</td>
</tr>
<tr>
<td>SF-36 physical component summary</td>
<td>30.0 ± 7.7</td>
<td>30.8 ± 6.6</td>
</tr>
<tr>
<td>SF-36 mental component summary</td>
<td>47.2 ± 10.9</td>
<td>46.8 ± 11.1</td>
</tr>
<tr>
<td>Preference for PTED (%)</td>
<td>86.0</td>
<td>77.9</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation unless otherwise indicated.
PTED, percutaneous transforaminal endoscopic discectomy; LC, learning curve; ODI, Oswestry Disability Index; VAS, visual analogue scale; QoL, quality of life; SF-36, 36-item Short Form Health Survey.

One patient in the microdiscectomy group had missing scores on the ODI, VAS for QoL and back pain, and SF-36 at baseline.
Table 2. Surgical outcomes of all cases stratified per surgeon

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTED</th>
<th>Microdiscectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Senior surgeon</td>
<td>LC surgeon 1</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>29.7 ± 11.3</td>
<td>51.5 ± 14.5*</td>
</tr>
<tr>
<td>Estimated blood loss &lt; 10 mL</td>
<td>106 (76.3)*</td>
<td>19 (61.3)*</td>
</tr>
<tr>
<td>Conversion to microdiscectomy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dural tear</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nerve root injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Repeated surgery within 1 year</td>
<td>3 (2.1)</td>
<td>15 (17.4)*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).

PTED, percutaneous transforaminal endoscopic discectomy; LC, learning curve.

*p < 0.05 between microdiscectomy and one of the senior and/or LC surgeons. 'p < 0.05 between the LC surgeon performing and the senior surgeon.

PTED was converted to microdiscectomy. LC surgeon 2 shows a trend towards a longer duration of surgery, while LC surgeon 3 shows a decrease in surgery duration. Table 2 gives an overview of surgical outcomes and complications. Duration of surgery was of statistically significant longer duration for the learning curve surgeons compared to the senior surgeon performing PTED (p < 0.001) and surgeons performing microdiscectomy (p < 0.001). Furthermore, estimated
Table 3. Patient outcomes at 12 months after surgery, divided by cases performed before or after the estimated learning curve

<table>
<thead>
<tr>
<th>Variable</th>
<th>PTED</th>
<th>Between-group difference</th>
<th>Microdiscectomy</th>
<th>Between-group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early cases</td>
<td>Later cases</td>
<td>Mean/%</td>
<td>With early cases</td>
</tr>
<tr>
<td>VAS leg pain</td>
<td>25.0 ± 31.0</td>
<td>20.7 ± 25.4</td>
<td>4.2 (-3.5 to 11.9)</td>
<td>27.0 ± 29.1</td>
</tr>
<tr>
<td>Oswestry Disability Index</td>
<td>15.6 ± 17.5</td>
<td>13.9 ± 15.4</td>
<td>1.7 (-2.8 to 6.4)</td>
<td>18.4 ± 18.8</td>
</tr>
<tr>
<td>VAS back pain</td>
<td>32.4 ± 29.8</td>
<td>24.9 ± 24.6</td>
<td>8.0 (0.5 to 15.4)</td>
<td>29.7 ± 27.7</td>
</tr>
<tr>
<td>VAS quality of life</td>
<td>71.2 ± 23.2</td>
<td>72.1 ± 19.1</td>
<td>-0.9 (-6.7 to 4.9)</td>
<td>67.0 ± 21.2</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>47.3 ± 11.3</td>
<td>48.0 ± 10.0</td>
<td>-0.7 (-3.7 to 2.3)</td>
<td>45.7 ± 10.4</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>50.1 ± 9.8</td>
<td>52.2 ± 8.0</td>
<td>-2.1 (-4.5 to 0.4)</td>
<td>50.3 ± 9.6</td>
</tr>
<tr>
<td>Recovered from symptoms</td>
<td>63.8%</td>
<td>76.0%</td>
<td>1.8 (1.0 to 3.3)</td>
<td>64.0%</td>
</tr>
<tr>
<td>Recovered from leg pain</td>
<td>69.0%</td>
<td>76.9%</td>
<td>1.5 (0.8 to 2.8)</td>
<td>69.0%</td>
</tr>
<tr>
<td>Satisfied with change in symptoms</td>
<td>62.1%</td>
<td>71.2%</td>
<td>1.5 (0.8 to 2.8)</td>
<td>61.0%</td>
</tr>
<tr>
<td>Satisfied with result of treatment</td>
<td>63.8%</td>
<td>75.1%</td>
<td>1.7 (0.9 to 3.2)</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

Mean values of continuous outcomes are described with their standard deviation. Adjusted between-group differences are shown with their 95% confidence interval (CI). For the Likert scales, proportions are shown with their adjusted odds ratio and respective 95% CI.

3. Patient-Reported Outcomes

Table 3 gives an overview of the PROMs comparing the early cases (first 20) of the LC surgeons with the later cases. Except for back pain which showed a higher VAS (8.0; 95% CI, 0.5–15.4) in favor for the later cases, there were no statistically significant differences in PROMs between the early and late cases. There were also no statistically significant differences between the early cases and the microdiscectomy group. When the microdiscectomy group was compared to the later cases, the later cases showed statistically significant more favorable outcomes in terms of leg pain reduction (-6.2; 95% CI, -11.2 to -1.3), ODI (-4.5; 95% CI, -7.7 to -1.4), back pain (-5.3; 95% CI, -10.0 to -0.6), quality of life (5.1; 95% CI, 1.7–9.1), recovery from symptoms (OR, 1.8; 95% CI, 1.2–2.6), satisfaction with change in symptoms (OR, 1.5; 95% CI, 1.1–2.3).

Fig. 3 shows the subgroup analyses comparing the PROMs of the senior surgeon and the LC surgeons, compared to the microdiscectomy group. Overall outcomes with or without the learning curve showed small differences in favor of the PTED-group on all outcomes. In general, all subgroup analyses showed a statistically significant difference between the experienced and LC surgeons on the VAS leg pain, ODI, and VAS QoL, but not the VAS back pain. Outcomes of LC surgeons 1 and 3 showed no differences between groups, while some outcomes of LC surgeon 2 and the senior surgeon showed more favorable outcomes in the PTED-group.

DISCUSSION

This study describes the clinical outcomes of the learning curve of the largest randomized study conducted on full-endoscopic versus open microdiscectomy for sciatica. This is the first study to compare the outcomes of the learning curve of PTED in multiple surgeons with the outcomes of microdiscectomy in a prospective randomized manner. For this study, 3 spine surgeons underwent training in PTED and performed their first cases under supervision of an experienced surgeon. Afterwards, they started performing PTED independently. Complications were comparable between the LC surgeons and the senior surgeons. All LC surgeons, however, had a longer duration of surgery and 2 out of 3 of the LC surgeons had a substantially higher rate of repeated surgery within 1 year of surgery. Except for back pain, clinical outcomes appear to be comparable between the early PTED cases and the later PTED cases. Moreover, clinical outcomes of the early cases, showed no sta-
Fig. 3. Subgroup analyses of the clinical outcomes of the experienced surgeon, compared to the outcomes of the 3 other surgeons during the learning curve phase. Outcomes regarding the VAS for leg pain (A), VAS for back pain (B), ODI (C), and QoL (D) are shown. PTED, percutaneous translaminar endoscopic discectomy; OM, open microdiscectomy; CI, confidence interval; VAS, visual analogue scale; ODI, Oswestry Disability Index; QoL, quality of life.

Statistically significant differences compared to the outcomes of microdiscectomy, enforcing that aside from a higher risk of repeated surgeries, surgeons naïve to PTED can achieve satisfactory PROMs during their learning curve. Results of the subgroup analysis, however, shows there is a significant heterogeneity in treatment outcomes between surgeons. It is to be no-
ticed, that most if not all statistically significant differences, may not reach established minimally clinically important difference thresholds.\(^{17,18}\)

Some previously published studies have tried to assess the surgical learning curve of full-endoscopic surgery for sciatica.\(^{5-7,19}\) In the literature, learning curves can be found consisting of 20 to 54 cases, but there is also evidence that the results may even further improve after these cases. Perhaps these first 20 to 54 cases are more considered to be a learning curve in order to achieve satisfactory results. In comparison, another retrospective study assessing the learning curve of microendoscopic decompression for lumbar spinal stenosis, showed that based on blood loss, the learning curve plateaus after the 30th case.\(^{20}\) Based on the duration of surgery, however, there seems to be a progressive reduction over 480 cases, with the biggest reduction during the first 100 cases. All of these studies, however, are retrospective analyses which mostly involved only 1 surgeon.

Some limitations have to be acknowledged. First are the limitations adherent to the PTED-study.\(^{12,21}\) First is that the study was not blinded due to the nature of both procedures. Furthermore, there was a high preference for PTED among the patients, which might have impacted the results. Nevertheless, results corrected for patient preferences appeared similar to the uncorrected results.\(^{2}\) Another limitation is the power of the post hoc subgroup analysis. Because 4 subgroup analyses were conducted, concerns on the loss of power are justified. We tried, however, to correct this by adhering a \(p\)-value of 0.0125 for the subgroup analyses. Furthermore, the PTED-study was overpowered due to the extra inclusion of controls. This increases the validity of our study results. Nevertheless, almost all subgroup analyses showed statistically significant differences which would not reach established minimum clinically important differences. An increase in statistical power would unlikely lead to other conclusions. Another limitation of this study is that we did not present results on the difficulties surgeons had while performing the procedures. For instance, median or migrated disc herniations might have been more difficult to be performed by surgeons and would result in longer durations of surgery. However, this might not be reflected in clinical outcomes as our previous study has shown.\(^{2}\)

As the study results show that learning is safe among spine surgeons, this data can be used to inform surgeons on adopting endoscopic surgery. Surgeons should be aware that in this study, 3 spine-dedicated surgeons were trained with 8 to 11 years of clinical experience and the learning curve may be different for surgeons of other tenure. Perhaps residents, who are more exposed to endoscopic surgery will be more easily able to adapt these procedures. On the other hand, experienced surgeons may find it more difficult to learn full-endoscopic procedures as it will be a new procedure they have to learn after performing other open or MIS procedures for long time periods. Another implication is for informing patients when a surgeon naïve to the procedure is performing his first cases. A longer operation duration would not necessarily affect the patients, but an increased risk for revision surgery will. Study results show that patients should be informed that their clinical outcomes may be comparable 1 year after surgery, but at the same time, they have a higher risk for undergoing a revision procedure compared to when they would undergo full-endoscopic surgery by an experienced surgeon or microdiscectomy.

**CONCLUSION**

In conclusion, PTED appears to be safe to be adopted by surgeons naïve to the procedure when they are supervised by an experienced senior surgeon. Duration of surgery and risk of repeated surgery are increased during the learning curve, but patient-reported outcomes of the early PTED cases are similar to the outcomes of later PTED cases, and to the outcomes of microdiscectomy cases. This study underlines the need for an experienced mentor for surgeons to safely adopt PTED.

**NOTES**

**Conflict of Interest:** The authors have nothing to disclose.

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**Acknowledgments:** We gratefully acknowledge the support of the Dutch Health Insurance Board, ZonMw, the participating patients, the patient organization ‘de Wervelkolom (nvvr)’, the enrolling physicians and the research nurses. The involved research nurses were Ms. Esther Willemse, Ms. Steffie van Beek, Ms. Chantal Ritskes, Ms. Monique Stuit (Park MC), Ms. Paula van Limpt (Elisabeth-TweeSteden Hospital), Ms. Moniek Vroemen, Annemiek Hol (Rijnstate Hospital), and Marjon Nuijten (LUMC, Alrijne Hospital).

**Author Contribution:** Conceptualization: PG; Data curation: PG, AV, PD, PS, BH; Formal analysis: PG, PD; Methodology: PG; Project administration: PG, AV, PD, PS; Visualization: PG; Writing - original draft: PG; Writing - review & editing: PG, BH.
REFERENCES

Comparative Analysis With Modified Inclined Technique for Posterior Endoscopic Cervical Foraminotomy in Treating Cervical Osseous Foraminal Stenosis: Radiological and Midterm Clinical Outcomes

Ji Yeon Kim1,*, Dong Hwa Heo1,*, Dong Chan Lee1, Tae Hyun Kim1, Choon Keun Park3

1Department of Neurosurgery, Spine Center, Wiltse Memorial Hospital, Anyang, Korea
2Department of Neurosurgery, Spine Center, Seoul Bumin Hospital, Seoul, Korea
3Department of Neurosurgery, Spine Center, Wiltse Memorial Hospital, Suwon, Korea

Objective: We compared the midterm clinical and radiological outcomes between 2 types of full endoscopic posterior cervical foraminotomy, including conventional posterior endoscopic cervical foraminotomy (PECF) and modified inclined technique for PECF.

Methods: One of the 2 types of PECF surgery was performed for defined cervical foraminal stenosis. The foraminal expansion ratio and facet resection rate and foraminal stenosis grade were measured using magnetic resonance imaging. Visual analogue scale (VAS) scores for neck and arm pain, neck disability index, MacNab criteria, operation time, hospital stay, and complications, including postoperative dysesthesia, were assessed. Clinical and radiological parameters were compared between the 2 surgical groups.

Results: There were 49 and 46 patients in the PECF and modified-PECF groups, respectively. The modified-PECF group showed significantly higher expansion of distal foraminal diameter and foraminal height, and a lower facet resection rate compared to PECF group (in all, p < 0.001). The modified-PECF group displayed significantly lower VAS score for neck pain at 1 day and 1 week after surgery and lower arm pain VAS score after 6-month follow-up (p = 0.002, p = 0.001, p = 0.002, respectively).

Conclusion: Compared with the PECF, the modified inclined technique has radiologic benefits, including enhanced facet joint preservation, restoration of the natural course of nerve roots, and prevention of restenosis by expanding the superior articular process base, especially in grade 2 foraminal stenosis. Furthermore, the modified inclined technique significantly improved the postoperative VAS score for neck pain within the 1-week follow-up and that of arm pain after 6-month follow-up.

Keywords: Endoscopy, Cervical vertebrae, Foraminotomy, Radiculopathy, Stenosis

INTRODUCTION

Cervical radiculopathy is a degenerative spinal disease that leads to neck and arm pain, a typical symptom of nerve root compression caused by foraminal stenosis or intervertebral disc herniation.1,2 When conservative treatment fails, surgical treatments, such as posterior cervical foraminotomy (PCF), anterior cervical discectomy with fusion, or disc replacement are considered.1,3 With the development of minimally invasive surgery, PCF has been performed using a tubular retractor or endoscop-
ic system and has shown favorable clinical outcomes with the benefit of blood loss, operating time, and hospital stay compared to open PCF surgery.\textsuperscript{4,6}

Full endoscopic PCF has shown good clinical and radiologic outcomes.\textsuperscript{7-10} Endoscopic systems offer a multi-axial viewing angle and a magnified clear endoscopic view that enable detailed bone decompression using various approaches.\textsuperscript{9,11} A recent comparative study by Kim et al.\textsuperscript{12} revealed that endoscopic PCF offered enhanced facet joint preservation and improved midterm clinical results compared to microscopic PCF. Furthermore, full endoscopy offers a safe surgical route for ventral foraminal decompression via partial pediculotomy or partial vertebrotomy, and it shows good surgical outcomes.\textsuperscript{13} We performed a full endoscopic PCF to treat osseous cervical foraminal stenosis using both pedicular-vertebrotomy techniques for ventral foraminal decompression and an inclined surgical route for improved facet joint preservation. Therefore, the objective of this retrospective study was to compare the clinical and radiological outcomes of full endoscopic PCF and modified inclined approach.

**MATERIALS AND METHODS**

**1. Study Patients**

This study was a retrospective analysis of patients who underwent 2 types of posterior endoscopic cervical foraminotomy (PECF) using a full endoscopic system to treat radiculopathy due to osseous foraminal stenosis between January 2020 and June 2021 at Wiltse Memorial Hospital. All the procedures were performed by 2 experienced spine surgeons, according to each surgeon’s preferences. One surgeon with 10 years of experience in PECF performed the foraminotomy with or without minimal pediculotomy. Another surgeon with 7 years of experience in PECF performed the foraminotomy using a modified inclined technique. All consecutive patients who met the inclusion criteria were included in this study. Physicians collected clinical and radiologic data during the follow-up period. We included all consecutive patients who met the following criteria:

1. Presence of radiculopathy symptoms in the neck, back, and arm with more than 6 weeks of failed conservative treatment.
2. Osseous foraminal stenosis was confirmed with magnetic resonance imaging (MRI) and computed tomography (CT) and was consistent with the symptoms of radiculopathy.
3. One of 2 types of PECF surgery was performed for defined foraminal stenosis at the unilateral side of a single cervical level.
4. If the operating patients had other asymptomatic foraminal lesion or had previously undergone different levels of PCF, we included.

We excluded patients if they met any of the following criteria:

1. Foraminal soft herniated disc was the primary pathology than osseous stenosis.
2. Operation history of fusion or artificial disc replacement in the cervical spinal levels.
3. Other cervical operations (discectomy, multilevel foraminotomy, decompression laminectomy, fusion, and artificial disc replacement) were performed simultaneously at different levels.
4. Accompanying segmental instability, symptomatic central stenosis, infectious disease, traumatic conditions, or musculoskeletal disorder.

**2. Surgical Procedures**

We performed PECF for osseous foraminal stenosis using 2 different techniques for bone decompression using the full endoscopic system (Fig. 1A, B). All the surgeries were performed under general endotracheal anesthesia in the prone position on a chest bar, while the flexed neck was fixed using a skin tape (Fig. 1A, B).

The conventional PECF used the interlaminar endoscopic system with an endoscope with a 12° viewing angle, an 8.4-mm outer diameter, 5.7-mm diameter working channel, and a 120-mm long endoscope (Spine Endoscope, TECHCORD, Daejeon, Korea). A 1-cm skin incision was made over the uncovertebral joint line at the target level (Fig. 1C–E). After serial dilations, the working cannula was docked on the medial border of the facet joint under image intensification. After soft tissue dissection, laminotomy was performed using a 3.5-mm endoscopic drill until the proximal and distal ends of the ligamentum flavum were exposed. Bone drilling was extended laterally until medial part thinning of the superior articular process (SAP), and extended craniodually until the border of the upper- and lower-level pedicles were exposed. According to the surgeon’s preference, pediculotomy was not performed in most patients, except for incidental pedicle violation during facet drilling. The bony spur under the nerve root could not be removed. After confirming the decompressed nerve root, operation was finished.

The modified-PECF utilized the endoscope with a viewing angle of 30°, outer diameter of 7.3 mm, 4.7-mm working channel, and a total length of 251 mm (TESSYS, Joimax, Karlruhe, Germany). A skin incision of 1 cm was made on the line, 1 cm medial to the uncovertebral joint line of the target level to ob-
tain an inclined surgical route by undercutting the facet joint (Fig. 1C, D). On the lateral C-arm image, a skin incision was made on the lower endplate line of the involved disc space at a caudocranial approach angle (Fig. 1E). Docking of the working cannula, soft tissue dissection, and initial laminotomy was performed in the same manner as in the PECF (Fig. 2A). Broad bone drilling of the lower-level lamina and SAP was performed while anticipating the bone extent covering the exiting nerve root, cranial part of the lower-level pedicle, and lateral aspect of the dural sac. Bone drilling was continued until the inner corti-
Fig. 2. Intraoperative endoscopic views of inclined pedicular-vertebrotomy posterior endoscopic cervical foraminotomy at the left C5–6 level. (A) Drilling is initiated from the anatomical V-point (black dotted line). (B) After broad drilling, the superior articular process (SAP) and cranialateral border of the lower-level lamina, contour of the pediculotomy, and distal part of the SAP were exposed. The exiting nerve root can be confirmed through the drilled inner cortical bone (yellow arrowheads). (C) The drilled inner cortical bone was elevated by detaching from the ligamentum flavum (LF) and dura using the dissector. (D) The distal part of the SAP was further resected using the 1-mm punch (white arrowhead). The nerve root was still compressed by the SAP base part at the lateral pedicular area (yellow asterisk). (E) After removing the SAP base and lateral pedicular portions, the decompressed nerve root was observed at the foraminal exiting zone (red asterisk). Features of bony removal after modified-PECF are observed on the computed tomography (CT). (I) The severely collapsed intervertebral foramen is remarkably expanded. The bony spur and superior pedicle are obliquely drilled out (red asterisk) to expand the foraminal width and height more. (J) Postoperative 3-dimensional CT images showing surgical route for modified inclined approach (red arrows) and well-preserved facet joint (black asterisk). The modified inclined technique offers a significant expansion of lower foraminal levels (blue arrows). IAP, inferior articular process.
ceral bone resembled a thin paper so that the contour of the pedicle and nerve root was confirmed (Fig. 2B). The thinned inner cortical bone was elevated and detached from the dura and nerve root, and the bone flap was removed with forceps (Fig. 2C). The exiting nerve root and the lateral border of the thecal sac were exposed, and thick peridural adhesions covered them (Fig. 2D). Subsequently, the thinned SAP was removed laterally using a 1-mm punch by undercutting the SAP along the exiting nerve root. The base of the SAP, where the SAP joins the pedicle, was removed using a punch to release the nerve root at the starting point that curves downward (Fig. 2E). The endoscope was tilted in the craniolateral direction and it accessed the ventral foraminal area through the space created by inclined laminotomy and pediculotomy. The bevel tip was docked in the nerve root axillary area and retracted the nerve root in an obliquely elevated pattern to prevent excessive neural retraction. Subsequently, oblique pedicular-vertebrotomy was performed to remove the bony spur and hypertrophied annulus with stepwise drilling (Fig. 2F, G). The natural downward course of the nerve root was restored through the space created by inclined pedicular-vertebrotomy (Fig. 2H). The severely collapsed intervertebral foramen is remarkably expanded, including foraminal height and lower foraminal area, without sacrificing the facet joint significantly (Fig. 2I, J). After the insertion of a closed drainage catheter, the skin was closed.

3. Data Collection

1) Clinical data collection

This study was approved by the Institutional Review Board (IRB) of Wiltse Memorial Hospital (NR-IRB 2022-W05). Patient characteristics including sex, age, and symptoms were recorded. The nature of the surgery, operation level, operating time, and hospital stay were also documented, as were any postoperative complications. The physicians collected clinical information preoperatively, postoperatively, and at 1 week, 1 and 6 months, and final follow-ups at the ward and an outpatient department. Clinical data at 1 week were collected to document the occurrence of postoperative dysesthesia due to nerve root retraction during the modified inclined procedures. Posterior neck and arm pain visual analogue scale (VAS) scores, neck disability index (NDI) scores, and MacNab criteria for evaluating disability and pain responses were collected. A translation ≥ 3 mm on a flexion-extension radiograph indicated instability. After the surgery, almost all the patients were monitored using the above protocol; however, those with complications were treated with additional management. A single observer who highly experienced endoscopic spine surgery has measured the parameters twice. The kappa value between the 2 measurements was 0.83, indicating excellent agreement.

2) Postoperative dysesthesia

Dysesthesia is defined as a painful, uncomfortable sensation described as burning, icy-hot, prickly, itchy-prickly, or intensely creepy-crawly. We documented postoperative dysesthesia when the preoperative dyesthetic pain character changed, dyesthetic pain severity deteriorated, and new dyesthetic symptoms were present.

3) Foraminal stenosis grading system

Cervical foraminal stenosis was classified into the following 2 grades based on MRI findings on axial T2-weighted images at the cervical disc level, using the grading system suggested by Kim et al.

Grade 0: Absence of foraminal stenosis
Grade 1: Narrowest width of neural foramen is 51%–100% of the width of the extraforaminal nerve root at the level of the anterior margin of the SAP.
Grade 2: Neural foramen width is the same as or less than 50% of the width of the extraforaminal nerve root.

4. Radiologic Parameters

We measured 4 parameters to document the changes in the neural foraminal space and facet on the pre- and postoperative T2-weighted MRI using the methods described by Nakamura and Taguchi and Kim et al. Two values for the middle and distal foraminal widths and one for the facet length were measured on axial MRI from the intervertebral disc levels. One foraminal height value was measured on oblique sagittal MRI from the middle pedicle level. The preoperative and postoperative values were measured along the same plane.

(1) Midforaminal diameter (MFD): A linear distance was measured on the line, vertical to the longitudinal axis of the intervertebral foramen at the midforaminal area (Fig. 3).
(2) Distal foraminal diameter (DFD): A linear distance was measured on the line, vertical to the longitudinal axis of the intervertebral foramen at the distal foraminal part indicated 2-mm lateral to the outer border of the vertebral body (Fig. 3).
(3) Facet joint width (FJW): A linear distance between the medial and lateral borders of the facet joint was measured from T2-weighted axial MRI of the middle of the facet joint (Fig. 3).
(4) Midforaminal height (MFH): A linear distance was measured on the oblique sagittal plane, vertical to the longitudinal axis of the intervertebral foramen at the midforaminal area (Fig. 3).

(5) Foraminal expansion ratio: We calculated the foraminal expansion ratio using the calculation formulas:
\[
\left( \frac{\text{Postoperative MFD}}{\text{Preoperative MFD}} \right), \left( \frac{\text{Postoperative DFD}}{\text{Preoperative DFD}} \right), \text{ and } \left( \frac{\text{Postoperative MFH}}{\text{Preoperative MFH}} \right).
\]

(6) Facet joint resection rate: We calculated the estimated amount of facet resection using the formula:
\[
\left( \frac{\text{Preoperative FJW} - \text{Postoperative FJW}}{\text{Pre FJW}} \right) \times 100.
\]

5. Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as means and standard deviations. Clinical VAS and NDI scores were measured preoperatively, postoperatively, and at 1 week, 1 month, 6 months, and final follow-up visits. The MacNab criteria were assessed at the final follow-up, which was reported by the patients and analyzed using the Wilcoxon rank-sum test. The values of radiologic parameters, other variances in operation times, and hospital stays were also analyzed using the Wilcoxon rank-sum test. A p-value of < 0.05 was considered significant.
Table 1. Patient information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PECF (n = 49)</th>
<th>Modified-PECF (n = 46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male:female</td>
<td>30:19</td>
<td>35:11</td>
<td>-</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.1 ± 8.4 (43–78)</td>
<td>56.4 ± 5.9 (41–67)</td>
<td>0.624</td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>10.7 ± 1.9 (9–18)</td>
<td>10.4 ± 1.3 (8–14)</td>
<td>0.353</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>61.0 ± 12.1 (45–80)</td>
<td>56.5 ± 9.8 (45–85)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospital stays (day)</td>
<td>5.1 ± 3.0 (3–24)</td>
<td>4.8 ± 2.6 (2–16)</td>
<td>0.632</td>
</tr>
<tr>
<td>Operated level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4–5</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>C5–6</td>
<td>19</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>C6–7</td>
<td>25</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>C7–T1</td>
<td>3</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Foraminal stenosis grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Grade 1</td>
<td>13</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Grade 2</td>
<td>36</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>Complications (n)</td>
<td>Dural tear (2), transient neuropraxia (weakness 2, hypesthesia 2), relapse of radiculopathy (2), excessive facet resection &gt; 75% with mechanical neck pain (2)</td>
<td>Dural tear (2), transient neuropraxia (weakness 1, finger hypesthesia 4), postoperative dysesthesia (2), C5 palsy (1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

PECF, posterior endoscopic cervical foraminotomy.

RESULTS

We included 49 (30 men and 19 women) and 46 (35 men and 11 women) patients who underwent PECF and modified-PECF, respectively. The mean age was 57.1 ± 8.4 years in the PECF group, and 56.4 ± 5.9 years in the modified-PECF group (Table 1). The mean follow-up duration was 10.7 ± 1.9 months in the PECF group, and 10.4 ± 1.3 months in the modified-PECF group. The mean operation time was 61.0 ± 12.1 minutes and 56.5 ± 9.8 minutes in the PECF and modified-PECF groups, respectively. The mean hospital stay in the PECF group was 5.1 ± 3.0 days, and 4.8 ± 2.6 days in the modified-PECF group. No significant differences were found in age, follow-up duration, operation time, and hospital stay between the 2 groups (Table 1). The most common operating levels in both groups were C5–6 and C6–7 levels (Table 1). Most patients in both groups had grade 2 foraminal stenosis (Table 1).

The PECF group had 4 transient neuropraxia patients, 2 motor weaknesses, and 2 hypesthesia through the involved nerve roots. There were 5 transient neuropraxia patients in the modified-PECF group: 1 motor weakness of the involved nerve root and 4 hypesthesia of the fingertips. Most sensory neuropraxia in the modified-PECF group was localized to the fingertips of the involved nerve root distribution (Table 1). All the transient neuropraxia occurred 1 or 2 days after the surgery, which resolved within 2 weeks of conservative treatment. One week after the operation, 2 patients had postoperative dysesthesia in the modified-PECF group, which may have been caused by dorsal root ganglion (DRG) retraction with a working cannula during partial vertebrotomy. The symptoms subsided after 1 or 2 weeks of conservative treatment (Table 1). Three patients underwent modified-PECF surgery at the C4–5 level. One patient with C5 palsy with shoulder drop occurred 2 days after surgery (Fig. 4A–C). Fortunately, the patient recovered from the weakness after 2 months of conservative treatment (Table 1). Two patients had dural tears in each group. In the PECF group, one dural tear occurred during the drilling, and another during the bone punching. However, 2 dural tears in the modified-PECF group occurred during the facet joint drilling (Table 1). All the dural tear was small and treated with a fibrin sealant patch without neurologic deficits. In 2 patients of the PECF group, posterior neck pain with a different character recurred 4 weeks later (Table 1). Postoperative MRI showed excessive facet violation over 75% of facet resection, which might cause a relapse of the neck pain (Fig. 4D–F). Two patients in the PECF group relapsed with radiating arm pain after a symptom-free duration.
Fig. 4. Illustrated cases of complications. (A–D) C5 palsy occurred after modified inclined approach for posterior endoscopic cervical foraminotomy (modified-PECF) at the right C4–5 level. (A) Preoperative magnetic resonance imaging (MRI) shows severe osseous foraminal stenosis (yellow arrow). (B) Postoperative MRI presents sufficiently decompressed neuroforamen. Prominent bony spur was adequately removed (white arrow). (C) The nerve root restored its natural downward path after removing the bony spur using a modified inclined technique (blue asterisk). (D–F) Mechanical posterior neck pain relapsed 10 months after the PECF at the left C5–6 level. (D) Preoperative MRI reveals severe foraminal stenosis caused by the prominent bony spur. (E, F) Excessive facet resection (red asterisks) over 75% of resection rate is observed on the postoperative MRI and computed tomography.

of 8 and 10 months (Table 1). One of the 2 patients underwent MRI at 1-year of follow-up, and MRI showed restenosis of the intervertebral foramen (Fig. 5A–C).

We measured the MFD, DFD, and MFH to analyze the change in foraminal width, focusing on the foraminal expansion ratio. The mean expansion ratio of MFD in the PECF group was 4.5 ± 1.9 and 5.4 ± 2.6 in the modified-PECF group (Table 2). Both surgical groups showed more than 4 times midforaminal expansion, and no significant difference was found between the 2 groups (p = 0.164) (Table 2). The mean expansion ratio of DFD in the PECF group was 1.6 ± 0.7 and 2.1 ± 1.0 in the modified-PECF group (Table 2). The DFD in the modified-PECF group was significantly expanded more than in the PECF group (DFD expansion ratio, p < 0.001) (Table 2). Furthermore, the modified-PECF group showed a remarkable expansion in MFH compared with the PECF group (MFH expansion ratio, p < 0.001) (Table 2). In the modified-PECF group, the mean expansion ratio of MFH was 1.5 ± 0.7 and 1.1 ± 0.1 in the PECF group (Table 2). These radiologic results of foraminal expansion revealed that the modified inclined technique enabled an improved expansion of the distal foraminal area and MFH compared with the PECF group. The facet resection rate in the PECF group was 40.2% ± 12.6%, and 30.4% ± 8.6% in the modified-PECF group (Table 2). Both surgical groups showed excellent radiological results of facet joint preservation. However, the modified inclined technique improved facet joint preservation compared to the PECF procedures (facet resection rate, p < 0.001) (Table 2).
Fig. 5. Illustrated cases with follow-up magnetic resonance image (MRI) in the 2 surgical groups. (A–C) Symptoms relapsed after performing the posterior endoscopic cervical foraminotomy (PECF). (A) Preoperative T2-weighted oblique sagittal and axial MRI shows osseous foraminal stenosis (red arrow), mainly in the middle and lower foraminal levels. (B) Postoperative MRI reveals sufficient decompression of the middle foraminal level, and the remaining stenosis (blue asterisk) was observed in the lower foraminal level. (C) On the 1-year follow-up MRI, definite restenosis is found in the lower foraminal level (red asterisk), but more minor in the middle foraminal level. (D–F) Follow-up MRI of modified inclined approach for posterior endoscopic cervical foraminotomy (modified-PECF). (D) Preoperative T2-weighted oblique sagittal and axial MRI showing severe osseous foraminal stenosis (red arrow), both in the middle and lower foraminal levels. (E) Postoperative MRI reveals sufficient decompression of the middle and lower foraminal levels and well-preserved facet joint. Partial pediculotomy (blue asterisk) induces the expansion of the lower foraminal level. (F) After 1 year of modified-PECF surgery, restenosis was not observed in any levels of the foramen, and the drilled pedicle is well-preserved without fracture (red asterisk).

Table 2. Radiological outcomes of the foraminal diameter and height

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PECF (n = 49)</th>
<th>Modified-PECF (n = 46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>Preoperative</td>
</tr>
<tr>
<td>MFD (mm)</td>
<td>1.8 ± 0.8</td>
<td>7.2 ± 1.7</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>DFD (mm)</td>
<td>2.8 ± 0.8</td>
<td>4.2 ± 1.3</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>MFH (mm)</td>
<td>8.9 ± 1.2</td>
<td>9.9 ± 1.1</td>
<td>7.5 ± 2.0</td>
</tr>
<tr>
<td>Foraminal expansion ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFD</td>
<td>4.5 ± 1.9</td>
<td>5.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>DFD</td>
<td>1.6 ± 0.7</td>
<td>2.1 ± 1.0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>MFH</td>
<td>1.1 ± 0.1</td>
<td>1.5 ± 0.7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Facet joint resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FJW (mm)</td>
<td>13.6 ± 2.1</td>
<td>8.1 ± 2.0</td>
<td>13.9 ± 2.4</td>
</tr>
<tr>
<td>Facet resection rate (%)</td>
<td>40.2 ± 12.6</td>
<td>30.4 ± 8.6</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
PECF, posterior endoscopic cervical foraminotomy; MFD, midforaminal diameter; DFD, distal foraminal diameter; MFH, midforaminal height; FJW, facet joint width.
*p < 0.05, statistically significant differences.
We analyzed the foraminal expansion and facet resection rates according to the severity of foraminal stenosis, including grades 1 and 2. In the grade 1 foraminal stenosis, there was no significant difference in the expansion ratio of MFD, DFD, and MFH between the 2 groups (expansion ratio of MFD: \( p = 0.94 \), DFD: \( p = 0.74 \), MFH: \( p = 0.09 \)) (Table 3). Even in the grade 1 patients, the modified-PECF group showed enhanced facet joint preservation compared with the PECF group (facet resection rate in grade 1, \( p = 0.03 \)) (Table 3). On the other hand, patients with grade 2 foraminal stenosis had the same radiologic outcomes as the overall patients, including MFD, DFD, MFH, and facet resection rate. These results revealed that the modified inclined technique might not benefit from foraminal expansion in patients with grade 1 foraminal stenosis. However, in patients with grade 2 foraminal stenosis, the modified inclined technique offers the advantage of significant foraminal expansion (MFD, DFD, MFH) and improving facet preservation compared to the PECF (Table 3).

Table 4. Clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>PECF (n = 13)</th>
<th>Modified-PECF (n = 9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS of neck pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>6.7 ± 1.0</td>
<td>7.2 ± 0.8</td>
<td>0.02*</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3.3 ± 0.7</td>
<td>2.9 ± 0.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>1 Week</td>
<td>2.7 ± 0.9</td>
<td>2.3 ± 0.7</td>
<td>0.01*</td>
</tr>
<tr>
<td>1 Month</td>
<td>2.2 ± 0.7</td>
<td>2.0 ± 0.7</td>
<td>0.17</td>
</tr>
<tr>
<td>6 Months</td>
<td>2.0 ± 0.6</td>
<td>1.9 ± 0.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Final follow-up</td>
<td>1.9 ± 0.5</td>
<td>1.7 ± 0.6</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VAS of arm pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.1 ± 0.8</td>
<td>7.3 ± 1.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Postoperative</td>
<td>2.4 ± 0.8</td>
<td>2.2 ± 0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>1 Week</td>
<td>1.8 ± 0.8</td>
<td>1.7 ± 0.8</td>
<td>0.38</td>
</tr>
<tr>
<td>1 Month</td>
<td>1.5 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>0.21</td>
</tr>
<tr>
<td>6 Months</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Final follow-up</td>
<td>1.3 ± 0.5</td>
<td>1.1 ± 0.3</td>
<td>0.02*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>23.9 ± 3.9</td>
<td>28.7 ± 3.4</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>1 Week</td>
<td>13.0 ± 2.7</td>
<td>14.0 ± 2.8</td>
<td>0.11</td>
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<tr>
<td>1 Month</td>
<td>9.7 ± 2.5</td>
<td>9.5 ± 3.0</td>
<td>0.66</td>
</tr>
<tr>
<td>6 Months</td>
<td>7.4 ± 3.0</td>
<td>7.0 ± 2.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Final follow-up</td>
<td>5.8 ± 2.6</td>
<td>5.7 ± 1.6</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>MacNab criteria</td>
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<td></td>
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</tr>
<tr>
<td>Excellent</td>
<td>6 (12)</td>
<td>15 (33)</td>
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<tr>
<td>Good</td>
<td>41 (84)</td>
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<td>Fair</td>
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<tr>
<td>Poor</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Success rate (good+excellent)</td>
<td>96%</td>
<td>98%</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.

PECF, posterior endoscopic cervical foraminotomy; VAS, visual analogue scale; NDI, neck disability index.

*p < 0.05, statistically significant differences.

Table 3. Radiologic outcomes according to the grades of foraminal stenosis

<table>
<thead>
<tr>
<th>Foraminal expansion ratio</th>
<th>Grade 1</th>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PECF (n = 13)</td>
<td>Modified-PECF (n = 9)</td>
</tr>
<tr>
<td>MFD</td>
<td>3.3 ± 1.3</td>
<td>3.3 ± 1.1</td>
</tr>
<tr>
<td>DFD</td>
<td>1.5 ± 0.3</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>MFH</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Facet resection rate (%)</td>
<td>39.3 ± 11.8</td>
<td>27.3 ± 6.3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

PECF, posterior endoscopic cervical foraminotomy; MFD, midforaminal diameter; DFD, distal foraminal diameter; MFH, midforaminal height.

*p < 0.05, statistically significant differences.
significant difference in the NDI scores between the 2 groups after the surgery (Table 4). The MacNab criteria revealed that both groups had remarkable success rates (PECF, 96%; modified-PECF, 98%; Table 4). In 2 patients who had a fair response in the PECF group, the symptoms of radiculopathy were not resolved after the surgery. Radiologic documents showed insufficient mid foraminal expansion and inadequate facet resection; expansion ratio of MFD: 1.6 and 1.4, expansion ratio of DFD: 0.1 and 0.2; facet resection rate: 23.5% and 4.2%, respectively, for 2 patients. However, an additional operation for the involved level was not performed during the follow-up.

DISCUSSION

Postoperative transient neuropraxia can occur through neural manipulation using dissectors, punches, and forceps without neural retraction. In this study, both groups had neuropraxia cases; 4 out of 49 (8%) in the PECF group, and 5 out of 46 (10%) in the modified-PECF group. In the modified-PECF group, 4 patients had finger hypesthesia and only 1 patient experienced transient motor weakness. Otherwise, 2 patients with motor weakness were observed in the PECF group, and 2 hypesthesia occurred through the involved nerve root dermatome, including the fingers. During ventral foraminal decompression with the modified inclined technique, sufficient space was created between the nerve root and distal part of the SAP. At this step, we can remove the distal portion of the SAP more safely and widely without compressing the nerve root, even in grade 2 osseous foraminal stenosis (Fig. 2J). On the other hand, during the usual PECF for grade 2 osseous foraminal stenosis, additional compression to the involved nerve root is inevitable during punching of the distal part of the SAP because the nerve root is severely squeezed between the hypertrophied SAP and prominent bony spur. Additional compression of the vulnerable nerve root may cause motor weakness and a broader area of hypesthesia. Therefore, during the PECF, excessive facet resection over 75% occasionally occurs for sufficient neural decompression (Fig. 4).

The 1 patient who underwent C4–5 modified-PECF experienced C5 palsy 2 days after the surgery. In this patient, severe osseous foraminal stenosis with prominent bony spur was observed on the preoperative images, and they were sufficiently removed using the modified inclined technique. However, more extensive neural retraction was necessary to remove the uncovertebral hypertrophy, which might cause C5 nerve root palsy (Fig. 4). Therefore, if the C4–5 operation level has severe osseous foraminal stenosis, the modified inclined technique is not recommended; rather, we consider the anterior cervical approach to prevent postoperative C5 palsy.

The overresection of the pedicle and vertebrae can lead to instability. Pediculotomy should be carefully performed only to drill no more than 3–5 mm combined dimension of the pedicle and corpus, which is measured by the 3.0- or 3.5-mm diamond drill. Furthermore, oblique pediculotomy using an inclined surgical approach can reduce the amount of pediculotomy required. This study did not show cases of instability caused by excessive pediculotomy or facet resection.

VAS score for neck pain in the modified-PECF group was lower on 1 day and 1 week after surgery than in another group. There is a possibility that less facet resection and facet capsule preservation were associated with decreased neck pain VAS score within 1 week after surgery. However, after 1-month follow-up, significant differences between the groups disappeared, possibly due to facet joint healing and stabilization.

Whether distal foraminal decompression improves clinical outcomes during the posterior cervical approach for foraminal stenosis treatment remains controversial. Nakamura and Taguchi reported a clinical series in which residual stenosis in the lateral portion of the intervertebral foramen was weakly associated with postoperative outcomes. However, no comparative study has analyzed the association between the degree of distal foraminal decompression and postoperative outcomes. Herein, a significant difference in the arm pain VAS score was not observed between the 2 groups within 6 months after the surgery, despite the modified-PECF group having a higher expansion ratio of the distal foraminal area and foraminal height. At the final follow-up, the modified-PECF group showed significantly improved arm pain compared with the PECF group. The extra space in the distal foraminal area may help maintain the expanded foraminal space. Furthermore, the modified inclined technique influences the contour and course of the nerve root. After SAP base resection, the DRG was decompressed entirely, and the nerve root restored its natural downward angulation (Fig. 1B). Restored nerve root course could also help enhance the postoperative arm pain VAS. However, if the bony spur indented the nerve root, its distorted course of the nerve root may not be restored (Fig. 1A).

In the PECF group, a patient who experienced a relapse of symptoms showed restenosis of the foraminal space outlined by the SAP base and lower-level pedicle on the 1-year MRI. This patient did not undergo pediculotomy, bony spur removal, and foraminal narrowing at the SAP base had not sufficiently ex-
panded. The restenosis may have occurred first at the SAP base area (Fig. 5A–C). However, the modified inclined technique offered sufficient expansion of the SAP base part, and restenosis was not observed in any foraminal area on the 1-year MRI, despite the presence of a prominent bony spur (Fig. 5D–F).

The present study had several limitations. This was a retrospective study, and the follow-up period was relatively short, though it was reasonable for assessing midterm results. A multicenter study with larger sample size and long-term follow-up is required to confirm the findings of this study. We measured the facet joint resection using a linear distance and not the total volume of the resected facet joint. Foraminal diameter expansion was measured at the most stenotic mid-disc level. This did not represent foraminal changes at the SAP base.

CONCLUSION

Both surgical groups showed excellent facet joint preservation, midforaminal expansion, and favorable midterm clinical outcomes without serious complications. The modified inclined technique has radiologic benefits over the conventional PECF, including enhanced facet joint preservation, natural course restoration of nerve roots, and restenosis prevention by expanding the SAP base of the intervertebral foramen in the grade 2 osseous foraminal stenosis. Furthermore, this technique can improve postoperative neck pain within 1 week after surgery by preserving the facet joint; it may enhance the postoperative arm pain after 6-month follow-up by preventing restenosis.

NOTES

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Multimodal Repair of Spinal Cord Injury With Mesenchymal Stem Cells

Yuan-huan Ma¹, Qing-yue Liang², Ying Ding³, Inbo Han⁴, Xiang Zeng⁵

¹Guangzhou Institute of Clinical Medicine, Guangzhou First People’s Hospital, South China University of Technology, Guangzhou, Guangdong Province, China
²Department of Clinical Nutrition, Chengdu 1st People’s Hospital, Chengdu Medical College, Chengdu, Sichuan Province, China
³Department of Histology and Embryology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, Guangdong Province, China
⁴Department of Neurosurgery, CHA University, CHA Bundang Medical Center, Seongnam, Korea
⁵National Institute of Stem Cell Clinical Research, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong Province, China

Spinal cord injury (SCI) is a result of a devastating injury to the central nervous system. Currently, there is no effective treatment available for these patients. The possible use of mesenchymal stem cell (MSC)-based treatment for SCI has been the focus of extensive investigations and is increasingly moving from the bench to bedside. Both experimental observations and clinical studies have shown the safety and efficacy of MSCs in managing SCI. However, the exact mechanism by which MSCs contribute to the repair of the injured spinal cord remains to be elucidated. In this review, we aim to summarize current research findings about the role of MSCs in improving complex pathology after SCI. MSCs exert a multimodal repair mechanism targeting multiple events in the secondary injury cascade. Our recent results showing the perineurium-like differentiation of surviving MSCs in the injured spinal cord may further the understanding of the fate of transplanted MSCs. These findings provide fundamental support for the clinical use of MSCs in SCI patients. Under experimental conditions, combining novel physical, chemical, and biological approaches led to significant improvements in the therapeutic efficacy of MSCs. These findings hold promise for the future of cell-based clinical treatment of SCI.

Keywords: Spinal cord injury, Mesenchymal stem cells, Multimodal repair, Perineurium, Clinical trials

INTRODUCTION

Spinal cord injury (SCI) is a devastating central nervous system condition, caused by direct physical impact. The lack of effective treatment causes significant public concerns. Following SCI, patients live with some degree of permanent disability and several complications can arise. According to the World Health Organization, the global estimated prevalence of SCI is 40 to 80 cases per million population. For example, in the United States, there were 17,810 new cases reported in 2020, with a total of 294,000 Americans living with SCI.¹ The provision of effective treatment for SCI remains an unmet medical need.² Alleviating the suffering of these patients and reducing the need for their extensive care is a challenge to society.

The recent emergence of stem cell-based tissue engineering is a promising strategy for SCI repair. Amongst the possible candidate seed cells, mesenchymal stem cells (MSCs) are the most extensively studied both in basic science experiments and in translational research. According to the Web of Science database, over 2,200 publications appeared on this topic and the National Library of Medicine database contains 40 registered clinical studies in various countries, including China (10), the United States (7), and the Republic of Korea (3). Due to their immunomodulatory, anti-inflammatory, and pro-angiogenic properties, MSCs show a strong potential to promote tissue repair,³⁵ with ongoing registered clinical trials.⁶⁷ Despite this extensive work, the mechanism that allows MSCs to repair SCI remains to be elucidated. Recently, we described a novel mech-
anism, where MSCs differentiate into perineurium-like sheaths to protect neural tissue damage. It seems that MSCs provide a multimodal repair, addressing several events in the multidimensional pathophysiology seen after SCI. In this review, we summarize the possible roles of MSCs in the treatment of SCI, highlighting multiple mechanisms that underlie their therapeutic benefits.

MULTIDIMENSIONAL PATHOPHYSIOLOGICAL FEATURES OF SPINAL CORD INJURY

A full understanding of the pathophysiological events that follow SCI is necessary to identify effective treatments. The primary injury is the physical impact affecting the spinal cord directly as a result of a traffic accident, fall, sports accident, or other violent events. This initial impact can displace bone fragments and components of the intervertebral discs. Alternatively, ligaments bruise or tear into the spinal canal. These mechanisms lead to the penetration, contusion, or compression of the cord tissue. The primary injury activates a rapid cascade of secondary pathophysiological changes that are collectively referred to as secondary injury. There are three early phases of secondary injury: the acute phase (within 48 hours), the subacute phase (2–14 days), and the intermediate phase (14 days–6 months). These are followed by a chronic phase (beyond 6 months). While characteristic pathophysiological changes occur during each of these phases, these are not entirely independent, but represent a step in a complex series of interlinked events. The main pathophysiological changes after SCI include hemorrhage, ischemia-reperfusion injury, alterations in ion distribution, excitotoxicity, oxidative damage, and axonal degeneration. The homeostasis of the spinal cord internal microenvironment is completely disrupted after injury, leading to a cascade of pathophysiological changes. Despite our current insight into the biochemical reactions and pathways involved in the progression of SCI, much remains to be explored. A fuller understanding of the pathophysiology after injury will help identify potential avenues to improve current therapies, and potentially create new approaches that may promote spinal cord tissue regeneration.

FUNCTIONAL MULTIPOTENCY OF MESENCHYMAL STEM CELLS

In the 1970s a new type of adherent stromal cell was isolated and cultured from the bone marrow. These cells exhibited fibroblast-like morphology and were multipotent cells that had the capacity to self-renew. Importantly, these cells could differentiate into a variety of cell types, including osteogenic, adipogenic, chondrogenic, and myogenic mesenchymal lineages in vitro. Based on these characteristics, they were referred to as “mesenchymal stem cells” by Caplan in 1991. MSCs adhere to plastic under standard culture conditions and express CD90, CD105, and CD73. At the same time, they are CD45, CD34, CD14, CD11b, CD79a, or CD19 negative. To date, no single marker has been identified that could distinguish MSCs from other cell types. Subsequent studies have shown that MSCs can be isolated from a variety of tissues, including bone marrow, umbilical cord, dental pulp, and adipose tissue. The ability to establish MSCs from such a wide range of tissues boosted their potential for clinical applications, as these cells could be obtained without serious ethical concerns. Furthermore, MSCs are considered to be immune-privileged, because of their low immunogenicity. They express very low levels of MHC class I molecules and are completely devoid of MHC class II. There is growing evidence suggesting that MSCs can suppress immune responses. Moreover, clinical studies showed the safety of MSC transplantation, excluding the risks of tumor formation. Apart from proving their safety, studies have also demonstrated that in SCI MSCs do not act via a single mechanism but promote a multimodal repair. This multitude of repair mechanisms can be regarded as the functional multipotency of MSCs, suggesting that they have the capacity to simultaneously treat multiple aspects of the complex pathology that characterizes SCI.

1. Proangiogenic Features of MSCs

MSCs are potent inducers of angiogenesis and vasculogenesis when transplanted into tissues. This property has been observed under several conditions, including cardiovascular disease, wound healing, and SCI. Reestablishing the blood supply is a critical requirement for successful tissue regeneration. The molecular mechanisms promoting angiogenesis by MSCs involve the secretion of the tissue inhibitor of metalloproteinase-1, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), platelet-derived growth factor, interleukin (IL)-6, and IL-8. Apart from the secretion of these cytokines, MSCs also contribute to blood vessel formation via additional mechanisms. These include providing physical contacts supporting growth and the production of components of the extracellular matrix (ECM). In a previous study, we found several
transplanted MSCs surrounding newly formed blood vessels while others encircled tightly the epithelial layer, forming pericytes in the injured spinal cord. MSCs surrounding these structures expressed hypoxia-inducible factor 1-alpha and VEGF, and deposited fibronectin (FN) around the blood vessel inside. This topology may contribute to synergistic effects, promoting the formation and maturation of blood vessels after SCI. This angiogenic nature of MSCs may counteract the effects of tissue ischemia developing after injury. By improving blood supply, MSC transplants promote the delivery of nutrients and oxygen necessary for tissue regeneration.

2. Anti-inflammatory and Immunomodulatory Capacity

MSCs can suppress the activity of a variety of immune cells, including T and B lymphocytes, neutrophils, monocytes, and macrophages. MSCs can strongly inhibit the proliferation of mitogen or alloantigen-activated T lymphocytes, irrespective of whether the T cells were autologous or allogeneic. MSCs were also able to modulate immune responses by interacting with regulatory T cells (Treg), involved in the maintenance of immune homeostasis and self-tolerance. Evidence suggests that MSCs can increase the number of Treg cells while simultaneously improving their immune suppressive action.

Key molecules involved in this interaction include MSC-derived soluble factors, such as prostaglandin E2 (PGE-2), transforming growth factor (TGF)-β1, indoleamine 2,3-dioxygenase (IDO), and HGF. Recent studies have also shown that MSCs can inhibit B cells by arresting their proliferation at the G0/G1 phase of the cell cycle. Furthermore, MSCs alter B-cell chemotaxis by significantly down-regulating the expression of CXCR4, CXCR5, CCR7, and their ligands, CXCL12, and CXCL13. It was also demonstrated that MSCs can directly inhibit the transformation of B cells into plasma cells. The key molecules involved in this inhibition include interferon (IFN)-γ and B-cell activating factor. MSCs can rescue resting and IL-8-activated neutrophils from apoptosis by constitutively releasing IL-6 in vitro. They can also sustain and amplify the function of neutrophils via endogenously produced IL-6, IFN-β, and granulocyte-macrophage colony-stimulating factor. MSCs seem to drive macrophage polarization towards the anti-inflammatory M2 phenotype through the suppression of nuclear factor-kappa B p65 and the activation of STAT3 pathways. This extensive immunosuppressive and regulatory action of MSCs has attracted considerable interest for potential clinical use. The infiltration of inflammatory cells into the injured SCI generates a microenvironment that is detrimental to recovery. The anti-inflammatory and immunoregulatory effects of MSCs may provide a promising approach to alleviate this neuroinflammation.

3. MSCs Show Strong Secretory Actions: Production of Nutritional Factors and Exosomes

There is a view that the therapeutic effect of MSCs transplantation does not occur via direct cell replacement, but through the modulation of the host microenvironment. Indeed, the nutritional activity of MSC has been widely confirmed and has become the focus of research in the treatment of several diseases. MSCs secrete a variety of growth factors, neuroprotective cytokines, and chemokines in an autocrine or paracrine manner. These include HGF, VEGF, fibroblast growth factor, brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF). All of these factors have been implicated in supporting the regeneration of damaged spinal cord tissues. In addition, our team found that transplanted MSCs can also deposit FN, a well-known component of the ECM necessary for axonal growth. MSCs can also secrete Laminin and TGF-β in the injured spinal cord to promote the recovery. Altogether, these changes result in a microenvironment that is conducive to regeneration.

Recently, an increasing number of studies confirmed that MSCs exert part of their therapeutic efficacy by secreting exosomes. These specialized membrane-coated nano-sized vesicles are secreted in large quantities by MSCs. Exosomes contain biologically active molecules, various proteins, mRNA, transfer RNA, long noncoding RNAs, microRNAs, and even mitochondrial DNA. They affect cellular function via different routes. Apart from MSCs a variety of cell types, including immune cells, can produce exosomes. However, MSC-derived exosomes have unique characteristics; they exhibit immunomodulatory properties, elicit anti-inflammatory responses, and promote angiogenesis. These actions of MSCs-derived exosomes replicate functions that the MSCs themselves provide. Their natural cell membrane packaging protects the content of the exosomes against systemic degradation, making them suitable for systemic administration in living organisms. Utilizing this feature attempts have been made to use MSC-derived exosomes for the treatment of SCI. Liu et al. found that exosomes from bone-derived MSCs can repair traumatic SCI by suppressing the activation of A1 neurotoxic reactive astrocytes. Intravenously delivered MSC-derived exosomes can repair SCI by targeting M2-type macrophages at the site of injury. The systematic administration of exosomes from MSCs can reduce apoptosis and inflammatory response, promote angiogenesis and functional recovery after SCI.
4. Transdifferentiation Into Neuron-Like Cells

Like other stem cells, MSCs have the potential to differentiate into a range of tissues. As progenitors of a mesenchymal lineage, they intrinsically differentiate into mesoderm-derived tissues such as chondrocytes, osteocytes, and adipocytes. Whether MSCs can be reprogrammed to transdifferentiate into neurons remains controversial.67 Decades ago, a number of studies suggested that such transdifferentiation was possible under specific conditions. In early studies of human MSCs, a chemical induction formula, containing a combination of dimethylsulfoxide (DMSO), butylated hydroxyanisole (BHA) and β-mercaptoethanol (BME) yielded cells that phenotypically appeared neuron-like.68 However, this ‘neuronal differentiation’ of MSCs after chemical induction was an artifact due to cytotoxic cell changes. Chemical induction, by BME, BHA, and DMSO, detergents, high sodium concentration, and extreme pH values, can shrink the cell bodies of MSCs within a few hours, leaving them with a neuron-like morphology. This change may even be accompanied by an increase in the level of neuronal markers, such as neuron-specific enolase and neuronal nuclear antigen. However, as reverse transcription-polymerase chain reaction experiments show, these changes in protein levels are not due to the up-regulated expression of corresponding mRNAs.69 Changes induced by cytotoxicity happen rapidly, do not last long, and do not indicate a true transdifferentiation of MSCs. A more reliable approach to induce neuronal differentiation by MSCs involves the use of morphogens and/or neurotrophic factors. When MSCs were treated by epidermal growth factor, retinoic acid (RA), or a combination of RA and BDNF, they differentiated into neuronal cells expressing markers such as nestin and NeuN.70 Using similar induction regimens, independent studies reported the neuronal differentiation potential of MSCs both in vitro and in vivo. A number of studies have shown evidence for action potentials being fired by MSC-derived neuron-like cells.71,72 It was hypothesized that the increase of intracellular cAMP concentration may be a key factor responsible for this transdifferentiation of MSCs.73 Our group was the first to report that a combination of neurotrophin-3 (NT-3) and RA could induce the differentiation of MSCs into neuron-like cells.74 Furthermore, the proportion of neuron-like cells was greatly increased when NT-3 expressing modified Schwann cells were cocultured with MSCs that were genetically modified to express tyrosine kinase C (TrkC), the receptor for NT-3.75 By tissue engineering, we have constructed MSC-derived neural networks on 3-dimensional (3D) scaffolds. Neuron-like cells in this environment exhibit characteristic electrophysiological behaviors, including the firing of action potentials, and postsynaptic currents.76,77 Furthermore, MSC-derived neuron-like cells formed on these scaffolds retained neuronal phenotypes and integrated into host neural circuits with synapse-like connections. More importantly, transplantation of MSC-derived neural network tissue into the injured spinal cord significantly improved motor function in the paralyzed limbs both in a rat and a canine model. We have ruled out the possibility of the morphological changes being cytotoxicity induced, as MSC-derived neurons survived for prolonged periods in culture (up to 14 days) and in vivo (up to 6 months).76,77 It has been argued that neuronal differentiation of MSCs is the result of cell fusion with host neurons, resulting in a neuronal phenotype of the fused cells.78 However, using karyotyping, we excluded this possibility.76 Nonetheless, MSC-derived neuronal cells do not possess all features of genuine neurons. The structure of synapses formed between MSC-derived neuronal cells or between MSC-derived neuronal cells and host neurons did show some of the characteristic features of a chemical synapse, when studied by electron microscopy. Thus, we prefer to call MSC-derived neuronal cells MSC-derived neuron-like cells, based on their functional similarity to neurons, rather than morphological reasons.

5. Perineurium-Like Differentiation

Our group recently identified a novel function of MSCs in treating SCI, the formation of perineurium-like sheaths protecting nerve fibers.4 MSCs used in these experiments were derived from transgenic rats expressing green fluorescent protein (GFP). These cells were grafted into the transected spinal cord tissue of allogeneic rats, using a biocompatible scaffold. With the use of immunosuppression, the transplanted MSCs survived for up to 8 weeks and formed tube-like structures wrapped around nerve fibers at the injured site (Fig. 1). When examined by electron microscopy, nerve fibers covered by these tubes showed more intact morphology and contained less 4-hydroxynonenal and Nitrotyrosine. These molecules are key indicators of lipid peroxidation and protein nitration in an inflammatory microenvironment. MSCs that formed perineurium-like sheaths around neurons expressed BDNF, HGF, VEGF, glial cell line-derived neurotrophic factor (GDNF), and SOD3, a secreted antioxidant enzyme.79 The latter indicates that perineurium-like MSC sheaths may protect nerve fibers from oxidative damage. Such MSC-derived perineurium-like sheaths also provide a physical barrier, isolating the enclosed nerve fibers from the deleterious microenvironment surrounding the injury. We performed a retrospective analysis of previously published studies transplanting
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MSCs to treat SCI, where donor MSCs survived beyond 3 weeks in the host spinal cord. The perineurium-like sheath structures were invariably visible on microscopic images, but were never identified or commented on by the original authors. These findings indicate that the formation of perineurium-like sheaths by transplanted MSCs is not a fortuitous phenomenon. As discussed earlier, the microenvironment surrounding the injured cord causes excitotoxicity, oxidative damage, and is affected by deleterious immune responses. The formation of a perineurium-like sheath by MSCs can provide protection against these, aiding the regeneration of nerve fibers.

CURRENT CLINICAL TRIALS USING MESENCHYMAL STEM CELLS IN THE TREATMENT OF SPINAL CORD INJURY

A number of clinical trials using MSCs from autologous (mostly bone marrow-derived) or allogenic (mostly umbilical cord-derived) sources have been carried out on patients with SCI. The safety of MSCs transplantation in humans was first demonstrated in 1995. In the initial studies, adherent stromal cells isolated and cultured from bone marrow samples of patients suffering from hematological malignancies were transfused back to the donors. This early demonstration of the safety of MSCs led to an increase in the number of translational studies and clinical applications of these cells. To date, dozens of registered clinical trials have been initiated to investigate the MSCs-based treatment of SCI around the world, and this number is continuously growing. Despite some encouraging observations, the fate of donor MSCs inside the human body remains largely unknown due to the absence of biopsy data, the limited number of post-mortem studies, and lack of relevant imaging. Animal studies suggest that these cells only survive for a short period within the spinal cord, typically less than 2 weeks. In a clinical study, autologous bone marrow-derived MSCs were labeled with superparamagnetic iron oxide nanoparticles and injected intrathecally to treat a single SCI patient. Magnetic resonance imaging detected the focal accumulation of signal 48 hours after administration. This signal faded 2 weeks later and disappeared completely 1 month after transplantation. Despite their low immunogenicity, transplanted MSCs fail to persist long-term in vivo without any immunosuppression, and are thought to provide therapeutic benefits via a “Touch-and-Go”/“Hit-and-Run” mechanism. However, with most of the conducted clinical studies being phase I, I/II, or II trials, the therapeutic efficacy of MSCs still needs further investigation. A phase III clinical trial showed limited efficacy of a single dose of autologous MSCs in treating chronic SCI. However, the administration of multiple doses of MSCs was effective in a previous study during long-term observation, suggesting that the therapeutic efficacy of MSCs may be dose-dependent. Thus, any intervention that increases the number of donor MSCs or promotes their survival, may produce better clinical outcomes. However, it appears that achieving this will remain a technical challenge in the treatment of SCI. There are several factors affecting therapeutic efficacy: (1) Heterogeneity of MSCs from different tissues: MSCs from the umbilical cord matrix, adipose tissue, or bone marrow show differences in their ability to inhibit peripheral blood B cells, T cells, and NK cells. There are similar differences in the differentiation and proliferation of MSCs derived from different tissues. (2) Differences in passage numbers: MSCs lose their stem cell characteristics and their telomeres get gradually shorter as the number of in vitro passages increases. Although the use of cells from an early passage is recommended for clinical use, it is difficult to control for changes in this parameter when comparing trial data. (3) Differences in cell preparation processes: The lack of reproducibility in producing the transplanted MSCs in vitro may also lead to different results. (4) Different routes of administration: Currently, MSCs are administered...
via intrathecal injection, intravenous dosing, intramuscular injection, injection \textit{in situ}, or being delivered using scaffolds.\textsuperscript{102} Intrathecal, intravenous, and intramuscular administration is less invasive but relies on the homing effect of MSCs.\textsuperscript{103} According to animal studies, intrathecal injections appear more effective than intravenous administration.\textsuperscript{104} Injecting MSCs directly into the spinal cord contusion cavity seems beneficial for the resolution of the glial scars and bridging axon regeneration. Thus, \textit{in situ} injection to the intramedullary injury area may also achieve better outcomes.\textsuperscript{105} More work is certainly needed to establish the optimal route of administration. (5) Different dose ranges: In various trials, the frequency of administration and the injected number of MSCs varied widely. Cell doses range from $0.5 \times 10^6$ to $10 \times 10^7$/kg, or even higher were tried using single or multiple dosage regimes.\textsuperscript{106} (6) Individual differences: Notable differences were observed in the response of individual patients. Some appear to show significant improvements while others do not.\textsuperscript{107} These differences could be due to several poorly quantifiable factors, including the differing extent and location of the damage, the patient's age, prior physical condition, and the presence or absence of underlying diseases. Currently, reports on completed phase III clinical trials are scarce. Although weaknesses in study design have triggered criticism and debates,\textsuperscript{108-110} the efficacy of MSCs in the treatment of SCI demonstrated in a trial led by Stemirac is promising. In summary, although the safety of MSCs in clinical has been verified, their efficacy in treating SCI remains controversial. Data available from current clinical trials are clearly inadequate to draw final conclusions from. Much more effort will be needed before the large-scale application of MSCs for the treatment of SCI will become reality.

## APPROACHES TO ENHANCE THE EFFICACY OF MESENCHYAL STEM CELLS IN SPINAL CORD INJURY REPAIR

The fact that MSCs can target multiple pathological changes associated with the secondary injury after SCI promises tantalizing benefits. Although the efficacy of MSCs for the treatment of SCI patients is still being studied, several strategies are being developed to enhance their effectiveness in pre-clinical studies. This work may produce new MSC-derived products with improved therapeutic characteristics.

### 1. Preconditioning MSCs

IFN-γ pretreatment could promote the secretion of soluble factors responsible for the immunosuppressive and immuno-modulatory effects of the transplanted cells.\textsuperscript{106,111} Hypoxic pre-conditioning followed by reoxygenation for 30 minutes improved the ability of MSCs to proliferate and migrate.\textsuperscript{112} Research showed that culturing the cells with the oxygen level reduced to 1% could significantly increase their survival and angiogenic capacity while reducing their sensitivity to the ischemic microenvironment of the damaged spinal cord. These effects were achieved without changing the biological behavior, immunophenotype or karyotype of MSCs.\textsuperscript{113} Transplantation of hypoxia preconditioned MSCs enhanced their protective effect during spinal cord ischemia/reperfusion injury.\textsuperscript{114} It appears that these therapeutic benefits are due to the up-regulation of the secretion of cytokines, such as HGF and VEGF.\textsuperscript{115} In other experiments, preconditioning with sevoflurane, an inhaled anesthetic, improved the survival and therapeutic potential of MSCs during serum deprivation and hypoxia. This was mediated through the up-regulation of HIF-1α, HIF-2α, VEGF, and p-Akt/Akt attenuating the initiation of apoptosis and the loss of mitochondrial membrane potential.\textsuperscript{115} Other small molecules, such as IFN-γ, IL-1β, and lipopolysaccharide have also been reported to enhance the immunomodulatory properties of MSCs, causing prominent PGE-2 secretion.\textsuperscript{116}

### 2. Three-Dimensional Culture

Biomaterial scaffolds can provide a 3D milieu for embedded cells, conferring enhanced biological function during SCI repair. The physical properties of such scaffolds may alter the functional status of the seeded MSCs. The stiffness of the biomaterials can affect the morphology, proliferation, and differentiation of MSCs. MSCs cultured in alginate hydrogels of varying stiffness showed changes in gene expression profiles. The production of inflammatory regulators, including IDO1 and PGE-2, increased in stiffer matrices.\textsuperscript{117} Other features, such as surface characteristics, or the pore size fundamentally changed the biological function of MSCs.\textsuperscript{118,119} Furthermore, chemical modification of the scaffold may introduce new features. A hydrogel scaffold modified with the bioactive peptide PPFLMLLKGR significantly improved the survival and adhesive growth of MSCs in 3D cultures in vitro. This translated into better hindlimb motor function in the treated animals.\textsuperscript{120} Coculturing MSCs with immune cells in the 3D matrix also affected their immunomodulatory potential.\textsuperscript{121} MSCs being cultured in a polystyrene scaffold produced more anti-inflammatory cytokines, such as PGE-2 and tumor necrosis factor-stimulated gene 6. At the same time the secretion of proinflammatory cytokines, such as IL-6, monocyte chemotactic protein-1, macrophage colony-stimulat-

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ing factor and receptor activator of nuclear factor κ-B ligand were reduced in cocultures with macrophages.122

3. Genetic Modification

Genetic modification of MSCs could introduce new features that are useful for therapeutic purposes.123 Transplanted MSCs genetically modified to produce insulin-like growth factor-1 have shown better survival with enhanced immunoregulation. This promoted myelination, leading to significant functional improvement after SCI.124 MSCs modified to produce VEGF and GDNF improved angiogenesis in the injured area. This, in turn, increased the survival of transplanted cells and the extent of axonal regeneration in a rat model.125 MSCs transduced with the BDNF gene protected the spinal cord tissue more, inhibited glial scar formation, and alleviated inflammatory responses.126 Grafting spheroids formed by MSCs expressing BDNF promoted the retention of myelinated axons in the area of SCI and led to a significantly enhanced recovery of hindlimb motor function in a mice model.127 Our group cocultured NT-3 expressing Schwann cells and MSCs expressing its receptor, TrkC, in a gelatin sponge scaffold. The constructed MSC-derived neural network tissue was used to repair SCI in rat and canine models.128,129 We found that combining tissue engineering with the genetic modification of MSCs improved neural differentiation and helped the functional recovery of animals. However, the use of vectors necessary for genetic modifications, such as modified adenovirus, lentivirus, and adeno-associated virus particles, causes concerns about the safety of such genetically modified MSCs in human trials. Thus, although promising, the safety of genetically modified MSCs should be fully investigated to reduce potential harm. If their safety could be guaranteed, genetic modifications of MSCs may enhance their therapeutic utility in the treatment of SCI.

4. Combination With Neurorehabilitation

MSCs transplantation has been combined with various forms of neurorehabilitation therapy. There are reports that combining MSC transplantation with treadmill training,128 electrical stimulation,129 electroacupuncture,130 transcranial magnetic stimulation (TMS),131 ultrashort wave therapy,132,133 and swimming training134 resulted in improved therapeutic outcomes. Several theories were put forward to explain the increased benefits of these combined treatment regimes. (1) Tissue sparing: The combination of MSCs and TMS displayed synergistic effects on alleviating SCI-induced spinal cord lesions and neuronal apoptosis in a rat model. Increased GAP-43, NGF; and BDNF expression levels, downregulated glial fibrillary acidic protein (GFAP) expression, and reduced activation of the Raf/MEK/ERK signaling pathway was reported with this combined treatment.131 MSCs transplantation together with physical activity such as treadmill training showed better tissue preservation, fewer microcavitations, and reduced degeneration of nerve fibers after SCI.128 (2) Promoting donor MSCs survival: Electrical stimulation and acupuncture can promote the survival and differentiation of MSCs in rats following SCI. We have previously found that electrical acupuncture could efficiently promote the survival and differentiation of bone marrow-derived MSCs. This could lead to better axonal regeneration and locomotor recovery.130 MSC transplantation combined with electroacupuncture therapy can also improve Basso-Beattie-Bresnahan scale scores and evoked motor potentials. The number of neurofilament-positive and Biotinylated dextran amine-labeled axons increased, leading to improved outcomes.135 There is evidence that treadmill training improves the survival of neural precursor cells in the post-SCI microenvironment, through the involvement of MSCs.136 (3) Modulation of neuroinflammation and reduction of glial scarring: Other experiments combined human umbilical cord MSCs with ultrashort wave therapy in SCI. This combination improved motor function, and decreased the number of infiltrating CD3+ T cells, while decreasing microglia and astrocyte inflammation.132,133 Moreover, decreased GFAP and chondroitin sulfate proteoglycans expression was detected in this combination treatment group.135 What is the mechanism behind the improved outcomes when MSCs transplantation is combined with neurorehabilitation? Our study showed that electroacupuncture increased the secretion of NT-3 from the injured spinal cord tissue. This, in turn, can promote the survival, differentiation, and migration ofrafted MSCs expressing the TrkC gene.137 Subsequently, we explored the mechanism that allows electroacupuncture to promote the increased secretion of NT-3 by the activation of the CGRP/RAMP1/aCaMKII pathway.138 In a recently published review, we summarized the potential mechanisms explaining the benefits of combining electroacupuncture with MSCs transplantation in the treatment of SCI.139

CONCLUSIONS AND PERSPECTIVE

The exact mechanism by which MSCs improve outcomes after SCI remains to be explored further. This work will offer further insights into enhancing their safe and effective therapeutic use. In this review, we have shown that MSCs have multiple func-
tional properties that can target a variety of pathological consequences of SCI (Fig. 2). One of these is a novel finding, the perineurium-like differentiation of MSCs, that warrants further investigation. Future basic research needs to be focused on developing MSC-based treatment strategies that improve the efficacy of treatment in SCI.

**NOTES**

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**ORCID**

Inbo Han: 0000-0002-0834-9325
Xiang Zeng: 0000-0003-4577-749X

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Multimodal Repair of Spinal Cord Injury With Mesenchymal Stem Cells: An Editorial Perspective

Sydney Brockie\textsuperscript{1,2}, Michael G. Fehlings\textsuperscript{1,2,3}

\textsuperscript{1}Division of Genetics and Development, Krembil Research Institute, University Health Network, Toronto, ON, Canada
\textsuperscript{2}Institute of Medical Science, University of Toronto, Toronto, ON, Canada
\textsuperscript{3}Division of Neurosurgery and Spine Program, Department of Surgery, University of Toronto, Toronto, ON, Canada

The science of regenerative medicine has undergone significant advances in the past 2 decades with the development of stem cells as a potential therapeutic option. Mesenchymal stromal cells (MSCs) represent a conceptually relatively safe therapeutic option owing to their low tumorigenicity and potential to differentiate into various cell types including osteogenic, adipogenic, chondrogenic, and myogenic lines. MSCs are highly viable, nonimmunogenic, and are known to provide structural support in spinal cord injuries when continually transfused.\textsuperscript{1}

As Ma and colleagues report,\textsuperscript{2} the regenerative contribution MSCs afford lies in their anti-inflammatory, structural, and trophic support in injury environments. As trophic supporters, MSCs are amongst the highest secreting cell types, allowing them to exert large effects by secreting numerous cytokines and growth factors. In fact, when injected intravenously into rats, MSCs have been shown to home to the spleen, where they exert immunomodulatory effects by increasing circulating levels of interleukin-10, thereby reducing lesion volume and tissue loss, ultimately improving functional recovery.\textsuperscript{3}

In the present paper, the authors reference a previous study uncovering a novel role for MSCs in establishing neuroprotective sheaths that deposit extracellular matrix components and prevent oxidative damage to nerve fibres. These MSC-derived sheaths, investigated by Ma and colleagues,\textsuperscript{4} were found to enwrap neurites stretching across the lesion site, despite lacking expression of myelin basic protein and Schwann cell markers. These findings demonstrate the potential for MSCs to act as reparative supporting cells that may be used to complement endogenous glial scarring and lesion compaction mechanisms in order to encourage axonal regeneration.

The authors describe previous unsuccessful attempts to differentiate MSCs into neurons using chemical treatment, and go on to explain more recent approaches using growth factors and morphogens to achieve a ‘neuron-like’ cell phenotype potentially capable of firing action potentials and synapse formation. While these findings provide an avenue for further investigation, MSCs appear most relevant in structural repair, acting as a sponge when administered systemically in order to limit immune cell infiltration into lesion sites, and inflammatory modulators when administered focally. Optimizing the survival and reparative phenotypes of these cells is an attractive field for further investigation. The authors describe
multiple strategies including ischemic preconditioning, 3-dimensional culturing, and tissue engineering that have been used to effectively yield cells with greater viability and anti-inflammatory potential. Use of these approaches with complementary therapies is likely to achieve the greatest neuroprotection and regeneration. Recent findings have successfully stimulated axonal regrowth in mature spinal neurons using osteopontin, insulin-, fibroblast-, and epidermal-growth factors, and ciliary- and glial-derived neurotrophic factors. MSCs may be used in combination with these approaches to facilitate a structural and trophic niche for functional regeneration, which may be further encouraged by rehabilitative therapy.

MSCs and stem cells in general show great potential for the future that has yet to be fully harnessed and understood. The mechanisms by which MSCs impose angiogenic, neurotrophic, and structural benefits continue to elude definition, though these represent attractive targets for optimizing their therapeutic capacity. In their review, the Zeng group describes current states of knowledge, existing gaps, and future directions of MSC research and highlights the necessity of continued research in this field. This represents a promising area of translational research.

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Extra Cellular Matrix Remodeling: An Adjunctive Target for Spinal Cord Injury and Intervertebral Disc Degeneration

Ashish Kumar*, Neeraj Kumar*, Zarna Pathak, Hemant Kumar

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER)-Ahmedabad, Gandhinagar, Gujarat, India

The extracellular matrix (ECM) is a protein-and-carbohydrate meshwork that supports a variety of biological structures and processes, from tissue development and elasticity to the preservation of organ structures. ECM composition is different in each organ. It is a remarkably dynamic 3-dimensional structure that's constantly changing to maintain tissue homeostasis. This review aims to describe the involvement of ECM components in the remodeling process of spinal cord injury (SCI) and intervertebral disc degeneration (IVDD). Here, we have also described the current ECM-based therapeutic targets, which can be explored for ECM remodeling SCI is a neurological condition with intense influences resulting from a trauma inflicted on the spinal cord. SCI leads to damage to the intact ECM that leads to regeneration failure. IVDD mainly occurs due to aging and trauma. Various ECM components enable fragmentation of the disc and are thereby involved in disc degeneration. ECM manipulation can be used as an adjunct treatment in SCI and IVDD. Current treatment approaches for SCI and IVDD are conservative and unsatisfactory. Targeting ECM remodeling as an adjunct therapy may result in better disease outcomes.

Keywords: Extracellular matrix, Spinal cord injury, Intervertebral disc degeneration, Extracellular matrix remodeling

INTRODUCTION

The extracellular matrix (ECM) is a scaffold for cells and tissues composed of proteins, proteoglycans (PGs), and glycosaminoglycans (GAGs). ECM influences cell adhesion, morphology, migration, proliferation, and differentiation. Consequently, ECM material contains specific cell surface receptor-interacting domains. It is an essential component of all multicellular organisms, consisting of a network of collagens, glycoproteins (GPs), and PGs that are spatially arranged. Each type of tissue develops a unique composition and topology of ECM; even though each tissue type contains the unique type of ECM, some molecules are constant with the all-tissue type; these molecules are collagens, hyaluronan, elastin, fibronectins, and laminins. This noncellular component is the critical modulator of cellular function and tissue behavior. The viscoelastic characteristics of the microenvironment, as well as imposed mechanical stress on cells, are mechanical properties sensed by cells. Other microenvironmental parameters, such as matrix porosity and cell density, can influence cell shape, which can govern even the most fundamental of cell actions. ECM is thought to have numerous physical traits that influence cell behavior, some of which vary depending on the strain applied to the matrix. Matrix stiffness is a fundamentally intrinsic feature of the matrix that cells feel by applying cell-generated tension. Multiple properties of 3-dimensional ECM, including pore size structural organization, cross-link density, and stiffness, have been identified as a modulator of cell motility. By modulating signaling pathways, the ECM helps to maintain tissue structural integrity and transduce cellular communication. Integrins, cadherins, selectins, synde-
cans, and other cell surface receptors interact with ECM components, influencing essential activities like proliferation, migration, and differentiation (Fig. 1).

ECM components demonstrate both regenerative and degenerative potential in the central nervous system. Spinal cord injury (SCI) is a catastrophic neurological illness that occurs as a result of damage to the spinal cord due to mechanical force or pathological conditions, which results in motor and sensory functioning below the injury site. Injury inflicted on the spinal cord initiates inflammation and subsequent degeneration of the ECM. In traumatic SCI, the severity of injury occurs due to cell death. It triggers a complicated secondary damage cascade that culminates in the death of neuronal cells and glial cells, in addition to ischemia and inflammation. This cascade results in the production of a glial scar and cystic cavities, as well as anomalies of spinal cord architecture and structural design. The spinal cord has a low intrinsic recuperation capability as a result of the glial scar and cystic cavities, as well as insufficient endogenous remyelination and axonal regeneration, resulting in lifelong neurological deficits after SCI. Intervertebral discs (IVDs) are fibrocartilaginous, avascular tissue of the body that resides between neighbouring vertebrae in the vertebral column. They serve as shock absorbers. They aid in the protection of the nerves which travel through the spine and vertebrae.

IVDD is a significant degenerative process and a precursor for disc herniation and low back pain. Disc degeneration is caused by cellular, metabolic, and morphological changes that lead to a decrease in the density of cells and ECM components that result in compromised structure and function of IVD. Early treatment appears to promote neurological recovery in preclinical models.

Fig. 1. A graphical overview of extra cellular matrix (ECM) and its major components. ECM is classified into 2 major types that are basement membrane (BM) and interstitial space (IS), BM is found between epithelial cells and connective tissues. BM is composed of collagen IV meshwork that attaches with ECM components like laminins, perlecan, and minor collagens. IS is made up of collagen fibrils, secreted proteoglycans (PGs), matricellular proteins, and hyaluronan. This unique connection produces a dynamic framework for cells to adhere to ECM using surface proteins, such as cell surface PGs, integrins, glypicans and, syndecan. The signal transduction takes place by these interactions which control the various functions. GFR, growth factor receptor.
cal research, case reports, and limited clinical trials. No conventional therapy approach has been shown to improve neurological outcomes to date. The current ECM-based therapeutic approaches include neutralization of inhibitory ECM factors, stimulation of axonal regeneration via modulating ECM components. Here, in this review, we have majorly focused on the structure and composition of ECM components, ECM remodeling, major approaches to modulate ECM in SCI and IVDD. This review aims to provide the insights about ECM targets that can be explored for the therapeutic approaches.

**EXTRA CELLULAR MATRIX COMPOSITION OF SPINAL CORD**

In the CNS, ECM is different from the other systematic tissues. The ECM plays various functions like the migration of cells, axonal guidance, and synaptogenesis and shapes the CNS. In the mature, healthy CNS, ECM acts as a transporter and storage for growth hormones and chemicals, directly via cell membrane receptors, or as a transporter and storage for chemicals and growth factors. The ECM regulates CNS function as it preserves synapses and prevents aberrant remodeling. The mature, healthy CNS includes the interstitial space (IS), basement membrane (BM), and perineuronal nets (PNNs). Collagen, laminin, fibronectin, syndecans, dystroglycan, and perlecan, which make up the majority of the BM, operate as a barrier between endothelial and parenchymal cells. PNNs have an ECM that is comparable to that of the IS. However, it is more compact, resulting in a more significant amount of Chondroitin sulfate proteoglycans (CSPGs) in the body and growth-inhibitory elements like the tenasin receptor and link proteins. PNNs surround the specific, but not all, neurons, as well as presynaptic terminals, nodes of Ranvier, and synaptic boutons. These components are diffused and arranged in IS or in the more complex and condensed structures that constitute the small axonal coats and surround presynaptic terminal fibers, and assemblies of clustered matrix encapsulating nodes of Ranvier and PNNs around the soma, initial axon segments, and proximal dendrites.

In a normal CNS, the interstitial ECM mostly consists of hyaluronic acid (HA), sulfated PGs, and tenascin. The most common GAG in the ECM is called HA. Following injury, high-molecular-weight HA (HMW-HA) gets fragmented and creates low-molecular-weight HA (LMW-HA) fragments which can modulate inflammatory responses. While HA is nonsulfated GAGs, there are various kind of sulfated GAGs found throughout the body, but the CNS is significantly abundant in them. Tenascin-C is a damage-associated molecular pattern that produces innate immune cell activation by interacting with toll-like receptor. Tenascins expression is essential for wound healing. Long-term expression can be harmful, and its termination lowers neurogenic pathology and inflammation.

**EXTRA CELLULAR MATRIX COMPOSITION OF INTERVERTEBRAL DISC**

IVD mainly consists of 3 parts, i.e., central region nucleus pulposus (NP), a highly hydrated structure containing 70%–80% water. This region contains collagen II majorly, along with other components. The second part is the annulus fibrosus (AF), which is the stiff circular outer of the IVD which surrounds the inner jelly-like NP, which mostly contains collagen I and other ECM components like collagen, PGs, HA, fibronectin, and laminin. Finally, the third part is the endplate which is made of hyaline cartilage. To maintain the homeostatic environment, the disc’s cells require nutrients like glucose and oxygen, and the endplate provides this via diffusion.

Disc degeneration is the breakdown of 2 or more discs leading to pain. IVDD results from an imbalance in catabolic and anabolic factors, which increases degradative enzymes like matrix metalloproteinase (MMPs), A disintegrin, and metalloproteinase with thrombospondin motifs (ADAMTs) and decreases the synthesis of ECM components. It is also caused as people become older due to calcification of the endplate, which can disrupt the delivery of nutrients and other metabolic components, resulting in a hypoxic environment and an acidic pH. Improper supply of nutrients causes hypertrophy, apoptosis, and reduced density of IVD cells. With increasing age, the disc’s ECM undergoes significant modifications. Reduced hydration is caused by lowering the aggrecan component in the NP, leading to mechanical dysfunction. Less hydrated, more fibrous NP does not uniformly distribute compressive stresses between vertebral bodies. In addition, inflammatory cytokines like interleukin-1 (IL-1β) and tumor necrosis factor-α (TNF-α) are upregulated, as the increase in disc degeneration leads to ECM remodeling.

ECM of IVD is composed of PGs, water, GAGs, collagen, and other components in lesser amounts and plays an essential role in structural integrity, stiffness, and tensile strength. ECM of the disc appears to have more collagen isoforms than any other connective tissue, namely collagens V, VI, IX, XI, XII, and XIV, contributing to the matrix. Collagen serves as the primary load-
bearing component in a wide range of soft tissue and is crucial to human physiology.26,27 HA is a critical ECM component of IVD that interacts with various protein molecules essential for the signaling and cell-cell interaction. Since it is negatively charged, HA can absorb water at a rate of 10–104 times its mass, making it an osmotically active molecule.28 It can occupy huge gaps due to its high volume when hydrated and serves as a shock absorber and lubricant.29 Aggrecan and versican create huge aggregates with HA that offer water-binding affinity to the disc due to their sulfated GAG chains in higher concentrations.30 Fibronectin is a huge, abundant GPs that participates in the correct construction of ECM. Collagen I, III, gelatin, thrombospondin, decorin, and latent transforming growth factor-protein-1 are among ECM molecules it may bind.31,32 Integrins, the family of cell adhesion molecules that govern cell ECM communication and have many unique integrin receptors, have been discovered, including the fibronectin-binding integrin receptor and collagen-binding integrin receptor.33 The broad family of unique, multiple domain trimeric BM proteins is laminins that regulate related cells behavior, including adherence, proliferation, migration, phenotypic stability, and resistance to anoikis.34

THE EXTRA CELLULAR MATRIX
REMODELING FOLLOWING SPINAL CORD INJURY

The breakdown of ECM after SCI adds to the damage of nerve tissues. Both native and permeating inflammatory cells begin secreting ECM components and MMPs, which destroy the ECM.35 ECM controls the health and activity of neural tissue. The ECM participates in several crucial activities, namely inflammation, survival of cells, axon development, gliosis, revascularization, and adaptability after an injury. As a result, manipulating the ECM after an injury may help heal nerve tissue. After SCI, there are various endogenous repair systems, such as axon development and sprouting,36 revascularization, and neural stem cell proliferation and differentiation.37 On the other hand, these processes may fail or succeed only partially. Following spinal cord damage, the functional impairment and tissue loss are irreversible.38 The spinal cord is protected, regenerated, and repaired in a variety of ways. The first approach involves increasing intracellular survival systems, lowering inflammation and bleeding, or activating antioxidative pathways to reduce oxidative stress. The second approach uses regenerative processes to promote axon development and sprouting. This is accomplished by increasing intracellular axon development or decreasing growth inhibition in the damaged environment. The third method improves neural plasticity by combining electrical stimulation and rehabilitative motor training.39

After CNS injury, the ECM’s composition alters dramatically. The nature of the injury controls this, and influences which cells are then targeted to the lesion location—for example, following blunt trauma that disrupts the blood-brain barrier but leaves the dura mater intact, such as contusive-type SCI and blunt traumatic brain injuries. Glia is generally the main source of scar matrix deposition, whereas penetrating spinal laceration, transection, or cortical stab injuries also confer more remarkable fibroblast invasion through disrupted meninges.40 The key players in ECM breakdown are MMPs, and thus the modulation of MMP expression and activity is critical for tissue homeostasis. Changes influence ECM biology in MMP pattern expression or the equilibrium between MMPs and their tissue-specific inhibitor.41 In addition, changes affect the modulation of cell responses facilitating tissue repair in ECM composition. Degradation of ECM proteins is used to remove dead cells and damaged tissue during the inflammatory phase of tissue restoration. This procedure produces bio-active ECM components known as matricryptins that regulate inflammatory, angiogenic, fibrogenic, and reparative pathways by interacting with cell membrane receptors.42

THE EXTRA CELLULAR MATRIX
REMODELING FOLLOWING DISC DEGENERATION

One of the essential regulators of the body’s cellular and tissue functions is ECM, which constantly responds to various central stimuli. ECM equilibrium must be strictly regulated for wound healing, proper organ homeostasis, and development.30 Homeostasis maintenance in IVD requires tight regulation of matrix quality and turnover, and proteases and their activity enhancers mainly regulate this. This homeostasis is vulnerable to change in the expression of the proteases, which may result in ECM remodeling if altered for a long time.30,43,44 ECM turnover increases when remodeling occurs, leading to changes in histology and architecture of tissue.45 Excessive ECM remodeling can be a life-threatening condition, including disrupted tissue growth, repair, and degradation, finally causing degeneration.45-47 This remodeling is governed by synthesis, secretion, alteration, deposition, and proteolytic degradation of the matrix components.47,48 Eliminating one or more of the ECM’s constituents is an effective way to modify it. MMPs proteolytic enzymes,
ADAMTs, tissue inhibitor of metalloproteinase (TIMPs), heparanase, cathepsins, hyaluronidases, and stripteases are powerful enzymes responsible for ECM remodeling and degradation of structural components of ECM involved in maintaining integrity.58-60 Various investigations over the last few decades demonstrate that an altered mechanical environment of the disc can result in remodeling, breakdown, and rearrangement of the ECM, leading to symptoms of accelerated disc degeneration in some situations.51-54

IVD can maintain the structural integrity and adjust to compressive loading, which regulates the anabolic and catabolic gene expression by ECM remodeling suggested in in vivo studies.55,56 In vivo study in rabbit punctured IVD remodeling in endplate occurs naturally with degeneration.57 Various molecules are involved in remodeling, but MMPs are supposed to cause degradation, and these MMPs are involved in angiogenesis, differentiation, apoptosis, proliferation, and migration.58-60 Out of 23 members of MMPs, MMP-1, MMP-3, and MMP-13 are more expressed in the degenerated disc suggesting their direct role in ECM remodeling.61 The matrix evolves throughout the remodeling phase, causing collagen bundles to expand in size and strength to substitute fibronectin, HA and PGs are also accumulated, contributing to tissue toughness.62 Though MMP-1, 3, and 13 are increased with disc degeneration, this is associated with the rise in their inhibitors (TIMPs 1 and 2). With progressive degeneration, higher expression of ADAMTS-4 was found in immuno-positive cells, which was not accompanied by a rise in its inhibitor TIMP-3.63 Heparanase is a type of endo-beta-glucuronidase that targets PGs upregulation of heparanase isoforms in degenerative IVD and herniated discs, suggesting that heparan sulfate PGs play an essential role in inflammatory responses and ECM remodeling.64

Cathepsin K is a newly found cysteine protease that breaks type I to II collagen's triple helical domains. Factor capable of promoting cathepsin K synthesis is the receptor activator of nuclear factor-B ligand (RANKL), which is well known for its function in generating ECM remodeling enzymes. It was found that the degenerative disc has a higher expression of RANKL than in healthy disc and cathepsin K gene expression levels were found to have a positive, strong relation with RANKL expression. Based on these observations, cathepsin K is found to play an essential role in the remodeling of the disc's ECM and degradation in the degenerative disc's proinflammatory cytokine-rich microenvironment.65

EXTRA CELLULAR MATRIX ASSOCIATED WITH SPINAL CORD INJURY AND INTERVERTEBRAL DISC DEGENERATION, THEIR CORRELATION

IVDD is one of the most prevalent neurological illnesses in dogs and is defined by a spontaneous explosive extrusion of the degenerative IVD into the vertebral canal, resulting in mixed contusive-compressive damage to the spinal cord.66 Although the spinal cord is protected within the spinal canal, dislocation or shattering of the vertebrae, disruption of the IVD, or contusion within a stenotic canal can cause injury to the cord.67 Acute thoracolumbar IVDD can result in rapid spinal cord functional impairment, ascending myelomalacia, and, eventually, decreased life expectancy and quality of life.68 Significant and early axonal swellings characterize axonopathy in the white matter, which is amplified in the ventral portions of the lesion epicenter during naturally occurring IVDD-related SCI in dogs. Significant data suggests that lower back pain and spinal cord compression nerve pain are common clinical and public health issues caused by IVDD.69 Degenerated discs are prone to out-pouching (herniation); the protruding disc can press against one of the spinal nerves that run from the spinal cord to the rest of the body. This pressure causes pain, weakness, and numbness in the back and legs. When the bone spurs compress the spinal cord, affected individuals can develop problems with walking and bladder and bowel control.

MMP-9 has been reported to have a severe injury in dog IVDD. Its activity in the cerebral fluid corresponds with injury severity in dogs with IVDD, suggesting that this may play a detrimental role in acute SCI.70,71 In spinal cord-damaged mice, inhibiting MMP-9 expression improves locomotion. These MMPs are more expressed in degenerated disc cells and tissues. Human IVDD has been linked to an increase in ADAMTS-4 expression at both early and late stages,72 whereas the level of expression did not indicate any meaningful difference in SCI; this suggests that ADAMTS-4 is present in the spinal cord at all times, whether it is normal or diseased condition.73 These findings imply that ADAMTs and CSPGs play an important role in SCI and IVD.

Various other collagen is present like types II, VI, IX, and XI also present in the NP and types I, II, V, VI, IX, and XI from the AF type I collagen was highly expressed in the spinal cord during the scar-forming phase and induced astrocytic scar formation via the integrin-N-cadherin pathway.74 Collagen type-III is present in both pathological and healthy IVD.75 In SCI collagen IV meshwork that acts as a binding matrix for a variety of ECM...
components and inhibitory compounds such as PGs and semaphorins, as well as growth-promoting proteins.\textsuperscript{76} After SCI, the HMW form of GAGs-HA is degraded in rat spinal cord.\textsuperscript{77} Degradation of natural HMW-HA, has been demonstrated to activate and proliferate astrocytes and contributes to glial scar.\textsuperscript{74}

**EXTRA CELLULAR MATRIX REMODELING-BASED THERAPEUTIC APPROACHES FOR SPINAL CORD INJURY**

ECM protein called Periostin is linked to scar formation through fibrosis, propagation, and inflammatory signaling.\textsuperscript{78,79} Preventing ischemia, minimizing inflammation-related secondary harm, controlling the cytotoxic and immunological response, and supporting cellular regeneration are some therapies for SCI.\textsuperscript{80} From day 4 to day 14 post-injury, daily i.p. injections of a monoclonal antibody of mouse against Periostin were demonstrated to minimize scarring and improve sensorimotor tasks in mice.\textsuperscript{80} In a recent study, it was found that severity of SCI could be attenuated within the 14 days after the SCI in mice when treated with N-cadherin neutralizing antibody, which disrupts the interaction between type I collagen and astrocytes, which is integrin and N-cadherin dependent which showed the reduced astroglial scar formation.\textsuperscript{74} Pharmacologically, the scar’s fibrotic components can also be addressed. Systemic injection of the antimitotic microtubule stabilizers taxol or epothilone B reduces scar-forming fibroblast migration and suppresses substantial scar development, allowing axon regeneration and functional recovery.\textsuperscript{82,83} In one of the studies, iron chelators 2,2-bipyridine-5,5-dicarboxylic acid inhibits prolyl 4-hydroxylase (which inhibits, a crucial enzyme in collagen IV synthesis) and cyclic adenosine monophosphate to stop collagen formation,\textsuperscript{84,85} increases neuroprotection and long-distance axon regrowth while reducing fibrotic scarring.\textsuperscript{80}

The termination of chondroitin sulfate glycosaminoglycan (CS-CAGs) through the chondroitinase ABC (ChABC) enzyme was found to improve axonal regeneration and neuroplasticity, as well as promote functional improvement, after experimental spinal cord damage.\textsuperscript{86-89} The thoracic and cervical region of the spinal cord when undergoing contusion injury, a gene therapy approach of enzyme administration in which host cells are transduced to express the ChABC gene leads to extensive CS-GAG breakdown, resulting in decreased pathology and increased functional improvement.\textsuperscript{90-93} Furthermore, viral administration of ChABC leads to broad CSPG regulation, which promotes macrophage conversion to a pro-resolving M2 polarization state\textsuperscript{94} and anti-inflammatory IL-10 modulated response.\textsuperscript{94} The enzyme Arylsulfatase B (ARSB, N-acetylgalatosamine-4-sulfatase), which terminates the C4S portion, particularly from CS-GAGs, is the other enzymatic method that is being used to reduce CSPG inhibition. A study conducted in mice of the spinal cord damaged by compression method when treated with ARSB treatment has recently been proven to induce increased axonal outgrowth and functional locomotor recovery.\textsuperscript{95}

Alteration of the CSPG receptor through modification of the receptor protein tyrosine phosphatase \( \sigma \) (PTP\( \sigma \)) is a potential therapeutic option. PTP\( \sigma \)’s intracellular phosphatase domains activity is controlled by a “wedge” structure that can obstruct the catalytic site, limiting phosphorylating action and signaling downregulation. The use of a membrane-permeable peptide mimicking this wedge inhibits PTP\( \sigma \) signaling when ligands like CSPGs activate it. In rats with spinal contusions, systemic infusion of these peptides was demonstrated to help them regain bladder and locomotor function.\textsuperscript{86} Wang et al.\textsuperscript{97} reported a novel hydrogel-liposome-hydrogel delivery system, SLIP@SF, in which DTX (docetaxel) and basic fibroblast growth factor (bFGF) are encapsulated. By mending the blood-spinal cord barrier, modulating the levels of inflammatory factors, decreasing the inhibitory CSPGs level, and affecting the bipolar architecture of the glia, bFGF decreases neuronal loss and cavity region by providing a favorable environment for axonal regeneration. By enhancing microtubule stabilization, DTX promoted intrinsic axonal development. Furthermore, bFGF reduced the amount of ECM that was removed too quickly.

In a recent report, a designed nanofiber hydrogel was combined with a prolonged release of growth factor cocktail to rebuild the ECM near the lesion after severe SCI. As established by immunochemistry, such an engineered milieu might modify local inflammatory reactions, eliciting substantial axon regrowth beyond the lesion site in a coordinated manner. As a result, locomotion and electrophysiological characteristics improved significantly.\textsuperscript{98} In a study, gene transfection and implants were used in vitro and in vivo, where they showed that lipoplexes could fix on ECM-coated poly lactic-co-glycolic acid (PLGA), with fibronectin allowing for the most efficient gene transfer. Treatment of lipoplexes with fibronectin-coated PLGA resulted in significant expression levels in vitro, allowing lipoplex attachment to complicated geometry pre-fabricated scaffolds. Several channel bridges stabilized with lipoplexes were inserted in the spinal cord following injury in vivo, leading to higher transgenic expression levels than a bare plasmid. Transport of lipoplexes
through spinal cord bridges after injury was shown to be an effective mechanism for DNA carrier, as a modest amount of DNA was enough to promote transgenic expression for 3 weeks (Fig. 2).99

**EXTRA CELLULAR MATRIX REMODELING-BASED THERAPEUTIC APPROACHES FOR DISC DEGENERATION**

The disintegration of matrix proteins predominantly causes IVDD so potential therapy options should focus on ECM regeneration as well as cellular components.100 Biomolecular remedies, cell-based treatments, and tissue engineering of a replacement disc have all been investigated as ways to repair and regenerate the IVD.101 Growth factors stimulate matrix production and change the matrix balancing toward a pro-anabolic phase, which regulates disc cell metabolism. Increased mRNA expression of aggrecans, collagen I, II was detected in rabbit NP cells grown in atelocollagen and subjected to tissue growth factor-beta (TGF-β) and bone morphogenetic protein-2 (BMP-2).102 Platelet-derived growth factor, bFGF, and insulin-like growth factor-1 are 3 effective mitogens that have been proven to amplify the proliferation of bovine NP cells.103 Therefore, the supply of these growth factors at the proper diseased stage will be a potential therapy for IVDD.

Studies with direct biomolecule injection into the degenerative disc in vivo have yielded promising outcomes. Takegami et al.104 found that rabbit IVD cells grown on alginate gel were treated with BMP-7 (also known as OP-1), a member of the TGF-growth factor superfamily, that showed an increase in PGs production. Synthetic peptides used to stimulate regeneration could be a highly cost-effective and safer biomolecular potential treatment. In vivo studies, Link N, a synthetic peptide with growth factor-like characteristics, has shown increasing aggrecan gene expression and downregulating protease expression.105 The idea behind gene therapy for IVDD is that by specifically delivering genetic materials to recognised and understood components of the pathways causing IVD degeneration, it may be possible to enhance the anabolic and catabolic balance.106,107 In recent work,

![Fig. 2](https://www.e-neurospine.org)

**Fig. 2.** Schematic representation of different extra cellular matrix remodeling targets and applied approaches for therapeutics. (a) Axonal guidance, which stimulates axonal sprouting, requires molecular signaling. (b) The intrinsic remyelination could be promoted. (c) Stem cells from the central canal could be mobilized or induced for regeneration. (d) Regeneration of neurons with the help of different growth factors. (e) The genetically modified cells factor expression is one of the approaches to increase neuronal survival and migration. (f) Different biomaterials are used as a scaffold that maintains structural integrity and promotes regeneration. (g) Glial scar limits axonal regeneration which can be degraded by chondroitinase ABC. (h) The regeneration and plasticity of new neuronal connections could be an approach.
Leckie et al.\textsuperscript{108} found that injecting adeno-associated virus to disc cells induced them to release BMP-2 or TIMP-1 proteins, which slowed the progression of degenerative changes in a rabbit disc degeneration model. siRNA molecules could be used to quiet, unwanted protein molecules associated with IVD degeneration. A study by Seki et al.\textsuperscript{109} mentioned that a single injection of ADAMTS-5 siRNA prevented degeneration and restored histological grades of NP cells in a rabbit disc degeneration model in an elegant \textit{in vivo} study. Matrix degradation has been linked to TNF-\(\alpha\).\textsuperscript{58} However, etanercept, a TNF-\(\alpha\) antagonist, was discovered to be a promising therapy, resulting in considerable improvement in individuals with chronic pain related to disc.\textsuperscript{110}

Mesenchymal stem cells (MSCs) are considered to be the best option for disc repair because they can develop along a chondrogenic lineage and synthesize the PGs and collagens found in the ECM of the disc.\textsuperscript{111} MSCs transplantation resulted in decreased height loss of disc and increased GAG content at 16 weeks in a rabbit degeneration model relative to controls, with no differences detected between MSCs and NP cell injection.\textsuperscript{112} When MSCs and degenerated human NP cells were cocultured, the NP cells produced more PGs and collagen.\textsuperscript{113} Hydrogel scaffolds have been employed extensively in the NP to preserve deposited PGs and facilitate the formation of osmotic pressure. Because of accessibility of manipulation and propensity to entrap released PGs, alginate\textsuperscript{114,115} and agarose-based\textsuperscript{116} hydrogels have been widely employed for NP cultivation. Hydrogels containing HA, a local NP ECM element, have also been employed to retain NP phenotype and improve disc biomechanics \textit{in vitro}\textsuperscript{117,118} and \textit{in vivo}\textsuperscript{119,120}.

Current research is focused on improving the mechanical properties of scaffolds by introducing collagen molecules, which has resulted in enhanced compressive and tensile mechanical properties of scaffolds by introducing collagen molecules, which has resulted in enhanced compressive and tensile mechanical

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**Fig. 3.** Therapeutic approaches for disc degeneration. Cells: Intervertebral disc (IVD) supplementation with reparative cells is essential due major role of cell loss in the degenerative changes. Prominently, Mesenchymal stem cells, stem cells and primary cells are considered as important source of regenerative approaches. Regulatory signals: The degenerative process can be stopped or slowed down by administering therapeutic molecules or proteins directly into the IVD and rebuilding its natural structure. Growth factors like, platelet-derived growth factor (PDGF), Insulin-like growth factor 1 (IGF-1), and basic fibroblast growth factor (BFGF) is widely used. The therapeutic approaches for regeneration of disc involve the gene transfer to localised cells inside the IVD. Biomaterials: It has been investigated to implant biomaterials to stimulate native disc cells, repair the degenerating disc structure, or even replace the complete disc. Hydrogels mimic the native extra cellular matrix and can be used as carriers for the delivery of drugs, proteins, and stem cells. Numerous natural and synthetic biomaterials have been thoroughly investigated for IVD regeneration. MSC, mesenchymal stem cell; HA, hyaluronic acid; PEG, polyethylene glycol.
Scaffolds of collagen peptide nanofiber can inhibit the development of IVDD and improve tissue function by increasing GAGs and collagen accumulation. Scaffold, such as polyglycolic acid and poly-DL-caprolactone and hydrogel-based natural polymers, such as collagen, fibronectin, HA, and synthetic polymers like polyethylene-glycol, the polyethylene oxide is being used. LM111-hydrogels may help boost or sustain the expression of particular markers associated with phenotypic immature NP cells. A potential biological therapy for initial stage IVDD involves encapsulating NP cells forming hydrogels in situ, and boosting the expression of numerous key ECM-related genes in NP cells, such as type I collagen, aggrecan, Sry-type high mobility group box transcription factor-9, and hypoxia-inducible factor-1 (Fig. 3).

CONCLUSION

The ECM is important throughout development and after a disease or injury. The ECM is involved directly in fundamental processes such as cell signaling, axon guidance, and synaptic plasticity, rather than simply providing a supportive environment. Manipulation of the ECM is a promising therapeutic method for recapitulating favorable developmental processes and/or minimizing negative remodeling following injury, either by targeting single ECM components or entire families of ECM molecules. The composition of the ECM can be deleterious to axonal regeneration, plasticity, and repair after CNS injury. Although the direct relationship between IVDD and SCI has not been established yet in humans, looking from the perspective of ECM remodeling, many ECM components share the same function in both diseases. In some of the studies, canine models of IVDD-induced SCI have shown that there is a structural and molecular interplay between IVD and SC. Correlative techniques for ECM remodeling in IVDD and SCI have not been investigated based on existing research data. Different approaches for treatment have been in use for the past few decades, but these therapeutic approaches do not provide the native microenvironment to IVD required for regeneration. We have discussed some of the regenerative methods as treatment and regeneration of the IVD using scaffolds, hydrogels, a combination of polymers. So, using ECM components as the therapeutic target would be a promising approach for regeneration.

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ORCID

Ashish Kumar: 0000-0002-2291-8176
Neeraj Kumar: 0000-0002-7966-8382
Zarna Pathak: 0000-0001-9036-7364
Hemant Kumar: 0000-0002-6434-0245

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Spinal Cord Injury Provoked Neuropathic Pain and Spasticity, and Their GABAergic Connection

Ankita Bhagwani, Manjeet Chopra, Hemant Kumar
Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER)-Ahmedabad, Gandhinagar, Gujarat, India

Traumatic spinal cord injury (SCI) is the devastating neurological damage to the spinal cord that becomes more complicated in the secondary phase. The secondary injury comes with inevitable long-lasting complications, such as chronic neuropathic pain (CNP) and spasticity which interfere with day to day activities of SCI patients. Mechanisms underlying CNP post-SCI are complex and remain refractory to current medical treatment. Due to the damage, extensive inhibitory, excitatory tone dysregulation causes maladaptive synaptic transmissions, further altering the nociceptive and nonnociceptive pathways. Excitotoxicity mediated GABAergic cell loss, downregulation of glutamate acid decarboxylase enzyme, upregulation of gamma-aminobutyric acid (GABA) transporters, overactivation of glutamate receptors are some of the key evidence for hypoactive inhibitory tone contributing to CNP and spasticity post-SCI. Restoring the inhibitory GABAergic tone and preventing damage-induced excitotoxicity by employing various strategies provide neuroprotective and analgesic effects. The present article will discuss CNP and spasticity post-SCI, understanding their pathophysiological mechanisms, especially GABA-glutamate-related mechanisms, therapeutic interventions targeting them, and progress regarding how regulating the excitatory-inhibitory tone may lead to more targeted treatments for these distressing complications. Taking background knowledge of GABAergic analgesia and recent advancements, we aim to highlight how far we have reached in promoting inhibitory GABAergic tone for SCI-CNP and spasticity.

Keywords: Chronic neuropathic pain, Spasticity, Glutamate, Hyperexcitability, Spinal cord injury, Dorsal horn

INTRODUCTION

Spinal cord injury (SCI) is the destructive neurological damage to the spinal cord that can cause temporary or permanent sensory and motor impairment in patients affecting their quality of life.1,2 Injury to the spinal cord may be of exogenous or endogenous origin, of which more than 90% of cases are considered traumatic in etiology and affect more adult males as compared to females.2 Traumatic causes of the injury may include sports or vehicular accidents, falls, bullet injuries, or any other forms of violence, whereas the nontraumatic injury may be due to acute or chronic illnesses, including tumors and infections.1 Depending upon the time sequence of the injury, SCI’s overall pathophysiology is split into 3 major phases: acute, subacute, and chronic, with each phase presenting progressive damage to the spinal cord over time.3 At the initial stages, the traumatic injury (primary injury) only affects the spinal cord mechanically by damaging the blood vessels and cellular membranes, causing ischemia and inflammation. This is followed by the secondary injury, a cascade of events that further exacerbates the neurological damage through vascular, biochemical, and cellular changes. Most of the secondary events (subacute and chronic phase) in SCI pathophysiology include complex mechanisms leading to calcium and glutamate excitotoxicity, vascular changes, ionic imbalance, reactive oxygen species (ROS) production, lipid peroxidation, inflammation, and apoptosis. This complex

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secondary cascade at later stages initiates the development of a glial scar and cystic cavities that impairs the normal myelination and axonal regeneration process resulting in a permanent detrimental state of the injury.1,3

Glutamate excitotoxicity during the postinjury period is one of the most concerning states responsible for connecting several other mechanisms, furthering the damage. Several studies report the role of overactivated N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in raising sodium and calcium levels intracellularly. In addition to the toxicity in the myelinated axonal region, the overactivation of the glutamate receptor, AMPA, in the white matter region is toxic to oligodendrocytes and astrocytes.4 The glutamate receptor overactivation and the downregulation of glutamate transporters are the leading causes of persistent hyperexcitability.5 Initially, acute primary damage to the spinal cord gives rise to hemorrhage at the injury site. Further, this results in ischemic insult due to ATP depletion at the site, raising energy demands, thus reducing the normal transporter-mediated uptake of glutamate.2 Downregulation of astrocytic GLT-1 (glutamate transporter 1) and GLAST (glutamate/aspartate transporter) postinjury period has already been reported.6 Besides this, injury-associated blood-brain barrier (BBB) disruption releases excitatory amino acids (EAAs) through nonspecific membrane micropores leading to astrocytic edema and glutamate extravasation. Altogether, these factors, receptor overactivation, downregulation of transporters, and BBB disruption contribute to raising the glutamate levels extracellularly. Furthermore, glutamate-mediated sustained depolarization causes heavy calcium influx through NMDA, AMPA, and G protein-coupled glutamate receptors, resulting in an ionic imbalance that increases the lesion damage, neuronal and glial cell loss in the spinal cord.6,6

Persistent glutamate-mediated hyperexcitability contributes to the insufficiency of GABAergic inhibitory tone in the spinal cord dorsal horn (DH), which is reported to be one of the leading bases for the emergence of chronic neuropathic pain (CNP) post-SCI.7 Previously Zhang et al.8 reported the loss of GABAergic cells in the lumbar region after photochemically induced spinal cord ischemia in rats. Another study showed that an early rise in oxygen free radicals due to oxidative stress caused a reduction in GABAergic neurotransmission by modulating GABA_{6} gated chloride channels.9 Also, alterations in levels of cation-chloride channels (upregulation of Na⁺-K⁺-Cl⁻ cotransporter isoform 1 [NKCC1] and downregulation of K⁺-Cl⁻ cotransporter isoform 2 [KCC2]) was observed after the injury on which GABAergic tone is dependent.10 There was also a loss of the enzyme glutamic acid decarboxylase (GAD) isoform GAD_{6}
in noticed in spinal DH post nerve injury, which is responsible for synthesizing GABA.11 Gene deletion of synapsin II by inhibiting glutamate release from primary afferent nociceptive fibers and promoting long-lasting GABA release alleviated mechanical and cold allodynia symptoms in neuropathic pain (NP) mouse model.12 Together, these changes outline the insufficiency of inhibitory GABAergic tone after the central nervous system (CNS) injury. Inhibiting this tone using GABA antagonists has shown NP like effects.13 Hence, raising GABAergic tone post-SCI remains a significant approach for alleviating CNP.

Another major complication of chronic nature after the injury is spasticity. It is one of the components of upper motor neuron (UMN) syndrome with hypertonia, hyperreflexia, and clonus-like symptoms. Various reports provide evidence of hypoactive GABAergic inhibition post-SCI as a major cause of spasticity development.14 Thus, enhancing GABAergic tone for easing the spastic symptoms is already a promising intervention that suggests the role of hypoactive GABA in causing spasticity. Several mechanisms of a complex nature have led to the development of spastic symptoms; hence absolute treatment to relieve spasticity remains challenging after the injury.14 In this review, we explore the role of GABA in producing CNP and spasticity which is experienced by most of the patients in post-SCI period. Several approaches that specifically target the inhibitory GABAergic tone for attenuating both these complications will be discussed in detail with special emphasis on ongoing research.

**GABA**

1. **Synthesis, Release and Spinal Distribution**

Even though glutamate is an excitatory neurotransmitter, it synthesizes GABA, which is the primary inhibitory neurotransmitter in the brain. Glutamate is the standard source for the synthesis of GABA in CNS using the enzyme GAD. In humans, GAD exists in 2 isoforms, GAD_{6} and GAD_{6}. Both the isoforms are expressed differently in brain regions. It is considered that 90% of GABA is produced utilizing the GAD_{6} isoform. Besides glutamate, GABA can also be synthesized using polyamine, ornithine, arginine, or homocarnosine pathways through putrescine using various enzymes.15

Conventionally, GABA is released from the axonal terminals of neurons by calcium-mediated vesicular exocytosis.16 However, a few reports suggest the release of GABA by some unconventional means. Dendritic release of GABA in a retrograde
manner through high depolarization mediated release of glutamate in the olfactory bulb and astrocytic GABA release through astrocytic synthesis or uptake mechanisms are the examples for unconventional GABA release.

GABA is abundant in the spinal cord, it is presented by interneurons only and not by the projection neurons. GABAergic interneurons are localized largely in superficial laminae, while some are in deeper laminae of the dorsal and ventral horn. The inhibitory part of the GABAergic system is also distributed through various synaptic organizations that are axosomatic or axoaxonic. Besides this, GABAergic myelinated fibers found in the white matter region also indicate the inhibitory system’s presence in the supraspinal region.

2. GABA Action – GABA-A, B, and C Receptors

The GABAergic inhibitory system functions by acting on 3 main receptors, GABA_A, GABA_B, and GABA_C, which are present on pre or postsynaptic membranes of neurons and glial cells. Structurally, GABA_A is a pentameric ligand-gated ionotropic receptor complex having subunits with various isoforms. The binding of GABA to this receptor in the unoccupied state is quite high, which causes a conformational change leading to postsynaptic Cl^- channel pore opening and thus allowing Cl^- influx-mediated hyperpolarization. Several exogenous compounds like benzodiazepines, barbiturates, picrotoxin possess binding sites on the GABA_A receptor, hence act as modulators.

GABA_B receptors are metabotropic G protein-coupled receptors linked with Ca^2+ and K^+ channels. They primarily have 2 receptor subunits GABA_B1 and GABA_B2. These receptors are localized either in the presynaptic region as autoreceptors that regulate the GABA release or in the postsynaptic region that causes hyperpolarization by activating K^+ channels.

GABA_C receptors were unresponsive to both bicuculline (GABA_A antagonist) and baclofen (GABA_B agonist). This gained attention as it illustrates, they are distinct from the GABA_A and GABA_B receptors. Though their ionotropic and ρ subunits (p1–p3) containing properties are identical to GABA_A receptors, they differ in that they are approximately 10 times more sensitive to GABA, have a greater number of binding sites, possess a poor ability to undergo desensitization, have homooligomeric assembly of ρ subunits (p1–p3) and prominent localization to retina rather than the entire CNS.

3. Glutamate-Glutamine-GABA Cycle Homeostasis

The glutamate-glutamine-GABA cycle helps balance the amino acid neurotransmitters GABA and glutamate, employing neuronal and glial transfer. In glutamatergic neurons, glutamate is synthesized using the tricarboxylic acid cycle (TCA) intermediate α-ketoglutarate. This is then taken up by astrocytes and is changed into glutamine using the enzyme glutamine synthetase. After astrocytic release, the extracellular glutamine is taken up by GABAergic neurons. Glutamate is produced using the enzyme glutaminase, which ultimately produces GABA using the GAD enzyme. Similarly, uptake of released GABA by astrocytes converts GABA to TCA intermediate succinate by the enzyme GABA transaminase and succinate semialdehyde dehydrogenase. This succinate can synthesize glutamine and further α-ketoglutarate via citrate. This makes way again for α-ketoglutarate to synthesize glutamate and the cycle continues.

GABA AND NEUROPATHIC PAIN POST-SCI

Quality of life post-SCI is often quite poor. Furthermore, centrally initiated NP observed in two thirds of the injured patients for chronic periods adds up more to the same. The pain of conventional inflammatory causes is protective, which generally subsides with the healing process of the injury or recovery from the disease. However, NP brought about by injury or disease of CNS, can last even after the resolution of disease or injury healing without giving any protective assistance to the patient. International Association for the Study of Pain classified CNP of SCI based on the location of its emerging, that is either above-level, at-level, or below the level of injury which may last for months or throughout the lifetime of the patients. Patients generally experience CNP differentially. Some describe it to be continuous, some interrupted, while in some, it is spontaneous or stimulus-induced. At-level pain generally involves allodynia, spontaneous and consistent pain representing the retention of partial sensory activity at the site. Factors like the age of more than 50 years, tetraplegia, and the traumatic cause of the injury make SCI patients more at risk of CNP. Most of the patients develop below-level pain after 6 months to one year of the injury. Several cellular, biochemical or electrophysiological mechanisms are responsible for CNP, of which neuronal and glial hyperexcitability, microglial activation, and alterations in somatosensory cortical reorganization majorly contribute. To study causal mechanisms of CNP, various animal models have been made, including inducing ischemic lesions, anterolateral spinal cord lesions, transection, clip compression, contusion, hemisection, quisqualic acid injection resulting in mechanical and thermal hyperalgesia and allodynia. The contusion model
is more frequently used to study NP-based mechanical hypersensitivity.22,26

The spinal cord plays a central role in nociceptive and nonnociceptive signal processing and control through afferent pathways carrying further inputs to the brain. Nociceptive neurons in the DH of the spinal cord having terminals of nociceptive afferent fibers Aδ and C fibers, project signals to the brain by direct and indirect inputs, respectively. The neurons in lamina II of the DH are either excitatory or inhibitory and show a response mostly to the received nociceptive inputs.27 Normally, there is a counterbalance between the excitatory and the inhibitory inputs. The inhibitory interneurons of the spinal cord limit the spinal nociception by pre and postsynaptic inhibition mechanisms mediated by GABAergic synapses and GABA and glycine synapses, respectively. The direct antinociceptive descending inhibition through GABA and glycine pathways also help in controlling nociceptive inputs, which are activated by bulbospinal projections of the brain stem.17

In contrast to this, some reports suggest that inhibitory GABAergic transmission may transmit pain impulses rather than inhibiting them. Nevertheless, the activation of GABA A, and GABAs receptors, in general, have shown antinociceptive effects.28 The presence of lesions or injury in the nervous system is responsible for CNP. The excitotoxic damage leads to the release of excitatory glutamate from afferent fibers. Further, glutamate in excess over activates its receptors causing high calcium influx, increasing persistent hyperexcitability and central sensitization of DH neurons leading to NP.27 The release of neuropeptides, ROS, adenosine monophosphate, and inflammatory cytokines due to neuronal and glial cell's hyperexcitability further enhances pain transmission.29 Sensory neurons experience phenotypic changes after the injury. Neurons are reported to possess more of wide dynamic range (WDR) neuron properties making them respond to both weak as well as strong stimuli in the DH.29 Alterations in pathways of sensory neurons allow painful response to noxious stimuli as the noxious, which is referred to as allodynia, generally experienced in NP.29 Many such mechanisms are responsible for an imbalance between inhibitory and excitatory tone in the postinjury period that is discussed later in this review.

**SCI DIFFERENTIALLY REGULATES GABA LEVELS**

The complex pathophysiology of SCI involves various events promoting imbalance between the excitatory-inhibitory tone by altering the levels of amino acids released in the DH. Panter et al.30 described that an early rise in levels of these amino acids were linked with the degree of traumatic injury induced in rabbits. The more severe the injury, the greater the increase in the levels of all 9 amino acids along with GABA and glutamate were observed. Similarly, in rats, the acute traumatic contusive injury produced an initial rise in GABA levels at early hours postinjury.31 This initial upsurge was observed due to increased GAD levels, which synthesized more GABA in the early 12 hours postinjury.32 Initial damage to the GABAergic cell membranes, more release of GABA from synaptic terminals, GABA uptake transporter downregulation are considered to be the primary reasons for the early rise in GABA levels after injury.33

In contrast to the above findings, the overall inadequacy of the inhibitory GABAergic tone promoting CNP is already well established.34 Persistent hyperexcitability in the postinjury period causes the overactivation of glutamatergic neurons, promoting cell death.6 Also, Fas/CD95, tumor necrosis factor R1 (TNFR1), and TNFR2 signaling mediated cell death of neurons and glia in the spinal cord is reported after the injury, which could relate to the loss of GABAergic interneurons.35 Meisner et al.34 reported the GABAergic neuronal loss in the DH post contusive injury, which led to mechanical and thermal hyperalgesia in mice, that was then relieved by tiagabine, an inhibitor of GABA transporter. The expression of protein GAD65, which is responsible for synthesizing GABA from glutamate, was downregulated in the DH after the injury suggesting low GABAergic tone.36 Likewise, reduction in levels of GAD67 was observed in chronic constriction of the infraorbital nerve model, causing mechanical allodynia, which was later attenuated using GABA transaminase inhibitor, vigabatrin.37 Gosselin et al.38 reported astrocytic and microglial activation mediated increase in GABA uptake by upregulation of GABA transporter 1 (GAT-1) in the gracile nucleus of spared nerve injury NP models of rats. In one study, administration of GABA A receptor antagonist bicuculline triggered allodynia-like behavior in rats signifying the decreased GABAergic tone, relating it to NP postinjury.39 Altogether, these studies of GABAergic cell loss, low expression of GAD isofrom, and high transporter-mediated GABA uptake provide a sound basis for associating GABAergic tone loss with CNP after the injury.

**MECHANISMS REDUCING THE GABAERGIC TONE**

Along with the explanations mentioned above of GABAergic...
cell loss, high GABA reuptake, and low GAD$_{65/67}$ proteins, a significant role is played by persistent hyperexcitability, microglial activation, and cation-chloride channel alterations, which together have a role in lowering the GABAergic tone. Also, these mechanisms go hand in hand postinjury to cause CNP (Fig. 1). A study reports that a GABA$_A$ agonist baclofen and NMDA antagonist ketamine when given in combination, were found to be more efficacious and worked synergistically to attenuate CNP (Table 1). However, as the definitive treatment to deliver complete relief from NP for long periods remains lacking, many researchers are working on addressing the underlying complex mechanisms to target CNP in SCI patients.

1. Persistent Hyperexcitability Post-SCI

The neuronal hyperactivity is considered the major mechanism in inducing CNP post-SCI. The early rise in toxic levels of EAAs after injury to the spinal cord is already recognized. The rising levels themselves present a threat to healthy cells because of damage due to the overactivation of glutamate receptors. So how do EAAs that are released in just minutes post-SCI,
affect the neurons? This was studied by administering exogenous glutamate and aspartate mixture in vivo, which resulted in the loss of neurons due to the excitotoxic secondary damage. Several such studies confirm the neurotoxic nature of EAAs after the injury. Injury to the spinal cord using AMPA agonist quisqualic acid also caused excitotoxic damage resulting in neuropathic pain.

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<td></td>
</tr>
<tr>
<td>CLP290 (i.p.)</td>
<td>Female C57BL/6 WT mouse and Vgatires-Cre VGlut2-ires Cre, ChAT-ires-Cre strains (double lateral hemisection)</td>
<td>KCC2 agonist promoted functional recovery&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

SCI, spinal cord injury; NP, neuropathic pain; CNP, chronic neuropathic pain; HFV, human foamy virus; s.c., subcutaneous; GAD, glutamate decarboxylase; SD, Sprague Dawley; GABA, gamma-aminobutyric acid; HSV, herpes simplex virus; i.t., intrathecal; NMDA, N-methyl-D-aspartate; FVB, FV-1b allele Friend leukemia virus B sensitive; GFP, green fluorescent protein; ESC, embryonic stem cells; i.p., intraperitoneal; WT, wild-type.
ral loss leading to spontaneous and evoked pain responses in rats.\(^42\) Normally, the descending inputs and presence of the inhibitory tone counterbalance the hyperexcitability but after SCI, the loss of inhibitory GABAergic inputs led to disinhibition facilitated neuronal sensitization.\(^43\)

Many previous studies link neuronal hyperexcitability in increasing nociceptive transmission. Overactivation of glutamate receptors causes heavy calcium influx, which further initiates several downstream signaling pathways by activating kinases.\(^44\) Upregulation in phosphorylated calcium/calmodulin-dependent kinase II was observed in neurons and oligodendrocytes after SCI contusion in rats. This resulted in WDR neuronal hyperexcitability mediated mechanical allodynia.\(^45\) Heavy calcium influx can trigger phospholipase A2 activation, which in turn can produce prostaglandins and leukotrienes or be a prevailing mediator for the production of ROS, reactive nitrogen species, and other pathways. ROS through transient receptor potential vanilloid 1 and ankyrin 1 channels can trigger glutamate release and the production of inflammatory cytokines.\(^23\) Lowering the neuronal activation threshold contributes to neuronal hyperexcitability mediated central sensitization.\(^46\) Neuronal hyperactivity is well characterized in SCI-NP animal models signifying electrophysiological changes brought about by long neuronal after discharges, reduced action potential generation thresholds, and alterations in their frequencies.\(^29\) Various studies that target CNP using glutamate receptor antagonists provide more relevance to this. In 1997, it was reported that NMDA antagonist MK-801 and AMPA antagonist NBQX could prevent excitotoxic neuronal loss and provide neuroprotection to the injured spinal cord.\(^47\) Similarly, when these compounds were tested on different phenotypes of lumbar spinal cord neurons of the thoracic SCI hemisection model, they helped in reducing the neuronal hyperexcitability mediated below-level pain by blocking inotropic glutamate receptors.\(^48\) Then Bennett et al.,\(^48\) with the use of D-AP5 (NMDA antagonist) and NBQX (AMPA antagonist) demonstrated that inhibiting glutamate overactivation could alleviate mechanical allodynia in SCI rats. Hyperexcitability of neurons after SCI is not just limited to the DH of the spinal cord, rather this inevitable event occurring in the supraspinal region and higher brain centers also has contributed to producing ongoing pain.\(^49\)

2. Reactive Microglia and CNP Association

Similarly, various receptors, transporters, ion channels, or signaling pathways presented by neurons are also expressed in glial cells. The mechanical damage to the spinal cord, through varied outcomes, initiates activation of resting microglia, contributing to CNP. Major mechanisms for microglial activation include glutamate-mediated hyperexcitability, stimulated excessive nociceptive neuronal firing in the DH, ionic imbalance, cytokines and chemokines release, T cells and leukocyte infiltration, and alterations in proteins that are regulating the cell cycle. In response to the injury-induced damage to the nerves, it is reported that upon activation, microglia undergo several morphological changes and express various markers like CD11b, glial fibrillary acidic protein, and Iba-1. An increase in CD11b expression was observed from 2 hours and up to 180 days after the injury.\(^49\) In addition, the expression of one such molecule, P2X4 (purinergic receptor), is found to be upregulated on reactive microglia after peripheral nerve injury, which is known to be associated with increased pain hypersensitivity.\(^23\)

Reactive microglia by activating signaling cascades like p38 and extracellular regulated kinase mitogen-activated protein kinase (MAPK) pathway, or the cAMP response element-binding protein signaling pathway leads to proliferation and recruitment at the injured site.\(^7,45\) A study conducted by Crown et al.\(^50\) suggests that high expression of neuronal, astrocytic and microglial p38 MAPK resulted in development of mechanical allodynia in rats post-SCI. Activation of transcriptional factors alters target gene expression, which further encourages phosphorylation of ion channels and receptors, upholding neuronal hyperexcitability.\(^51\) These reactive microglia are found not only in the entire spinal axis but also in supraspinal regions like the hippocampus, anterior cingulate cortex, and posterolateral nucleus of the thalamus.\(^49\) Reactive microglia promote regeneration and sprouting of primary afferent fibers by releasing nerve growth factors. They induce maladaptive synaptic reorganization and alter neuronal networks through neuronal-glial interactions. Further, these alterations enable the release of pain mediating substances such as ROS, TNF-α, brain derived neurotrophic factor (BDNF), and interleukins from activated microglia.\(^7,29\) The BDNF receptor truncated isoform tropomyosin-related receptor kinase type B (TrkB.T1), which is solely present on astrocytes, is upregulated after SCI. This upregulation promotes astrogliosis, further contributing to NP. Deleting TrkB.T1 in knock-out mice decreased the proliferation and migration of astrocytes further attenuating NP.\(^32\) Detloff et al.\(^32\) recognized and correlated the onset of microglial activation with induction of allodynia-like behavior after SCI in rats. Intrathecal administration of propentofylline not only modulated microglial activation but also decreased the downregulation of GAD65. This links microglial activation with reducing inhibitory GABAergic...
tone. Also, agents such as minocycline, lipoxin A4, resolin E1, estrogen, and rapamycin, by inhibiting microglial activation could positively attenuate the injury related CNP behavior which signifies the role of microglial activation in CNP.36

3. Cation–Chloride Cotransporters and CNP Association

GABAergic inhibitory tone in the DH is maintained typically through GABA release from interneurons that can block the nociceptive primary afferent inputs by maintaining chloride concentration. The 2 main cation–chloride cotransporters, NKCC1 and KCC2, support in maintaining chloride homeostasis in the spinal cord.31 GABA_\text{A} responses in the initial developmental stage of neurons are considered excitatory, however after birth they develop and shift to produce inhibitory responses due to enhanced KCC2 expression, responsible for causing chloride extrusion. Normally, the expression of KCC2 is specifically high in neurons, whereas NKCC1 is more expressed in the respiratory system and kidneys of mice.34 Alterations in levels of both the cotransporters are reported to contribute to developing CNP postinjury. Upregulation in the expression of NKCC1 and downregulation in the expression of KCC2 was reported 2–14 days after the injury.35 Loss of KCC2 causes chloride accumulation thus reducing inhibition required for maintaining chloride homeostasis upon activation of GABA_\text{A} receptors.22 Factors like microglial activation and raised BDNF significantly contribute to KCC2 downregulation post-SCI.23 Recently, in an open label trial, it significantly reduced the pain intensity in SCI patients by enhancing KCC2, confirming its significance in GABAergic disinhibition mediated NP induction (Table 2).35

Some studies have emphasized the effect of NKCC1 inhibition in reducing the depolarizing GABA_\text{A} currents; however, its wide distribution in kidney and respiratory system showing undesirable side effects limit its use.34 NKCC1 antagonist bumetanide, positively aided in reducing the injury initiated CNP by inhibiting the upregulated transporter. But, some patients reported adverse effects like diuresis, difficulty in evacuation and incontinence.35 Considering this and low levels of KCC2 (chloride extruder protein) in NP, promoting intracellular chloride efflux by enhancing KCC2 cotransporter or decreasing its downregulation is a promising therapeutic approach for reducing NP. A KCC2 agonist, CLP290, was found to be effective in attenuating peripheral nerve injury pain in rats. It provided analgesia without compromising the motor function.36 Another study helped promote functional recovery in a double hemisection SCI model of mice with staggered lesions (Table 1).37 Further studies with this compound would provide more significance for its use in the future.

RESTORING THE INHIBITORY TONE RELIEVES SCI-CNP

Years ago, the ‘gate control theory of pain’ explained that the spinal cord DH’s inhibitory neurons can control the peripherally sensed nociceptive inputs by directing them towards the higher centers.38 GABAergic drugs have been long used as sedatives, anxiolytics, and antiepileptics. Nevertheless, their usage for relieving CNP is new and needs additional exploration. Anticonvulsants like lamotrigine, topiramate, and gabapentin have been shown to increase GABA levels for 4 weeks in healthy adults.39 This suggests they might be used during the chronic period in NP.

Promoting presynaptic inhibition allows GABAergic neurons to connect with primary afferent la fibers, which inhibits EAA release from la fibers, further preventing the nociceptive transmission to motor neurons.40 Several strategies help restore the hypoactive GABAergic tone by acting through diverse mechanisms and hence providing a more fundamental understanding to target GABA-associated CNP (Fig. 2; Tables 1, 2).

1. Enhancing GAD Expression

The approach of enhancing GAD expression to reduce CNP using gene therapy has shown positive results in studies.41 GAD_{67} protein can be overexpressed using human foamy virus transduction in rat neurons, resulting in decreased NP in rats (Table 1).42 When a herpes simplex virus vector encoding GAD_{67} was constructed and transduced in the SCI hemisection model, it decreased mechanical allodynia and thermal hyperalgesia by increasing GABA release (Table 1).43 Similarly, when a recombinant helper-dependent adenovirus as a vector targeting dorsal root ganglion and overexpressing GAD_{67} was made, it alleviated allodynia in a spinal nerve transection mice NP model by suppressing Cav3.2 mRNA expression.63 In another study, exercise training relieved NP-linked mechanical and thermal hyperalgesia, which increased GAD_{68/67} expression through BDNF elevation. Overall, this suggests that raising GAD levels which are depressed in the postinjury period, could cause more synthesis of GABA to increase inhibitory GABAergic tone. Delivering GABA directly to the site is effective but its short half-life requiring continuous infusion and systemic side effects limits its use. Gene therapy circumventing such drawbacks provides a promising approach for NP attenuation.63
Table 2. Clinical studies promoting inhibitory tone for SCI-NP

<table>
<thead>
<tr>
<th>Approach and route</th>
<th>Duration</th>
<th>No. of participants</th>
<th>Mechanism and conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing hyperexcitability</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ketamine (i.v then p.o.)</td>
<td>17.2 Days (acute), 59 days (subacute)</td>
<td>13</td>
<td>Ketamine reduced alldynia in acute phase significantly by antagonizing NMDA receptors&lt;sup&gt;142&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Epidural injection)</td>
<td>7-, 15-, 30-, 45-, and 60-day postinjection</td>
<td>40</td>
<td>Showed effects till 30 days post injection by antagonizing NMDA receptors&lt;sup&gt;143&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ketamine and Alfentanil (i.v. infusion)</td>
<td>-</td>
<td>9</td>
<td>Both markedly reduced evoked pain by antagonizing NMDA receptors&lt;sup&gt;144&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ketamine (i.v.)+Lidocaine (i.v.)</td>
<td>-</td>
<td>10</td>
<td>NMDA antagonist ketamine but not lidocaine was effective&lt;sup&gt;145&lt;/sup&gt;</td>
</tr>
<tr>
<td>Valproic acid (p.o.)</td>
<td>8 Weeks</td>
<td>20</td>
<td>Voltage-gated ion channels blocker showed no significant analgesic effects&lt;sup&gt;146&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lamotrigine (p.o)</td>
<td>9 Weeks</td>
<td>30</td>
<td>Pain reduction in patients with incomplete SCI by blocking sodium channels&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lamotrigine (p.o.) vs. amitriptyline (p.o.)</td>
<td>3 Weeks</td>
<td>147</td>
<td>Sodium channel blocker and monoamine reuptake inhibitor both showed similar efficacy&lt;sup&gt;73&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lidocaine (i.v.)</td>
<td>1 to 3 weeks</td>
<td>24</td>
<td>Sodium channel blocker reduced pain at and below injury&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>(5% plaster)</td>
<td>160 Days</td>
<td>1</td>
<td>Superficial NP symptoms completely disappeared by blocking sodium channels&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lumbar subarachnoid cathe- terization</td>
<td>-</td>
<td>21</td>
<td>Response to diagnostic spinal anaesthesia using sodium channel blocker in chronic SCI pain is complex&lt;sup&gt;147&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lidocaine (i.v.) vs. sodium amobarbital (i.v.)</td>
<td>-</td>
<td>5</td>
<td>Amobarbital by promoting GABA&lt;sub&gt;A&lt;/sub&gt; inhibition was more superior in relieving pain&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>5 Weeks</td>
<td>15</td>
<td>Sodium channel blocker showed no significant pain reduction&lt;sup&gt;48&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>-</td>
<td>55</td>
<td>Sodium channel blocker was more effective in patients without evoked pain&lt;sup&gt;106&lt;/sup&gt; well tolerated, efficacious and safe for monotherapy</td>
</tr>
<tr>
<td>20 Weeks</td>
<td>37</td>
<td></td>
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<tr>
<td>Fosphenytoin (i.v.) vs. Lidocaine (i.v.)</td>
<td>-</td>
<td>17</td>
<td>Significant pain reduction by Sodium channel blocker fosphenytoin&lt;sup&gt;160&lt;/sup&gt;</td>
</tr>
<tr>
<td>Botulinum toxin type A (s.c.)</td>
<td>4, 8, and 12 weeks</td>
<td>40</td>
<td>Showed significant pain reduction&lt;sup&gt;75&lt;/sup&gt; and mainly controlled at-level SCI pain by inhibiting release of glutamate and substance P</td>
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<td>Gabapentinoids</td>
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<tr>
<td>Gabapentin (p.o.)</td>
<td>4–24 Weeks</td>
<td>7</td>
<td>Decrease in pain intensity, burning sensation,&lt;sup&gt;151&lt;/sup&gt; frequency and NP refracto-ry to other analgesics by GABA modulation</td>
</tr>
<tr>
<td>Gabapentin (p.o.)+ketamine (infusion)</td>
<td>4 Weeks</td>
<td>40</td>
<td>NMDA receptor antagonist ketamine was safe and efficacious adjuvant&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gabapentin+amitriptyline (p.o.)</td>
<td>8 Weeks</td>
<td>38</td>
<td>Serotonin enhancer amitriptyline was more efficacious&lt;sup&gt;152&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gabapentin vs. pregabalin (p.o.)</td>
<td>8 Weeks</td>
<td>30</td>
<td>GABA analogs showed no difference in efficacy&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregabalin (p.o.)</td>
<td>9–17 Weeks</td>
<td>137</td>
<td>Pregabalin relieved moderate to severe NP&lt;sup&gt;154&lt;/sup&gt; was effective and well tolerated&lt;sup&gt;52&lt;/sup&gt; and also effective in NP related sleep interference&lt;sup&gt;155&lt;/sup&gt; by GABA modulation</td>
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</tbody>
</table>

(Continued)
Table 2. Clinical studies promoting inhibitory tone for SCI-NP (continued)

<table>
<thead>
<tr>
<th>Approach and route</th>
<th>Duration</th>
<th>No. of participants</th>
<th>Mechanism and conclusion</th>
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<tbody>
<tr>
<td>GABA agonist</td>
<td></td>
<td></td>
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<tr>
<td>Baclofen (i.t.)</td>
<td>24 Hours–12 months</td>
<td>16</td>
<td>GABA\textsubscript{A} agonist decreased chronic musculoskeletal pain but not chronic neurogenic pain,\textsuperscript{156} suppressed spontaneous and evoked pain\textsuperscript{157} and showed significant analgesic effect\textsuperscript{99}</td>
</tr>
<tr>
<td>KCC2 enhancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide (p.o.)</td>
<td>19 Weeks</td>
<td>14</td>
<td>Produced analgesia by upregulating KCC2 protein\textsuperscript{55}</td>
</tr>
</tbody>
</table>

SCI, spinal cord injury; NP, neuropathic pain; CNP, chronic neuropathic pain; i.v., intravenous; p.o., peroral; NMDA, N-methyl-D-aspartate; GABA, gamma-aminobutyric acid; i.t., intrathecal; s.c., subcutaneous; KCC2, K\textsuperscript{+}–Cl\textsuperscript{-} cotransporter isoform 2.

Fig. 2. Schematic representation of strategies targeting GABAergic system for attenuating chronic neuropathic pain post-spinal cord injury (SCI). Restoring the hypoactive inhibitory GABAergic tone favors analgesia post-SCI. GABA analogs remain the first-line treatment. Other strategies include inhibiting GABA transporter, GABA transaminase enzyme, Ca\textsuperscript{2+}, and Na\textsuperscript{+} channels. Current therapies focus on gene therapies using viral vectors that encode GAD enzyme synthesizing GABA. GAD, glutamate acid decarboxylase; GABA, gamma-aminobutyric acid; GAT, GABA transporter; HFV, human foamy virus; HSV, herpes simplex virus.

2. Reducing Hyperexcitability

In clinical studies, various established drugs are being studied to reduce the hyperexcitability and promote inhibitory tone for relieving CNP post-SCI. NMDA antagonist ketamine prevents hyperexcitability mediated central sensitization, thus preventing NP. However, patients in trials experienced disturbing side effects such as sedation, dizziness, and visual distortions limiting its use in SCI.\textsuperscript{64} In another trial, when ketamine was given as an adjuvant to gabapentin in low doses for 7 days, it was found efficacious for 2 weeks with only mild side effects (Table 2).\textsuperscript{65} Drugs like lamotrigine, lidocaine, oxcarbazepine, and fosphenytoin block sodium channels further by inhibiting the release of EAA, reducing neuronal firing, and thus are found to be effective in reducing NP post-SCI.

The effect of lidocaine is examined in post-SCI NP topically, intrathecal as well as intravenously.\textsuperscript{64} A randomized controlled
GABA Role in SCI

Bhagwani A, et al.

A Cochrane review published in 2013 suggests no or very less significant evidence showing prominent effects of lamotrigine in NP. However, in a comparative trial 3-week study of amitriptyline versus lamotrigine done in SCI NP patients, both the drugs were found efficacious with no difference in efficacy between them (Table 2).

Botulinum toxin type A (BTX), which is considered as a third-line treatment for NP, inhibits pain progression by suppressing the release of neurotransmitters and neuropeptides like glutamate, substance P, and calcitonin gene-related peptide. It is also known to reduce spasticity-related post-SCI pain. It relieves mechanical allodynia and hyperalgesia by blocking neuronal sodium channels. Results from a randomized, double-blind placebo-controlled trial suggested that BTX decreased post-SCI pain intensity in patients at weeks 4 and 8 (Table 2). A recent study reports that BTX reduces the expression of upregulated CXCL13 and GAT-1 in NP chronic constriction injury (CCI) rat models. Presently, lack of studies, low patient numbers, and lack of standardized optimum dose and delivery are the shortcomings that need sound research for BTX approval in NP post-SCI.

Already an approved drug for amyotrophic lateral sclerosis, riluzole reduced below-level cutaneous hypersensitivity in SCI-NP rats by inhibiting the glutamatergic transmission (Table 1). It induced long-term depression from pain fibers to spinal superficial dorsal horn (SDH) neurons, thus inhibiting the excitatory synaptic transmission. Previous reports also suggest that riluzole potentiates GABAergic responses inhibiting the GABA uptake in a dose-dependent manner. A study revealed that inducing the outward current in substantia gelatinosa neurons potentiated the GABAergic transmission in the SDH thus attenuating mechanical allodynia in the NP rat model. Newly synthesized N-alkylated derivatives of riluzole also increased the hot plate latency time and showed antinociceptive effects. Such derivatives carry the potential to be investigated further in NP models.

3. Structural Analogs of GABA

Structural analogs of GABA, gabapentin, and pregabalin are the first-line treatment available for NP post-SCI. Their efficacy and tolerability are demonstrated in phase 3 randomized trials of SCI-NP patients (Table 2). They are known to act by binding α2δ calcium channel subtype, thus reducing spinal excitatory glutamate and substance P release, without showing any serious side effects. Other favorable mechanisms include promoting the descending inhibitory pathway, a decrease in glial activation and proinflammatory cytokine release. They also promote axonal regeneration and are found to be neuroprotective in several animal models of neurotrauma. When administered in the acute phase of the injury, they carry the potential to prevent the CNP development. A recent meta-analysis report suggested that compared to the other drugs used, pregabalin was found to be more effective, and gabapentin safer for CNP post-SCI. Gait instability, sedation, and dizziness are some of their common reported adverse effects. Gabapentin may cause cognitive dysfunction. They generally have less tolerance capability as compared to other used drugs like opioids.

4. Inhibiting GABA Uptake and Metabolism

Vigabatrin, the irreversible inhibitor of the GABA transaminase enzyme, produced analgesia in the rat NP model. It has also shown neuroprotective effects in spinal ischemia. Tiagabine, riluzole, and R-nipeptic acid by inhibiting GABA transporters (GATs) prevent GABA reuptake, and increase GABA in order to lessen NP after the injury (Table 1). Pyridoxal 5-phosphate serves as a cofactor in GABA reuptake using GATs. Derivatives of hydrazine inhibit the binding of this cofactor and thus reduce the activity of GATs to raise GABA.

Although tiagabine is the only clinically approved GAT inhibitor for NP, several molecules and drugs are under investigation for the same. In a recent study, novel functionalized amino acids that were designed and synthesized exhibited inhibitory effects on mGAT4 and mGAT2 transporters and showed analgesic effects in preclinical studies of 3 different NP mod-
Similarly, in another report, novel compounds inhibiting mouse GABA transporters (mGAT3/4), showed an antiallodynic effect by making GABA more available in diabetic and oxaliplatin-induced NP models. Also, GAT-1 inhibitor NNC-711 and GAT-3 inhibitor SNAP-5114, by decreasing the amplitude of pain fibers mediated excitatory postsynaptic currents produced analgesia in NP mice models. Further, administration of GABA_3 antagonist CGP55845 antagonized the analgesic effects suggesting GAT inhibition's role in producing GABAergic analgesia. These studies could make way for testing these compounds for CNP post-SCI in the near future.

5. GABA Agonists

Muscimol is a GABA_A agonist, and baclofen, which is a GABA_B agonist, both can attenuate NP by activating the GABAergic receptors to release GABA. Knabl et al. in their work reported that drugs modulating α_2 and α_3 subunits of GABA_A receptors and sparing α_1 subunit would be more antinociceptive for relieving chronic pain. α_2 GABA_A receptor modulation and maintaining chloride homeostasis using KCC2 enhancer when combined worked synergistically to attenuate NP post nerve injury. Muscimol by stimulating GABA_A receptors has alleviated NP symptoms in various animal studies of nerve injury models. A recent study reported that muscimol, by reducing WDR neuronal overactivity suppressed both mechanical allodynia and thermal hyperalgesia in CCI-induced rats. The combination therapy of muscimol and endomorphin-1 intrathecal raised the pain threshold in the SCI-NP rat model. This study also reported an increase in the expression of α_2 GABA_A receptor subunit post-administration (Table 1).

Baclofen is already used for spasticity. It showed an anti-alarodynic effect in rats with induced spinal ischemia, reversing WDR neuronal hyperexcitability. Several other preclinical findings report its antinociceptive property in NP by promoting GABAergic tone. In a case report, intrathecal baclofen combined with clonidine relieved intractable post-SCI NP. In a randomized, double-blind, placebo-controlled trial, intrathecal administered baclofen bolus significantly improved NP in SCI patients (Table 2). This shows that baclofen could be a promising NP therapy in the future.

6. Cell Therapy Promoting GABA for SCI-NP

Stem cell therapies avoid deleterious effects of conventional drugs, such as increasing drug tolerance and the development of addiction. Transplanting GABAergic cells in the spinal cord has shown promising effects for NP of nerve injury and SCI. Stem cell therapies avoid deleterious effects of conventional drugs, such as increasing drug tolerance and the development of addiction. Transplanting GABAergic cells in the spinal cord has shown promising effects for NP of nerve injury and SCI.

Fig. 3. Intrathecal transplantation of neural stem cells especially gamma-aminobutyric acid (GABA) precursor cells is currently in research for attenuating chronic neuropathic pain (CNP) post-spinal cord injury (SCI). For neuropathic pain (NP), stem cells hold promising therapeutic potential. Although the major mechanisms remain unclear, they are considered to promote recovery and survival of nerves and restore the hypoactive inhibitory tone in countering CNP.

https://doi.org/10.14245/ns.2244368.184
When grafted in the paraplegic model of spinal ischemia, human spinal stem cells successfully developed into GABAergic phenotype restoring the inhibitory circuits. In one study, GABAergic precursor cells attenuated NP accompanied hyperalgesia and allodynia in rats when transplanted intrathecally. Correspondingly in other studies, embryonic stem cells from mice, differentiated in vitro into spinal GABAergic neurons, when transplanted postinjury, favored in relieving NP for long term by re-establishing the hypoactive GABAergic tone (Fig. 3, Table 1). Transplanting selective subpopulations of cells like GABAergic neurons restores the underactive presynaptic inhibition in DH neurons. Transplanting the predifferentiated human neuronal cell line NT2 capable of releasing inhibitory GABA helped reverse NP after quisqualic acid-induced excitotoxic SCI in rats (Table 1). Similarly, one other study reported reduced overgrooming behavior in SCI rats when transplanted with in vivo predifferentiated GABA immunoreactive cells, for alleviating CNP. The combination therapy of GABAergic neural precursor cells transplantation and intensive locomotor training significantly alleviated the NP symptoms in SCI rats showing mutually beneficial effects. A recent analysis report suggests that GABAergic cells transplantation improves allodynia and hyperalgesia conditions only in rats and not in mice. Additionally, intraspinal transplantation produces more significant effects than intrathecal transplantation. It also suggests that although there are possibilities of genetic defects with genetically modified cells, they are still the best sources for alleviating NP compared to GABAergic cells and stem cells.

Studies also report the beneficial effects of bone marrow-derived mesenchymal stem cells (BMSCs) in reducing post-SCI NP and promoting sensory recovery. BMSCs showed effects by inhibiting the activation of MAPK signaling pathway mediated neuronal hyperexcitability. In a case report, BMSCs were administered in a cervical SCI patient, adverse effects including fever, headache, myalgia, and motor dysfunction were observed 48 hours post-transplantation and increased the NP. Although cell therapies with BMSCs are considered safe, it can cause serious adverse effects like hyperthermia and malignant hypertension which requires further investigation.

**SPASTICITY AND GABA ASSOCIATION**

Spasticity and NP are both responsible for affecting the quality of life in patients with SCI by impairing their normal daily activities. They usually have late-onset after the injury and persist for long periods. In patients with the incomplete lesion, spasticity may lead to pain, sleep disorders, or result in loss of motion. Incidence of spasticity after the injury is reported to happen in about 70% of the patients. It is more commonly experienced by quadriplegic patients and in cases with incomplete lesions. Spasticity is defined as ‘a disordered sensorimotor control resulting from an UMN lesion, presenting as intermittent or sustained involuntary activation of muscles.’ Spasticity is one of the parts of UMN syndrome, which is considered as ‘sensorimotor’ (presents motor responses due to sensory inputs). Although spasticity is considered a detrimental side effect for SCI patients, it is reported to have a beneficial role in locomotor function. So, administration of baclofen even if relieving the spastic symptoms comes with the loss of preserved ambulatory ability in SCI patients. Several mechanisms, including hyperexcitability of motor neurons, the excitability of interneurons, inhibitory GABA-glycinergic decline, and loss of integrity in descending tracts, support the development of spasticity. Neuroplasticity brings about alterations in neural circuits, which affect neurotransmission. Although neuroplasticity after SCI promotes locomotor recovery through deafferentation of neurons and neurotrophins, it causes negative effects leading to NP and spasticity after the injury. Activation of plateau potentials due to persistent calcium and sodium inward currents in motor neurons also has a role in spasticity after SCI. By increasing the activity of motor neurons, these persistent inward currents produce uncontrollable spasms that can be provoked even by innocuous stimuli or a muscle stretch. Reduction in expression of cotransporter KCC2 is detected postinjury, triggering E_{\text{RSP}} (reversal potential of glycine receptor and GABA_{\alpha} receptor-mediated inhibitory postsynaptic potentials) depolarization resulting in spasticity below the lesion. Plantier et al. reported the association of Calpain-1 in raising persistent sodium currents and downregulating KCC2 for causing spasticity. Alterations in the transmission of both inhibitory and excitatory tone cause hyperexcitability of neurons, contributing to spasticity. Overall, these mechanisms reduce the motor unit activation threshold and raise the responsiveness to stimuli.

The increase in excitability of motor neurons during spinal ischemia, leading to a spasticity-related increase in muscle tone, is already reported. Baclofen (GABA{\text{a}} agonist) and nipecotic acid (GABA reuptake inhibitor), effectively inhibited the spasticity suggesting the decline in inhibitory GABAergic neurons as a contributing factor to spasticity post-SCI. Progressive loss of cholinergic and GABAergic neurons causing spasticity after sacral SCI is reported in rats. Also, upregulation of down-
regulated GABAergic receptors was seen after repetitive transcranial magnetic stimulation, which relieved spasticity post-SCI. The global gene expression analysis report of spastic SCI rats signifies the upregulation in the expression of kainate receptors, NMDA receptor complex promoting excitability, and downregulation in gene coding of GABA_A receptor subunit isoforms (Gabra1, Gabra5, and Gabrg2). All in all, inhibitory GABAergic tone insufficiency is a key link involved in spasticity post-SCI.

RESTORING THE INHIBITORY TONE RELIEVES SCI-SPASTICITY

Spasticity post-SCI, although a complication, is beneficial in some aspects requiring no treatment. It may help in the daily activities of SCI patients by increasing stability in sitting and standing, raising muscle bulk, strength, and venous return. Almost 40% of patients find spasticity beneficial. However, depressing the spinal excitability raises motor recovery complications. There is no objective measure for the reference that spasticity should be treated or not, it depends upon achieving the balance of its positive and negative impacts on the patient. Nevertheless, the passive problems of involuntary muscle spasms, persisting pain, and positioning difficulties affecting daily activities need to be treated. Several studies target the promotion of inhibitory GABAergic tone in attenuating spastic symptoms (Tables 3, 4).

**1. GABAergic Drugs**

Several pharmacological agents help in improving spastic conditions (Tables 3, 4). Such interventions classically act to reduce the muscle tone. These drugs, by reducing muscle overactivity, can also attenuate spasticity-mediated NP. Commonly used pharmaceuticals include baclofen, botulinum toxin, tizanidine, whereas diazepam, clonazepam, clonidine, gabapentinoids, skeletal muscle relaxants, cannabinoids, and cyproheptadine are also used, but less commonly. Baclofen, diazepam, tizanidine, and dantrolene sodium are Food and Drug Administration-ap-

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SCI, spinal cord injury; i.p., intraperitoneal; SD, Sprague Dawley; GABA, gamma-aminobutyric acid; s.c., subcutaneous; KCC2, k⁺-Cl⁻ cotransporter isoform 2; i.v., intravenous.
proved drugs for spasticity of which only baclofen and tizanidine have reported significant efficacy.\textsuperscript{120} Of all the options, baclofen is widely used and considered a safer antispastic drug in promoting neurological recovery.\textsuperscript{121} Its adverse events are noticed in a dose-dependent way, generally occurring at doses $\geq 60$ mg/day when taken orally.\textsuperscript{120} When given intrathecally, it has proven to be more potent and efficient than oral baclofen in relieving hypertonia postinjury and avoids its typical side effects of cognitive impairment and sedation.\textsuperscript{122}

Diazepam by binding GABA$_A$ receptors facilitates chloride conductance and promotes presynaptic inhibition, thus attenuating painful spasms in SCI patients. Diazepam and clonazepam carry the risk of dependence and withdrawal syndrome, and on abrupt withdrawal, diazepam can cause seizures.\textsuperscript{120} In an open level withdrawal trial, pregabalin worsened the spasticity symptoms in patients on withdrawal protocol.\textsuperscript{123} In addition, the development of tolerance and the inability to reach the injury site in effective doses are other causes limiting their use in spasticity. Tolerance to intrathecal baclofen within months after initiating treatment is a complicating factor. Furthermore, some case reports suggest that taking a ‘baclofen holiday’ for 15 days and replacing it with intrathecal morphine infusion is effective in such cases.\textsuperscript{124} To counter these complications, other approaches like stem cell therapies are currently being considered.

2. Calcium Channel Blockers
Some studies suggest the use of calcium channel blockers for ameliorating spastic symptoms. Nimodipine, decreased spasticity by blocking persistent inward calcium currents after SCI in spastic mice and rats (Table 3). A recent study in SCI rats demonstrated that long-term administration of nimodipine reduced pain and spasticity, raised KCC2 expression, spared neurons with the overall promotion of functional recovery. Additional studies in the future with nimodipine might provide further evidence for its use in SCI (Table 3).\textsuperscript{125} Likewise, case reports suggest that ziconotide, by blocking N-type calcium channels, could also relieve spasticity-mediated pain post-SCI. (Table 4).\textsuperscript{85,126} In case reports of baclofen tolerant patients with intrathecal spasticity, intrathecal ziconotide administration in increasing doses made them spasm free.\textsuperscript{126} Sodium and calcium channel blocker tolperisone combined with physical therapy was tested in Chinese SCI patients. It inhibited spasticity with no adverse effects. However, its efficacy was less than baclofen combined with physical therapy (Table 4).\textsuperscript{127} Voltage-gated L-type calcium channel inhibitor 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione attenuated SCI-induced muscle spasms in mice by inhibiting Cav1.3 subunit specifically. This suggests Cav1.3 channel-mediated excitability inhibition could be a promising target for relieving SCI-spasticity in

<table>
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<tr>
<td>Reducing hyperexcitability</td>
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<td>6 Weeks</td>
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<td>Slightly effective by blocking sodium and calcium channels$^{127}$</td>
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i.m., intramuscular; GABA, gamma-aminobutyric acid; i.t., intrathecal, p.o.; peroral, TENS, transcutaneous electrical nerve stimulation.

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Table 4. Clinical studies promoting inhibitory tone for SCI-spasticity

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i.m., intramuscular; GABA, gamma-aminobutyric acid; i.t., intrathecal, p.o.; peroral, TENS, transcutaneous electrical nerve stimulation.
3. Cell Therapy

Researchers are now focusing more on cellular approaches for treating SCI-spasticity. Cells like bone marrow-derived stromal cells can positively acquire GABAergic type and migrate towards the injury site preserving the neuronal survival and regeneration in the spinal cord. The study conducted by Gong et al. transplanting the GABAergic neurons into the rats after their successful differentiation from progenitors established the role of inhibitory GABAergic neurons in relieving spasticity (Table 3). Intraspinal grafting of human spinal cord-derived stem cells (NSI-566RSCs line) had promising effects on the functional recovery of SCI rats. It attenuated spasticity and NP symptoms by developing putative synapses between GABAergic neurons and the host's interneurons and motor neurons (Table 3). Human trials have demonstrated the safety of neural stem cell transplantation post-SCI. However, the major hurdles include lack of proper differentiation, glial scarring, host-immune reactions, and risk of tumorigenesis.

4. KCC2 Cotransporter Enhancers

The cotransporter KCC2 required to maintain inhibitory GABAergic tone is downregulated post-SCI contributing to spasticity development. Consequently, current studies also focus on upregulating KCC2 levels to increase chloride extrusion to reduce spasticity. The antipsychotic drug prochlorperazine, showed increased KCC2 expression to relieve spasticity and the antispastic effect was comparable to baclofen (Table 3).

NEUROPATHIC PAIN AND SPASTICITY INTERLINKED

Maladaptive neuroplasticity post-SCI is the reason for a number of negative consequences, such as spasticity and NP. Both NP and spasticity are linked with common causal mechanisms like hypoactive inhibitory tone and neuronal hyperexcitability, which reduce the threshold and enhance responses of spinal neurons to non-painful stimuli. A cross-sectional survey reported that the prevalence of spasticity is more common with NP patients when compared to patients with no pain. The key mechanism connecting both is KCC2 downregulation. The only difference is the reduction in expression of KCC2 in NP is observed mainly in DH neurons, whereas in the case of spasticity, its expression is reduced primarily in motor neurons.

Many approaches target SCI-induced NP and spasticity simultaneously. BTX-A shares antispastic and antinociceptive properties. The first-line agent used for NP, gabapentin, also suppresses spasticity (Table 3). Similarly, cannabinoids that modulate the neuronal hyperexcitability and neurotransmitter release, can attenuate NP and spasticity. However, their uncertain efficacy in relieving spasticity requires more research and could be confirmed from the results of ongoing trials.

CONCLUSION

The secondary phase of SCI brings more distressing complications as a result of alterations at cellular, molecular and genetic levels. Changes occurring due to damage alter normal synaptic transmissions and causes neuroplasticity contributing to the development of CNP and spasticity post-SCI. Their prevalence post-SCI is high and remains refractory to the conventional approaches. Current pharmacological therapies lack effectiveness and come with a wide range of side effects. Also, targeting complex pain mechanisms itself becomes challenging. Thus, defining these mechanisms becomes a need to develop new approaches. Newly synthesized drugs targeting the GABAergic system to relieve CNP bring the possibility of investigating them in SCI. Similarly, repurposing of GABAergic drugs for the chronic period in SCI, gene therapies designed to promote GABAergic tone, and stem cell transplantation, primarily GABAergic neurons, are some of the recent advancements in CNP and spasticity post-SCI that provide insight to the ongoing research.

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ORCID
Ankita Bhagwani: 0000-0001-5529-7604
Manjeet Chopra: 0000-0002-0390-1301

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The Role of GABA in Spinal Cord Injury

Xue Yao¹,²

¹Tianjin Key Laboratory of Spine and Spinal Cord, International Science and Technology Cooperation Base of Spinal Cord Injury, Department of Orthopedics, Tianjin Medical University General Hospital, International Chinese Musculoskeletal Research Society Collaborating Center for Spinal Cord Injury, Tianjin, China
²Shandong University Center for Orthopaedics, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Spinal cord injury (SCI) leads to lifelong neurological disorder as well as many complications in the chronic phase.¹ Around 80% of the SCI patients suffer from chronic pain, which significantly lower their quality of life. Spasticity is another common sequela. Finding the mechanism of chronic neuropathic pain (CNP) and spasticity after SCI is vitally important for the effective intervention.²

GABA is the major inhibitory neurotransmitter which is abundant in the spinal cord. There is emerging link between the GABA and the SCI neuropathic pain (NP) and spasticity. Glutamate excitotoxicity is responsible for the inhibition of GABAergic inhibitory tone. After SCI, there is GABAergic cell loss, glutamic acid decarboxylase downregulation, GABA transporters upregulation and overactivation of glutamate receptors. Upregulation of Na⁺ cotransporter 1 (NCC1) and downregulation of K⁺ cotransporter 2 (KCC2) leads to Cl⁻ concentration imbalance, which further leads to NP and spasticity.³ Excitotoxicity as well as hypoactivation of inhibitory GABAergic tone make the imbalanced neuromodulation.

Bhagwani et al.⁴ made a comprehensive survey of the literature on GABAergic in the NP and spasticity in chronic SCI. GABAergic neurotransmission in NP has 3 aspects of impact in the cellular and molecular level: neuronal hyperexcitability, microglial activation as well as cotransporter alterations. Spasticity is caused by the motor neuron hyperexcitability induced increased muscle tone, which can be inhibited by GABA agonist Baclofen effectively. Preventing loss of GABAergic neuron and restoring the inhibitory tone is beneficial in both the NP and the spasticity. The authors summarize the preclinical and clinical study of promoting the inhibitory tone for SCI CNP and spasticity. Promising treatment includes GABAergic drugs, calcium channel blockers and cell therapy.

In this editorial, I would like to extend the concern about the GABAergic neurotransmission to all aspects of SCI. Not only NP and spasticity were involved in the GABAergic, but also the locomotion is involved. KCC2 expression as well as its agonist could restore locomotion by modulation of the dormant relay.⁵ Treatment such as transplantation of GABA neurons not only promotes locomotive recovery but also reduced spasticity in SCI.⁶ Since the neuromodulation is promising in SCI,⁷ the GABAergic role in electrical stimulation in SCI to promote functional recovery is also an interesting direction that worthy to explore.

Conflict of Interest: The author has nothing to disclose.
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Physical rehabilitation is essential for enhancing recovery in individuals with spinal cord injury (SCI); however, aside from early surgical intervention and hemodynamic management, there are no proven interventions for promoting recovery in the acute phase. In general, early rehabilitation is considered beneficial, but optimal parameters and potential contraindications for implementing rehabilitation at very early time points are unclear. Moreover, clinical trials to date are limited to studies initiating rehabilitation 2 weeks after injury and later. To address these gaps, this article reviews the preclinical literature on physical interventions initiated within the first 8 days postinjury. Effects of early rehabilitation on molecular and structural nervous system changes, behavioral function, and body systems are considered. Most studies utilized treadmill or cycle training as the primary intervention. Treadmill training initiated within the first 3 days and terminated by 1 week after injury worsened autonomic function, inflammation, and locomotor outcomes, while swim training during this period increased microvascular dysfunction. In contrast, lower-intensity rehabilitation such as reach training, ladder training, or voluntary wheel or ball training showed benefits when implemented during the first 3 days. Rehabilitation initiated at 4 days postinjury was also associated with enhanced motor recovery. Cycling appears to have the greatest risk-benefit ratio; however, the effects of cycle training in the first 3 days were not investigated. Overall, research suggests that lower intensity or voluntary rehabilitation during the hyperacute phase is more appropriate until at least 4 days postinjury, at which point higher-intensity activity becomes safer and more beneficial for recovery.

**Keywords:** Spinal cord injury, Acute intervention, Rehabilitation, Early mobilization
spite this, a cure for disabling sensorimotor deficits caused by SCI remains elusive for the nearly 18,000 individuals who experience SCI each year. While the most obvious effects of SCI are physical, the emotional and financial well-being of individuals and their families are also impacted. With rehospitalization rates as high as 36%, the first year costs of living with SCI range from $400,000 to more than $1.2 million depending on level and severity. Importantly, gains in mobility reduce both rehospitalization and overall lifetime costs and ultimately improve individuals’ quality of life. As such, there is a critical unmet clinical need for acute interventions that can jumpstart recovery of functional mobility.

Fig. 1. Effects of acute physical interventions on functional recovery from SCI. Recovery was broken down into 12 areas encompassing molecular, structural, systemic, and functional responses to acute physical activity. This figure highlights important takeaways and indicates whether overall effects on each system were positive, negative, or neutral based on the placement of either a check, x, or dash, respectively, in each box. 4E-BP1, eukaryotic translation initiation factor 4E binding protein 1; 5HT, serotonergic axon; AKT, protein kinase B; BDNF, brain-derived neurotrophic factor; BOS, base of support; CST, corticospinal tract; Eif-4E, eukaryotic translation initiation factor 4E; GABA, gamma-aminobutyric acid; GAD65/67, glutamate decarboxylase 65/67; GDNF, glial cell-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; H-Reflex, Hoffmann’s reflex; H/M ratio, H-wave/M-wave; IBA1, ionized calcium-binding adapter molecule 1; IGF1, insulin-line growth factor 1; IGFBP4/5, insulin-like growth factor binding protein 4/5; KCC2, potassium-chloride cotransporter 2; NKCC1, sodium-potassium-chloride cotransporter 1; miR, micro ribonucleic acid; mRNA, messenger ribonucleic acid; mTOR, mechanistic (or mammalian) target of rapamycin; myoD, myogenic differentiation 1; NT3, neurotrophin-3; P-Erk1/2, phosphorylated extracellular signal-regulated kinase 1/2; SCI, spinal cord injury; TGFα, transforming growth factor alpha; TrkB, tropomyosin receptor kinase B; TrkC, tropomyosin receptor kinase C.
Activity-based rehabilitation paradigms use principles of motor learning and neuromuscular plasticity, such as repetition, specificity, and intensity in an effort to minimize compensation and promote recovery of function after neurologic insult. To date, these rehabilitation approaches have demonstrated significant promise for promoting functional recovery after SCI and will likely be vital adjuncts to pharmacological, cellular, or technological interventions in the future. However, despite the fact that rehabilitation may be required to guide neuroplasticity and harness the beneficial effects of novel therapeutics, standardized physical therapy regimens are rarely included when studying pharmacological interventions. Moreover, despite intensive rehabilitation, recovery from SCI is often incomplete.

As such, additional understanding of the neurobiology of SCI and recovery, both natural and training-induced, is essential to maximize outcomes.

The timeliness of physical intervention may improve functional outcomes after SCI, but our understanding of this effect is incomplete, and results are mixed. Indeed, while some studies indicate a positive effect of early physical intervention others suggest that early intervention has no effect on recovery or that delayed rehabilitation may be more beneficial. More concerning, early rehabilitation may be detrimental in certain circumstances. Clinical trials on acute physical intervention in SCI to date initiate rehabilitation between 2 weeks and 6 months postinjury, bypassing what may be a critical window of recovery very early after SCI. To improve understanding of the risks and benefits of very early physical interventions for SCI, we reviewed the preclinical literature on physical interventions delivered within the first 8 days postinjury (Fig. 1).

SUMMARY OF INJURY MODELS AND TRAINING PARAMETERS

To date, the preclinical literature on acute rehabilitation includes studies on rats (n = 46) and mice (n = 6). The most commonly used SCI model is contusion (n = 29), followed by transection (n = 13), and then hemisection (n = 10). Studies using the contusion injury model most often included a moderate impact at mid- to low-thoracic levels and treadmill training as the primary intervention. Of the studies that used transection or hemisection, the majority chose mid- to low-thoracic injuries with bicycle training as the primary intervention. Additional training paradigms included environmental enrichment, ladder stepping, reach training, swim training, exercise ball training, and forced or voluntary wheel running.

Substantial variability exists regarding training dose. Most studies implemented rehabilitation 5 to 7 days per week. Frequency ranged from 1 to 3 bouts of training per day. Duration varied based on intervention type. Treadmill training was delivered between 10 and 40 minutes per day. Bicycle training was most frequently prescribed in two, 30-minute bouts with a 10-minute break between bouts. Other dosages of bicycle training included 10 or 15 minutes per day. Swim training occurred in either 2 bouts of 3 minutes or 4 bouts of 6 minutes per day. Wheel running was prescribed either forced for 20 minutes per day or voluntary, ad libitum access. Reach training typically occurred for 10 minutes per day. For the purpose of this review, we consider voluntary interventions or those performed at a self-selected pace, such as ad libitum wheel running, ball training, reach training, etc. to be "low intensity," while forced interventions where animals are allowed to rest only at prescribed intervals, like treadmill, cycling, and swim training, are considered "high intensity."

EFFECTS OF EARLY REHABILITATION ON SCI PATHOPHYSIOLOGY

1. Lesion Pathology, Cell Death, and Apoptosis

To promote functional recovery after SCI, interventions must either limit tissue damage, enhance plasticity of spared or damaged axons, or improve the ability of neuroplastic axons to find appropriate targets. Given that early rehabilitation can alter the spinal microenvironment remote from the injury, it is feasible that rehabilitation can modify secondary injury cascades to influence tissue damage at the injury site. Although most studies show little effect of early rehabilitation on lesion parameters, such as tissue damage or white matter sparing, at least 2 studies suggest potential benefit. Indeed, exercise ball training initiated 1 day postinjury preserved tissue caudal to the injury, and both cycle training and treadmill locomotion reduced lesion volume when initiated 8 days postinjury. Early rehabilitation may also have favorable effects on lesion pathology when combined with neuroprotective agents, such as polypyrrole/iodine mesoparticles.

Rehabilitation also has the potential to improve cell survival via caspase inhibition and neuroprotection. Acute passive cycling reduced injury-induced caspase-7 and caspase-9, but not caspase-3 mRNA in the lumbar cord of rats with SCI. Surprisingly, caspase mRNA was unaffected by either SCI or acute rehabilitation in the lumbar intermediate laminae and motor neurons. At the protein level, acute cycling reduced both 32-
and 40-kD isoforms of caspase-7, the only lumbar caspase increased by injury. In large dorsal root ganglia (DRG) neurons, acute rehabilitation decreased injury-induced increases in caspase-3, -7, and -9. When continued long-term after SCI, cycling decreased injury-induced caspase-3 mRNA in the whole cord but increased caspase-3 in motor neurons and both caspase-3 and -9 in large DRG neurons. Given the role of caspas in synaptic plasticity, it is possible that late caspase increases serve a nonapoptotic role in response to continued rehabilitation; however, this effect should be further investigated. Overall, it appears that in most instances acute rehabilitation, especially over the short term, decreases caspase expression and may enhance neuroprotective effects during SCI recovery.

Cycling may also selectively influence microRNAs (miRs) involved in apoptosis. For example, miR21, miR16a, and miR217 all decrease caspase expression via inhibition of pro-apoptotic phosphatase and tensin homolog, thus reducing apoptosis. Passive cycling increased miR21 expression in the lumbar cord of rats with SCI but had no effect on miR16a or miR217 following 10 days of training. By 31-day postinjury, no differences were observed for any miRs studied regardless of training suggesting a transient effect early after SCI. Conversely, both early and late cycling reduced the injury-dependent increase of miR199a-3p expression, thereby blocking inhibition of the prosurvival mechanistic (or mammalian) target of rapamycin (mTOR) kinase important for cell survival and proliferation.

The effects of rehabilitation on apoptotic pathways suggests that passive cycling is a viable intervention for mitigating aspects of SCI-induced apoptosis early after SCI, despite lesion size and tissue sparing being largely unaffected. Although not directly investigated, rehabilitation effects on mTOR may also reduce necroptosis after SCI. Additional research is needed to investigate the role of other rehabilitation interventions on mediators of apoptosis and necroptosis following injury.

2. Plasticity, Sprouting, and Regeneration

Physical interventions rely on repetitive activation of the nervous system to produce effects; therefore, these interventions may have more efficacy for promoting and guiding plasticity than preserving or limiting damage. Several studies investigated early rehabilitation effects on corticospinal tract (CST) sprouting and regeneration given its role in skilled motor functions, but results are, again, mixed. In mice, running wheel exercise specifically enhanced the number of CST collaterals in the thoracic lesion site early after SCI. In the cervical cord, early rehabilitation-induced CST sprouting increases were maintained through chronic time points. In rats, overground locomotor training beginning at 7 days postinjury and using a robotic weight-support system increased CST sprouting and cortico-reticulo-spinal bridge formation when combined with an electrochemical prosthesis and treadmill training. Two studies assessing CST axon sprouting and length after early reach training also show conflicting results. Despite both using rats, similar injury models, and interventions, one study showed significant improvement in CST axon length rostral to the lesion while the other showed no effect of rehabilitation. Immunohistochemistry from another study revealed that following SCI, treadmill-trained rats had greater axonal arborization and fiber elongation than sedentary animals. Similar results were found where assisted stepping increased fiber density but not elongation in the CST of rats with SCI.

While CST axons are important for skilled movement, serotonergic axons of the raphespinal tract are essential to locomotor function due to their influence on lumbar central pattern generator networks. To date, only one study has investigated serotonergic axon plasticity after early rehabilitation in mice with SCI. In this study, voluntary wheel running did not affect lumbar serotonergic fiber density, but early intervention increased serotonergic contacts on motor neurons in the lumbar cord. By the experiment’s conclusion, both trained and SCI+ sedentary mice exhibited similar lumbar serotonergic reorganization and recovery of rhythmic stepping. While the authors suggest rhythmic stepping can be gained without rehabilitation in incomplete SCI, it is unclear whether the early training-dependent serotonergic fiber reorganization can be exploited by continued rehabilitation to enhance recovery.

Rehabilitation can also modify plasticity of sensory afferents. Indeed, 3 studies histologically quantified calcitonin gene-related peptide (CGRP)-positive fibers in rats due to their role in pain transmission. Long-term reduction in CGRP-positive fiber area and length occurred following treadmill training in one study while another study showed no overall effect of training on CRGP fiber density. Passive hindlimb cycling also appears to play a role in reducing CGRP-positive fiber density compared to untrained control rats.

Specific acute post-SCI rehabilitation effects on motor neurons remain understudied. While dendritic withdrawal occurred in rats following SCI, acute treadmill training modified these effects by either preventing withdrawal or enhancing extension. Effects occurred primarily in neurons controlling the soleus and to a lesser degree the tibialis anterior muscle. There was no training effect on motor neuron soma size.
Perineuronal nets (PNN) are embedded in the extracellular matrix surrounding neurons and facilitate plasticity and maturity of synaptic circuitry. Density of PNNs is greatest in the lumbar region and is both location- and activity-dependent. Both wheel running and treadmill training reversed SCI-induced decreases in lumbar PNNs, but wheel running was most effective in rats. Above the injury, rehabilitation reduced PNNs in gracilis and cuneate nuclei compared to SCI+sedentary mice. Interestingly, treadmill training beginning at 7 days postinjury in rats did not alter PNNs when combined with epidural and pharmacologic stimulation. These findings suggest that rehabilitation differentially modulates PNN expression above and below the injury site to potentially allow greater plasticity in descending systems rostral to the injury while stabilizing lumbar networks susceptible to maladaptive changes and hyperexcitability.

At the synaptic level, treadmill training significantly increased synaptophysin, a synaptic vesicle glycoprotein used to quantify synapses, compared to SCI+sedentary rats. Another study in mice found similar results where treadmill training prevents loss or restores synaptic numbers distal to the lesion. The same effect occurred with postsynaptic density protein 95. In summary, several preclinical studies demonstrate widespread positive changes in neuron/fiber density and axon growth with rehabilitation. Importantly, no negative effects occurred for structural or neuroanatomical parameters following rehabilitation. These findings support rehabilitation in the first week postinjury as a viable approach to enhance structural plasticity.

3. Neurotransmitter Expression

Neurotransmitters are essential to efficient and effective neural network function. The major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), regulates synaptic excitability and is also affected by rehabilitation. Magnetic stimulation, treadmill training, and combined treatment significantly increased the number of GABA-positive cells compared to SCI+sedentary rats. Histologic evidence also suggests that bike and treadmill training may upregulate GABA and sprouting of dopamine beta-hydroxylase fibers in the ventral horn compared to SCI+sedentary rats.

The inhibitory action of GABA is dependent on the intracellular chloride concentration which is heavily influenced by both potassium-chloride cotransporter 2 (KCC2) and sodium-potassium-chloride cotransporter-1 (NKCC1). Cycling mitigates SCI-induced decreases in lumbar KCC2 following spinal transaction in rats. Enriched environment and wheel running increased KCC2 expression compared to SCI+sedentary mice while treadmill training did not. Other sources suggest positive effects of treadmill training where trained rats showed increases in pKCC2/KCC2 ratio and a higher ratio of pKCC2/KCC2 compared to SCI+sedentary rats at all time points. Moderate positive correlations occurred between pKCC2 levels and spasticity, tactile allodynia, and thermal hyperalgesia, and a weak positive correlation occurred between pKCC2 levels and open field locomotion. Cycling also mitigated SCI-induced NKCC1 increases in the rat lumbar cord and maintained KCC2/NKCC1 ratio in the lumbar cord at baseline levels, while SCI+sedentary rats show decreases in this ratio.

Additional enzymes that affect GABA neurotransmission are glutamic acid decarboxylase (GAD)-65 and -67. Spinal cord magnetic stimulation (TMSsc) and treadmill training both significantly increased GAD-67 expression in rats with SCI, but combined TMSsc and treadmill showed the greatest increase compared to individual treatment conditions. Similar results occurred in another study where treadmill trained rats had significantly higher GAD-65 and GAD-67 expression compared to all other treatment groups and did not differ from the uninjured group.

Cycling, treadmill training, and treadmill plus magnetic stimulation all enhance neurotransmitter expression following SCI. Due to the necessary role that neurotransmitters play in regulating the efficiency and effectiveness of neural function, implementing rehabilitation during the acute phase of SCI recovery is an appropriate method for enhancing neural communication and facilitating recovery postinjury.

4. Intracellular Signaling Pathways

Rehabilitation may also affect functional outcomes through modulation of intracellular signaling pathways. For example, the phosphorylated form of Erk1/2 kinase, p-Erk1/2, influences neurite outgrowth, survival, and differentiation in both the central and peripheral nervous system and is increased by treadmill training in healthy animals. Recent research also suggests that p-Erk1/2 may enhance regenerative responses in damaged CST axons following treadmill rehabilitation in rats. Indeed, 1 or 2 weeks of treadmill training increased p-Erk1/2 levels significantly beyond injury-induced levels at the injury site and in the motor cortex compared to sedentary rats.

The mTOR pathway influences intracellular signaling and regulates protein synthesis, cell growth, and proliferation. Similar to p-Erk1/2, mTOR expression following SCI is affected by rehabilitation. Cycling significantly increased lumbar mTOR

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levels in rats following 10- and 31-day bouts of rehabilitation.62 Expression of upstream mTOR positive mediators, including transforming growth factor alpha and phosphoinositide 3 kinase in the lumbar cord was significantly increased following cycling.62 Additionally, positive downstream effectors, such as S6K1 and S6, were not affected by SCI but still increased following rehabilitative intervention,63 while downstream inhibitory effector, eukaryotic initiation factor 4E but not eukaryotic translation initiation factor 4E binding protein 1 was decreased by short-term rehabilitation.62

In summary, there is clear evidence of positive intracellular signaling changes in response to rehabilitation early after SCI. Rehabilitation during acute recovery upregulates expression of cell signaling molecules that promote neurite growth, survival, and differentiation as well as protein synthesis, cell growth, and cell proliferation. Each of these molecular changes has the potential to enhance functional outcomes and should be targeted by prescribing treadmill or bicycle training during acute recovery.

5. Neurotrophic Factors, Growth Factors, and Their Receptors

Neurotrophic and growth factors enhance survival, maintenance, and synaptic strength and regulate processing of sensory and motor stimuli.68,79 Rehabilitation is a noninvasive means of increasing these factors, thereby mitigating neuropathic pain and other potential deficits.58

Brain-derived neurotrophic factor (BDNF) is a multifunctional protein with wide-ranging effects, including acting as a chemo-attractant for regenerating axons.80 Running wheel exercise increased BDNF in the ipsilateral hemicord at all time points compared to uninjured and SCI+sedentary rats.80 Passive cycling also increased BDNF in the spinal cord, motor neurons, and intermediate grey matter, but not the DRGs of rats that received short- and long-term rehabilitation compared to uninjured and SCI+sedentary rats.80 Treadmill, swimming, and standing all increased BDNF levels compared to SCI+sedentary rats; however, only treadmill training maintained soleus BDNF levels comparable to uninjured animals. All other groups showed levels below baseline.81 Wheel training produced mixed results for BDNF protein expression where some groups’ expression surpassed controls while others showed no significant results.80,81 Treadmill training enhanced BDNF protein levels,68,78,79 however, combining treadmill with magnetic stimulation showed the greatest increases.79 In contrast, cycle training increased BDNF protein expression in several studies, but only some studies showed long-term benefit.60,77,79,82,83

Tropomyosin receptor kinase B (TrkB), the BDNF receptor, regulates its ability to function.64 In rats, 10 days of passive cycling increased TrkB mRNA expression in the whole cord, specifically in motor neurons. These effects were not observed after 31 days of training.60 There was no training effect in the intermediate grey matter or large DRG neurons.60 Treadmill and passive cycle training significantly increased TrkB protein expression in rats with SCI in several additional studies as well,68,77,78 while bike training had no effect.82 Interestingly, early rehabilitation did not affect TrkB signaling effector phospholipase C-gamma or the TrkB docking site, Shc.64 Wheel running in rats with SCI normalized injury-induced decreases in cyclic AMP response element binding protein (CREB) mRNA and protein, which mediates downstream expression of TrkB, although no effects on phosphorylated CREB expression were found at the conclusion of the study.60 Treadmill trained rats had higher levels of CREB in the dorsal horn compared to SCI+sedentary and TrkB-blocked rats.78

Synapsin I is downstream of BDNF and influences neurotransmitter release, axonal elongation, and synaptic maintenance.80 Voluntary wheel running increased synapsin I mRNA compared to SCI+sedentary rats.80 Swimming and standing showed greater benefit in the lumbar cord than treadmill training.53 Standing trained rats also showed significant improvement versus SCI+sedentary rats while swimming showed nonsignificant improvement.51 In the soleus muscle, synapsin I was also significantly increased by standing training compared to SCI+sedentary, treadmill, and swimming groups.51

Glial cell-derived neurotrophic factor (GDNF) modifies neural circuitry by enhancing strength and promoting synapse development.60 Cycle-trained rats showed increased GDNF mRNA in the whole spinal cord, motor neurons, and intermediate grey matter compared to uninjured and SCI+sedentary rats; however, no differences occurred in large DRG neurons for any group.60 Protein levels also significantly increased following wheel and step training compared to SCI+sedentary groups.49,79 Short- and long-term passive cycling increased whole cord RET expression, a cell signaling receptor for GDNF.60 Passive cycling also increased another GDNF receptor, GFRα1, in large DRG neurons but not in the whole cord or motor neurons following SCI.60

Neurotrophin-3 (NT-3) is another factor that mediates synaptic transmission and regeneration.80 Associated with sensory neuron survival and function, NT-3 deficits can lead to sensory neuron loss and subsequent gait dysfunction.80 Voluntary wheel running in rats with SCI restored injury-induced NT-3 mRNA levels after hemisection.81 Further, passive cycling for 10 days...
increased NT-3 mRNA in the whole spinal cord, motor neurons, and intermediate grey matter while a 31-day regimen showed no significant effects.60 No rehabilitation effects were seen in large DRG neurons with either paradigm.60 Treadmill and swimming rehabilitation significantly increased NT-3 mRNA in the lumbar cord compared to control, but only treadmill training showed significant increases compared to sedentary rats.31 Soleus NT-3 mRNA was significantly increased following treadmill, swimming, and standing training compared to SCI+sedentary rats; however, treadmill training was the only approach that significantly increased levels beyond uninjured values.71 Protein levels were increased by passive cycling and stepping but not wheel running exercise.60,79,80

Tropomyosin receptor kinase C (TrkC), the receptor for NT-3, showed increased protein expression in the whole cord of rats who received passive cycling intervention compared to SCI+sedentary rats after SCI.81 No differences were found for TrkC mRNA expression in the whole cord, motor neurons, or large DRG neurons following injury or rehabilitation.60

Similar to those above, neurotrophin-4 (NT-4) functions as a chemo-attractant for regenerating axons while strengthening and enhancing synapse formation.60 Step training significantly increased NT-4 mRNA and protein in rats with spinal cord transection.79 Passive cycling also significantly increased NT-4 protein expression in transected rats.60 Whole cord expression of NT-4 mRNA was not affected by passive cycling; however, NT-4/5 mRNA expression was increased in motor neurons and intermediate grey matter but not large DRG neurons following transection.60

Growth associated protein 43 (GAP-43) is expressed in growing axon terminals and influences growth, neurotransmitter release, learning, and memory.60 Following SCI, GAP-43 expression is often decreased, but rehabilitation may reverse these effects.80 Indeed, training-induced normalization occurred following wheel running in rats with SCI.60 Reach training significantly increased GAP-43 expression contralosional to the preferred paw compared to injured, untrained rats and ipsilesional to the preferred paw.50 Bike training did not affect GAP-43 expression in rats;42 however histologic evidence suggests that passive cycling increased the percentage of GAP-43 positive processes in the lesion area.83

In summary, various training paradigms including wheel, step, treadmill, cycling, and swimming training have the potential to induce molecular changes in spinal trophic and growth factor expression following SCI. Differential results suggest that early rehabilitation largely upregulates neurotrophic and growth factor expression which in turn has the potential to enhance synapse formation, survival, and strength. Factor expression in DRG neurons is largely unchanged by rehabilitation, potentially due to inherently high intrinsic capacity for growth and repair.64 Utilizing rehabilitation as a means of enhancing neuroplasticity through synaptic changes may be another viable target for promoting functional recovery in this population.

### 6. Inflammation

Inflammation can both positively and negatively influence recovery following injury.45–49 As a crude marker for microglial and macrophage activation state, ionized calcium-binding adapter molecule 1 (IBA1) is often used to assess inflammatory response following SCI.72 Enriched environment and voluntary wheel running initiated 1 week postinjury significantly increased IBA1 expression at L5 compared to uninjured, while treadmill trained and SCI+sedentary groups showed no difference from control in mice with thoracic contusion.73 No difference in lumbar IBA1 expression occurred for any group.73 The same study showed that wheel running and treadmill training significantly decreased microglial/macrophage isolectin B4 (IB4) expression while enriched environment and sedentary mice showed no difference from control.73 Wheel running initiated at 5 days post-injury that continued for 4 weeks did not influence C7–8 dorsal horn IBA1 expression in rats with cervical contusion injuries.47 Treadmill training beginning 2 days postinjury shifted the lumbar microenvironment toward a more proinflammatory state by increasing mRNA of inflammatory and trafficking genes while decreasing pre reparative genes of infiltrating macrophages in the mouse lumbar cord. This occurred without influencing the total number of infiltrating cells in the spinal cord or DRG.46,47

Similar to IBA1, glial fibrillary acidic protein (GFAP) is a classic marker used to assess astrocyte reactivity.71 In rats, passive cycling at 5 days postinjury increased GFAP levels after both 10 and 31 days.80 Enriched environment was also shown to enhance GFAP levels at L6 compared to uninjured, SCI+ sedentary, and wheel trained mice in a separate study; however, L5 GFAP levels were significantly higher in all treatment groups compared to control.73

Currently, it appears that intense rehabilitation initiated too early can negatively impact inflammation during SCI recovery. Further research is needed to conclude whether changes in microglia, macrophage, or astrocyte responses confer the negative impacts of hyperacute treadmill training or if other cell types are involved. These results would help better understand the risks and rewards of implementing rehabilitation during the
hyperacute phase of recovery.

7. Muscle Tissue

Muscle is essential for functional capacity and an important source of metabolic support that undergoes tremendous change after SCI. Early treadmill training increased cross-sectional area in the soleus muscle compared to untrained animals. Although not statistically significant, 5 days of treadmill training showed a trend toward attenuation of mixed I+IIa fibers and prevented the appearance of type IIa+IIx fibers compared to SCI+sedentary rats. Fatigue analysis showed significantly lower fatigue levels in the treadmill trained rats compared to the SCI+sedentary group. Despite changes in cross-sectional area and fatigue, no significant difference was found for twitch force or peak tension in the soleus muscle between uninjured, SCI+treadmill, or SCI+sedentary rats.

Muscle growth and regeneration are affected by myogenic regulatory factors influenced by rehabilitation. Although protein levels remained unchanged, myogenic differentiation 1 mRNA was significantly increased in SCI+sedentary rats at 14 days postinjury while trained rats showed significant increases in expression at 8 and 14 days postinjury compared to uninjured. Treadmill training significantly increased myogenin mRNA and protein levels compared to uninjured rats and those with SCI alone. Expression of myogenic factor 5 mRNA was not influenced by treadmill training in rats with contusion SCI; however, protein expression was significantly increased. Embryonic myosin demonstrates a muscle-specific response to early rehabilitation after SCI. In the soleus, treadmill training significantly increased embryonic myosin compared to SCI+sedentary and uninjured treadmill trained rats. In contrast, embryonic myosin in the tibialis anterior of SCI rats was significantly greater compared to the tibialis anterior of all other groups.

Insulin-like growth factor 1 (IGF1) also alters muscle mass and repair. Overexpression of IGF1 promotes hypertrophy, and under expression can cause muscle fiber abnormalities. At 14 days postinjury, SCI+sedentary rats had significantly higher IGF1 expression compared to control rats, while treadmill trained SCI rats showed significantly higher expression compared to uninjured and SCI+sedentary rats. Similar results were found for IGF1 peptide. Additionally, higher IGF1 peptide concentration was found in the rat soleus muscle compared to tibialis anterior for uninjured, uninjured+treadmill, and SCI+treadmill groups. Treadmill trained rats had significantly higher IGF1 peptide in the soleus than all other groups. Receptor expression was also increased in trained rats compared to uninjured and SCI+sedentary rats following 14 days of training. By 8 and 14 days postinjury, treadmill trained rats showed a 10-fold increase in IGF1B mRNA compared to uninjured and SCI+sedentary rats while SCI+sedentary rats showed a significant increase in mechano-growth factor mRNA, an IGF isofrom, compared to uninjured only at 14 days postinjury.

A family of IGF binding proteins (IGFBP) influence IGF1 activity. This family includes 7 different binding proteins, but only IGFBP4 and IGFBP5 affect muscle fiber changes. Treadmill trained rats showed higher levels of IGFBP4 after 8 and 14 days compared to uninjured and SCI+sedentary rats; however, IGFBP5 was significantly higher only after 14 days of treadmill training.

Rehabilitation enhances muscular adaptation and strength in rodents with SCI. Specifically, data supports the use of treadmill training within the first 8 days postinjury to enhance muscle regulatory factors, increase cross-sectional area, and decrease fatigue. Using acute treadmill training to target muscle fiber adaptation can facilitate functional recovery by mitigating SCI-induced strength deficits.

EFFECTS OF EARLY REHABILITATION ON CLINICAL OUTCOMES

1. Gross Motor Function

Earlier admittance to acute care facilities and earlier time to rehabilitation following SCI has the potential to improve patients’ functional ability for tasks including, but not limited to, standing, bathing, grooming, and balance but does not affect scores on the Walking Index for Spinal Cord Injury. Simiar results were found in rats where early rehabilitation involving reach, wheel, and treadmill training showed improvements in motor function based on Forelimb Movement Score, Forelimb Locomotor Score, and Motor Function Score. Importantly, task-specific reach training resulted in significant reaching improvement but significantly worsened performance on ladder tasks in the same group of rats, highlighting the potential for interference with skill learning.

Regarding hindlimb motor function, treadmill training yields an overwhelmingly positive response on open field locomotor scores at early and late time points after injury. Treadmill trained rats also showed significant reduction in muscle coactivation in ankle flexor and extensors and spasticity compared to SCI+sedentary rats. Only 2 studies showed no significant difference in open field locomotor performance after early treadmill training. In fact, Hansen et al. observed a signifi-
cant positive effect of early treadmill training in mice, but only when inflammation was controlled. Use of exercise balls for activity following SCI showed significant improvement in open field locomotor scores compared to delayed training in rats; however, performance in all groups plateau roughly 2 weeks postinjury.\(^{56}\) Passive hindlimb cycling, swimming, wheel running, and enriched housing had no effect on open field locomotor scores in mice or rats following SCI.\(^{36,81,96,97}\)

Stepping analysis revealed that rats trained on a horizontal ladder task immediately after injury had significantly greater stepping ability after 1 week of training compared to those who received delayed training.\(^{54}\) Additionally, a strong positive correlation was found between damage in the thoracic dorsal and dorsolateral funiculi at T8 and initial error rate for stepping in early and delayed training groups.\(^{54}\) Ladder task performance significantly improved when flat running wheels were used for mice instead of traditional, runged wheels and for rats with lateral funiculus and dorsal funiculus lesions but not entire dorsolateral quadrant lesions.\(^{36,53}\) Early and late voluntary wheel training elicited significant improvement in Rotarod performance and decreased the number of foot falls on a ladder task compared to baseline in mice with dorsal hemisection.\(^{49}\) Wheel trained mice also covered significantly greater distances on a running wheel assessment compared to treadmill trained mice.\(^{73}\) Hindlimb or locomotor-type rehabilitation did not affect grip strength in rats with SCI.\(^{81}\)

The current body of literature suggests that the effects of early rehabilitation on gross motor recovery following SCI are largely positive with only one study reporting unwanted outcomes associated with rehabilitation. Negative outcomes in this study may be attributed to the use of high-intensity rehabilitation initiated 2 days postinjury, at which point the injury may be too dynamic for subjects to tolerate this level of exertion unless inflammation is controlled.\(^{41}\) In contrast, treadmill, wheel, and cycle training initiated later during the acute phase following SCI are highly effective and should be used to promote gross motor recovery.

### 2. Fine Motor Performance and Kinematic Analysis of Function

Evidence from footprint analysis of treadmill trained mice showed improvement in hindlimb alternation and stride length; however, smearing of hindlimb pawprints at push-off and absent heel contact were also noted.\(^{75}\) In contrast, enriched housing, wheel running, and treadmill training had no effect on maximal foot contact or footprint score following SCI in rats.\(^{55,97}\) Kinematic analysis of mouse joint angles and limb movement showed that treadmill training improved hip and ankle joint movement with decreased variability in foot posture.\(^{75}\) Treadmill training also decreased the angle of rotation in the feet following contusion injury in rats.\(^{57}\) Combined treadmill and TMSsc in rats mitigated SCI-induced increases in wrist but not ankle lift off angle compared to control and TMSsc only groups.\(^{76}\) Cycling and treadmill training in rats showed improvement in base of support, while running wheel and enriched housing had no effect.\(^{57,97}\) Wheel running, enriched housing, and treadmill training also had no effect on thoracolumbar height, maximal leg extension, or yield during stance following SCI in rats.\(^{55,97}\) Reach training showed improvement on reaching tasks without changing reaching style.\(^{50,53}\)

Treadmill training provides the most benefit regarding changes in fine motor performance and kinematics in animals with acute SCI, while enriched housing and wheel running are largely ineffective. To promote recovery of fine motor skills following SCI, treadmill training or task-specific reach training should be the first-choice intervention; however, careful consideration of dosage timing and intensity is still needed to maintain safety and maximize benefit.

### 3. Sensory Function

Hutchinson et al.\(^{51}\) found that treadmill, swimming, and standing training all significantly increased time to peak flexion withdrawal following noxious pinch stimulus to the rat hind paw; however, only treadmill trained rats showed significant improvement in mechanical sensitivity following contusion injury.\(^{51}\) Treadmill training also improved mechanosensory thresholds in rats receiving more severe contusion injury in 2 of 3 models that investigated these effects.\(^{68,71,79}\) Rats trained with exercise balls immediately following injury showed significantly higher tactile withdrawal thresholds compared to those that received delayed training.\(^{56}\) Importantly, delayed training did not reverse allodynia once it had developed.\(^{56}\) Five weeks of wheel running initiated at 5 days postinjury decreased prevalence of at-level allodynia from 42% to 6% in rats with SCI.\(^{48}\) Moreover, rats that received rehabilitation throughout the remainder of the study did not develop allodynia in the ipsilateral or contralateral forepaw.\(^{48}\)

Early treadmill training effects on thermal withdrawal thresholds after SCI show mixed results. Some studies in rats show significant improvement in withdrawal threshold in response to thermal stimuli,\(^{68,79}\) while others show no effect of rehabilitation.\(^{48,56,71}\) Although there was variation in training paradigm
and injury models, both studies that found positive effects on thermal withdrawal threshold utilized body weight-supported treadmill training.

Running wheel exercise also restored thermal withdrawal latencies to baseline levels in mice, while enriched housing had no significant effect.

Various paradigms including treadmill, swim, stand, wheel, and exercise ball training enhance at least one aspect of sensory function following SCI. Despite this, treadmill and wheel training are the most effective for promoting recovery of sensory processing and should be prioritized when choosing interventions. Effects of rehabilitation on thermal processing are not as clear, but treadmill and wheel training show benefit in several studies and should be prioritized over enriched environment.

4. Reflex Function

Following SCI, supraspinal control is diminished while afferent feedback becomes augmented. These changes lead to decreased spinal reflex modulation and can cause hyperreflexia, spasticity, and inappropriate timing of movement. To investigate reflex changes following SCI, numerous studies have assessed H-reflex modulation and $H_{max}:M_{max}$ ratio changes, a relative indicator of motoneuronal excitability.

Frequency-dependent H-reflex depression was enhanced in bike and step-trained rats after 30 days of training. No differences were found for $H_{max}:M_{max}$ ratio in response to increasing stimulus intensity beyond the motor threshold; however, slope of the recruitment curve was significantly higher in step-trained rats compared to bike-trained and untrained groups. A subsequent study by the same group showed that spinal excitability in SCI+sedentary rats had significantly increased $H_{max}:M_{max}$ ratios in the first 2 weeks following injury that plateaued around 28 days postinjury. Implementing early cycle training restored spinal excitability at 14 and 28 days postinjury by increasing frequency-dependent modulation of the H-reflex. Rehabilitation also significantly reduced $H_{max}:M_{max}$ ratio by 28 days postinjury. Additional research in rats also supports the idea that frequency-dependent depression is improved with bicycle and treadmill training.

Wheel training in mice showed significant decreases in $H_{max}:M_{max}$ ratio over time while other treatment groups did not. Additionally, the percentage of rate-dependent depression as a function of frequency showed that wheel trained animals did not differ significantly from control animals while sedentary, enriched housing, and treadmill trained groups all showed significantly higher values when the experiment concluded.

The current body of research suggests that various training paradigms, including treadmill, bike, and wheel training, mitigate SCI-induced decreases in H-reflex modulation and simultaneously reverse increases in the $H_{max}:M_{max}$ ratio following injury. These findings show only positive effects of early rehabilitation on spinal excitability and reflex recovery after injury and should be utilized readily in future studies.

5. Autonomic Function

The effects of SCI extend beyond somatic functions to include numerous autonomic and systemic changes. Early rehabilitation has the potential to enhance protective effects on cardiac indices at early time points following SCI in rats, but only if rehabilitation is continued over time. Rehabilitation initiated at later time points can still elicit positive effects, but subsequently increases time to recovery. In rats, resting heart rate and heart rate responses to colorectal distension-induced autonomic dysreflexia are largely unaffected by treadmill training and passive hindlimb cycling following SCI while changes in systolic blood pressure (SBP), mean arterial pressure (MAP), and the severity and frequency of autonomic dysreflexia show varied results between studies. Indeed, one study found that treadmill trained animals had increased MAP during training and significantly decreased MAP following training while another showed that MAP was unaffected by passive cycling initiated early or late after injury. Treadmill trained rats also had larger MAP responses during periods of autonomic dysreflexia compared to SCI+sedentary rats. Delayed passive hindlimb cycling increased the pressor response to colorectal distention at 5 but not 9 weeks postinjury and decreased the incidence of autonomic dysreflexia by the study’s conclusion. Additionally, West et al. found that passive hindlimb cycling reduced the SBP response to colorectal distention while Popok et al. showed no difference between groups at any time point for pressor response during autonomic dysreflexia, or maximal SBP reached. Early initiated treadmill training has little to no effect on vascular conductance following rat spinal cord transection while swim training initiated at 3 days postinjury increased microvascular dysfunction.

Changes to the urinary system in response to early intervention show that locked and unlocked flat surface running wheel groups were not different in the number of days to micturition, while the rung wheel group showed longer time to micturition compared to uninjured and SCI+sedentary mice. A trend between higher open field locomotor scores and earlier micturition was described, but significance and correlational values were not included.
Data show that treadmill training initiated within the first 3 days after injury negatively impacts cardiovascular function while bicycle training initiated later in the acute phase of recovery has only positive effects. Continued research is needed to determine effects of bicycle training within the first 3 to 4 days after injury to ascertain whether cycle training is genuinely more beneficial than treadmill training during this period. Treadmill training should be avoided within the first 4 days of injury to protect cardiovascular function; however, other high-intensity interventions such as bicycle and swim training should also be utilized with caution.

**EFFECT OF EARLY TRAINING PARAMETERS ON OUTCOMES**

Four of the 9 studies that initiated rehabilitation within the first 3 days found negative effects regarding autonomic dysreflexia, inflammation, microvascular dysfunction, and long-term locomotor outcomes.\(^{41,46,69,102}\) Additionally, 3 of the studies that showed negative effects used treadmill training in their rehabilitation paradigm.\(^{41,46,69}\) Two of these studies implemented body weight-supported treadmill training with manual paw placement in two, 10-minute bouts separated by 20-minute rest periods for roughly 1 week following injury in moderately confused mice and showed worsened locomotor function.\(^{41,46}\) The other used 10 minutes of treadmill training per day, 5 days per week for 6 weeks which worsened autonomic dysreflexia but improved open field locomotion in rats with transection injury.\(^{69}\) The fourth and final study implemented swim training 3 days after SCI in rats and showed worsened microvascular dysfunction.\(^{102}\)

A single study that implemented treadmill training between 2 and 4 days postinjury showed positive effects on function using three, 10-minute bouts of treadmill training with a 5-minute break in between bouts at 5 days per week for 12 weeks in rats with microballoon compression injuries.\(^{52}\) Results of this study showed improved open field locomotion at 2 weeks that plateaued at 7 weeks but remained higher compared to sedentary animals.\(^{52}\) Another study implemented 15 minutes of daily treadmill training beginning 4 days postinjury and showed slightly larger exploratory behavior but no additional benefit on locomotor outcome.\(^{55}\) Other studies that started rehabilitation in the first 3 days without negative effects used ladder stepping, exercise balls, and voluntary wheel training.\(^{49,54,66}\)

Continuing rehabilitation beyond the first week postinjury may overcome the negative effects of treadmill training within the first 3 days.\(^{52,69}\) Both the studies of Hansen et al.\(^ {49}\) and Norden et al.\(^ {46}\) implicate enhanced inflammation as a potential cause for negative outcomes from early rehabilitation. Although Multon et al.\(^ {52}\) and Laird et al.\(^ {69}\) did not investigate inflammatory changes, they saw locomotor improvement after 6 and 12 weeks of continuous training, respectively. It is important to note that Laird and colleagues saw significant, nonfunctional gains in locomotor performance which may be related, in part, to the administration of nonsteroidal anti-inflammatory drugs during recovery.\(^ {59}\)

In summary, effects of rehabilitation during the hyperacute phase of SCI are largely dependent on injury and rehabilitation paradigms. It appears that lower-intensity or self-paced rehabilitation, such as reach or ladder training, in shorter, more frequent bouts elicits better outcomes when implemented between 0- and 3-day postinjury. These benefits may be attributed to less inflammation resulting from lower rehabilitation intensity, but additional research is needed to confirm this. Higher-intensity rehabilitation is more beneficial when started after 4 days of recovery and can be dosed in longer bouts with less frequent

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rest breaks. Despite differences in dosage and intensity, rehabilitation initiated during the hyperacute phase should continue past the 1 week recovery mark to ensure that all short- and long-term effects are recognized (Fig. 2).

CONCLUSION

Treadmill training is the most studied rehabilitation approach in the first week post-SCI and shows the greatest effect on locomotor outcomes. Independent of training parameters, cycle training shows the least risk of adverse effects and is the topic of an ongoing clinical trial. However, no studies implemented cycle training within the first 3 days after injury and is a major gap in the literature. Early physical activity is most beneficial for synaptic plasticity, structural plasticity, neurotransmitter/neurotrophic/growth factor expression; least effective for tissue sparing; and potentially detrimental if too intense too soon under uncontrolled inflammation.

To promote positive outcomes during acute SCI recovery, low-intensity or self-limiting rehabilitation such as reach training or voluntary wheel or ball exercise should be utilized for the first 3 days postinjury. Activity dosage during this period should include short, frequent bouts of rehabilitation with rest breaks, and the duration should extend long-term to maximize benefit. Higher-intensity rehabilitation including treadmill, bike, and enriched environment can be implemented safely from 4 days postinjury onward. Rehabilitation at this point can be dosed in longer bouts with less frequent rest breaks but should also extend beyond the first week of recovery (Fig. 2). It is important to recognize that these data and recommendations are limited by the discrepancy between animal and human biological and recovery timelines. Comparative biological studies are warranted to identify cross-species timelines for effective translation of these findings to humans.

While we have a general idea which interventions and dosages are safe and effective in acute SCI, data in the hyperacute phase are scarce. As such, future research should focus on identifying which interventions are safe and most effective during the hyperacute phase; how to best manipulate the hyperacute window to allow greater intensity intervention; multisystem effects of spinal cord stimulation or bicycle training during the first 3 days postinjury; whether interventions other than passive cycling can reduce post-SCI apoptosis; and the effect of acute rehabilitation on nonmyeloid cell function. Given the tremendous beneficial effects of physical rehabilitation in the acute phase, particular emphasis should be placed on combining emerging therapeutics, particularly those targeting regenerative or inflammatory responses, with acute rehabilitation.

Lastly, substantial variability in injury models, rehabilitation paradigms, and chosen outcomes makes systematic review of the literature, drawing definitive conclusions, and thus making recommendations challenging. Some degree of standardization within the field may speed knowledge development and clinical translation. As such, increased focus on clinically relevant injury models, such as contusion, is warranted. It is also prudent for basic and clinical scientist in SCI research to collaborate in developing, standardizing, and validating a translational battery of measures spanning behavioral, electrophysiological, and imaging modalities to assess outcomes across species. It is our hope that this work and recommendations can be used to guide future systematic reviews of the literature and facilitate these discussions. Investigating these effects along with implications for the areas mentioned previously would greatly benefit our ability to understand and prescribe effective rehabilitation during this delicate stage to enhance long-term recovery.

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ORCID

Nicholle E. Lewis: 0000-0002-4292-7897
Troy Q. Tabarestani: 0000-0003-1485-3605
Brianna R. Cellini: 0000-0002-5857-8732
Nina Zhang: 0000-0002-1821-2744
Eric J. Marrotte: 0000-0001-7930-4258
Haichen Wang: 0000-0001-7926-9835
Daniel T. Laskowitz: 0000-0003-3430-8815
Muhammad M. Abd-El-Barr: 0000-0001-7151-2861
Timothy D. Faw: 0000-0001-7794-0074
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Sang Ryong Jeon

Spinal cord injury (SCI) is a debilitating disease that affects patient's family as well as the patient's physical, mental, and social status after injury. For treatment of SCI, rehabilitation following appropriate surgical procedure provides another opportunity for recovery. The optimal methods and effects of acute physical interventions for SCI are important subject of research, but not clearly proven yet, as the authors of this article says. Due to the heterogeneity of the timing, method, duration, and intensity of physical interventions, the appropriate use of rehabilitation has been the subject of debate.1,2 This article comprehensively reviewed 52 preclinical studies on the effect of acute physical interventions after SCI regarding histopathological aspects and clinical outcomes.3

In this paper, the authors classified physical interventions as 2 types: “high intensity” like treadmill, cycling, and swim training, and “low intensity” such as wheel running, ball training, reach training. It is interesting that high intensity rehabilitation initiated within the first 3 days and terminated by 1 week after injury worsened autonomic function, inflammation, and locomotor outcomes, which might be from association with dynamic inflammation in the hyperacute stage,4 while lower intensity exercise such as reach training, ladder training, or voluntary wheel or ball training showed benefits when implemented during the first 3 days. The author’s conclusive suggestion that “lower intensity or voluntary rehabilitation during the hyperacute phase is more appropriate until at least 4 days postinjury, and then, higher intensity activity becomes safer and more beneficial for recovery” is also impressive.

Because the acute management of SCI is so crucial to the prognosis in the long term, an international committee of spinal surgeons has continuously performed and issued consensus recommendations.5 The meticulous dissection of the literatures and precise evaluation of the methods used in this review will be extremely helpful to readers who have been considering various rehabilitation options for SCI patients. It is really meaningful to figure out the flow of the acute intervention after SCI as this review article introduces the general concept of rehabilitation, despite the fact that the subjects are the preclinical data and heterogeneous background resources. I recommend this article with obvious pleasure to clinicians and neuroscientists participating in SCI management and research.
Conflict of Interest: The author has nothing to disclose.

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Acute traumatic spinal cord injury (SCI) can be a devastating and costly event for individuals, their families, and the health system as a whole. Prognosis is heavily dependent on the physical extent of the injury and the severity of neurological dysfunction. If not treated urgently, individuals can suffer exacerbated secondary injury cascades that may increase tissue injury and limit recovery. Initial recognition and rapid treatment of acute SCI are vital to limiting secondary injury, reducing morbidity, and providing the best chance of functional recovery. This article aims to review the pathophysiology of SCI and the most up-to-date management of the acute traumatic SCI, specifically examining the modern approaches to surgical treatments along with the ethical limitations of research in this field.

Keywords: Spinal cord injuries, Spinal injuries, Neurosurgery, Hemodynamics, Surgical decompression, Ethics

INTRODUCTION

Spinal cord injury (SCI) affects more than 27 million people worldwide and is the second leading cause of paralysis in the United States. Among the 329 million people in the United States, approximately 299,000 persons live with SCI with nearly 18,000 new cases occurring each year. Most commonly the result of motor vehicle accidents and falls, SCI greatly affects life outcomes from personal, social, and economic standpoints. Health care costs and living expenses associated with SCI vary depending on education levels, the severity of neurological impairment, and preinjury employment history. Limited ability to return to work may exacerbate the financial burden that SCI patients experience, as only 18% of persons with SCI are employed 1-year postinjury. Although employment rate nearly doubles over time, the majority of those affected by SCI are left without stable forms of income.

In addition to the functional disabilities and economic impact associated with acute injury, individuals with SCI face high rates of rehospitalization. One study found that 36.2% of SCI patients were hospitalized at least once within the first-year postinjury. Younger age, female sex, unemployment or retirement, and Medicaid coverage were all associated with increased odds of rehospitalization. Surgical, medical, and rehabilitative interventions, especially when used together, have been shown to improve neurological recovery, lead to higher postoperative sensorimotor function, and reduce rehospitalization after SCI.

Given the inability to modify the damage caused by primary injury and the poor regenerative capacity of central nervous system (CNS) neurons, recovery from SCI is often incomplete. However, timeliness of surgical intervention and spinal hemodynamic management could limit secondary damage.
mal timing, approaches, and parameters for acute surgical and medical interventions are understudied. Moreover, there are distinct ethical considerations for performing clinical trials in this population and setting. This gap must be addressed, as increased mobility improves quality of life, demonstrating the need to improve the efficacy of early interventions and enhance outcomes. Further research can improve point of injury care and management, as well as facilitate neuroprotective strategies to optimize functional outcomes.

**SPINAL CORD INJURY PATHOPHYSIOLOGY**

To determine the best plan of care, it is essential to consider and understand the pathophysiology of acute, traumatic SCI. The acute phase of SCI is highly dynamic and associated with primary and secondary damage. Primary damage, or frank disruption of axons and vasculature, results from one or more of 4 primary mechanisms: (1) impact plus persistent compression, (2) impact alone with transient compression, (3) distraction, and (4) laceration/transection. Impact plus persistent compression is the most common type of SCI observed in humans, with damage rarely affecting the entirety of the cord. Upon injury, some spared and damaged axons traverse the lesion site, resulting in a subpial rim of myelinated and demyelinated axons. The ability of these axons to effectively transmit signals across the injury site ultimately determines clinical classifications of complete versus incomplete injuries. Neurological outcomes can often be predicted as soon as 72 hours after injury based on American Spinal Injury Association Impairment Scale scores, the presence of motor evoked potentials, or via emerging magnetic resonance imaging (MRI) biomarkers. Recovery is greatest during the first 3 months postinjury, with progress plateauing at around 9 months in the absence of continuing rehabilitation. However, long-term outcomes are closely related to the level and severity of the initial injury.

Primary damage from SCI triggers a cascade of biochemical, mechanical, and physiological change within affected tissues. This is known as secondary damage, beginning within minutes following primary impact and continuing for months postinjury. Secondary damage mechanisms can be subdivided into acute, subacute, and chronic phases, and extend beyond the area of injury to adjacent segments and throughout the neuraxis. These mechanisms include vascular disruption, infarction, lipid peroxidation, ionic imbalance, oxidative stress, cell death, axon degeneration, demyelination, matrix remodeling, glial barrier formation, and neuroinflammation, which are expertly reviewed by Alizadeh and colleagues.

Briefly, frank disruption of vasculature causes infiltration of blood products and peripheral immune cells into the damaged spinal cord parenchyma as well as intact distal regions resulting in glial activation. Microglia are among the first CNS cells to become activated in response to injury participating in phagocytosis and clearing of myelin debris. They also contribute to the inflammatory response resulting in further blood spinal cord barrier breakdown and immune cell infiltration.

Similarly, astrocytes react quickly to SCI and in a severity-dependent manner with proliferation, migration, exaggerated hypertrophy, overlapping physical domains, increased cytokine production, and border formation. Like microglia, astroglialosis has beneficial and maladaptive functions, regulated by specific signaling mechanisms in specific contexts. Reactive astrocytes limit the spread of inflammation and pathology, but they also secrete toxic factors that contribute to neuron and oligodendrocyte death, recruit peripheral leukocytes, and may later impair regeneration via inhibitory molecules such as chondroitin sulfate proteoglycans. Additionally, extracellular levels of glutamate increase rapidly following impact and are likely linked to apoptotic mechanisms, which causes a neurotoxic increase in excitatory amino acid concentrations and further cell death.

Oligodendrocytes are particularly vulnerable excitotoxicity and are lost in tremendous numbers as early as 15 minutes postinjury. This is especially detrimental as the loss of a single oligodendrocyte can compromise the functioning of numerous myelinated axons. Facilitated in part by the inflammatory response, oligodendrocyte progenitor cells undergo robust proliferation in response to injury contributing to both the glial border and remyelination, which is a slow but largely complete process.

Axonal dieback is another clinically relevant consequence of SCI, occurring in 2 stages. During stage 1, the proximal and distal ends of the axon begin to diverge. The proximal end undergoes immediate axonal degeneration within an hour upon primary damage, and slower dieback over the next 48 hours. During stage 2, axon bulbs continue to swell and retract from the injury site, roughly doubling in distance. This process closely corresponds with inflammatory cell infiltration. Macrophage-mediated axotomy progresses dieback as well as a phenomenon known as Wallerian degeneration, which is the progressive degeneration of distal axon tracks. The processes associated with Wallerian degeneration are mediated by pathways like those observed during apoptosis.

Each of these cellular and molecular responses occur in a se-
Randomized controlled trials (RCTs) for surgical interventions raise several ethical issues.\textsuperscript{79} By setting a null hypothesis, it may seem investigators are hypothesizing that one treatment is superior to the other, which means in theory that some patients will be randomized to a less favorable treatment.\textsuperscript{79} Randomization also limits a surgeon's ability to make surgical treatment decisions based on their patient's individual situation,\textsuperscript{79} which may raise conflict of interest concerns and challenge the principles of autonomy and beneficence.\textsuperscript{80} Placebo groups, such as sham surgery, pose significant risk to patients, such as general anesthesia and infection, without possibility of benefit.\textsuperscript{79,81} Finally, trauma patients—which represent a subset of patients with SCI—pose additional challenges with informed consent. Patients with acute SCI who need surgery eminently would need to decide about joining a prospective research study in a narrow time window. For patients with concomitant head injury or decreased level of consciousness (e.g., shock), this puts surrogate decision-makers under pressure to decide unexpectedly if the patient lacks decision-making capacity.\textsuperscript{79,81-84} Patients or their decision-makers during vulnerable situations, such as following traumatic injury, may make decisions out of desperation which can beget eagerness to participate and blur the lines of informed consent, particularly when the time window for the intervention is narrow.\textsuperscript{79,81,84}

Several proposals have been made to mitigate these ethical issues. Freedman proposed the widely accepted idea that RCTs are ethical if there is truly \textit{clinical equipoise} between the 2 treatments—that is, there is no consensus between experts in the field on which treatment is superior.\textsuperscript{85} This rationale provided the basis for a recent RCT of early surgical intervention for acute thoracic SCI.\textsuperscript{86} Another way of thinking about this is having the control group receive the standard of care (usual care), rather than withholding a therapy with known benefit.\textsuperscript{82} Conflict of interest can be reduced by having the patient's surgeon be a different person than the study investigator—termed \textit{parallel care}.\textsuperscript{79} Finally, in research in emergency settings, such as traumatic acute SCI, the U.S. Food and Drug Administration has granted a waiver of consent if a study meets certain criteria.\textsuperscript{82,88} Still, a waiver of consent raises concerns about patient's rights and autonomy, as well as impact on vulnerable groups. Other ideas include studying how to better consent trauma patients and obtaining consent from a patient's surrogate decision maker after detailed discussions of risks versus benefits.\textsuperscript{81,88}

**ACUTE SURGICAL MANAGEMENT**

1. **Initial Diagnosis and Hospital Presentation**
Once a patient is stabilized in the trauma bay, a trauma series computed tomography (CT) is performed, which includes a CT brain/cervical spine without contrast and CT chest, abdomen and pelvis with maximum intensity protocol with and without contrast.\textsuperscript{89} If there is an injury pattern suspicious for a vascular injury, a CT head and neck angiogram is also ordered. If a spinal fracture, dislocation, or abnormality is identified on imaging, the spine surgery team is consulted for further recommendations. If surgery is applicable, the stabilization procedure should be performed as soon as possible; if the patient is not a surgical candidate, medical and therapeutic treatment is initiated instead for optimum recovery potential.\textsuperscript{89} Interestingly, a recent study aimed to understand how the center type a patient presents to can influence their management and outcome after a SCI. Williamson et al.\textsuperscript{90} reported that among a total of 11,744 incidents of SCI, those patients who were admitted directly to level I trauma centers had significantly higher odds of receiving a decompressive surgery compared to those who were either transferred to a level I center or went directly to a level II/III/IV center. As with all major health issues, social factors always play in role in accessibility of care and should be kept in mind when generalizing the results for SCI treatment.

2. **Timing of Acute Decompression for SCI**
With respect to preventing and mitigating the secondary injuries after SCI, there has been increased discussion regarding the advantages of acute surgical decompression. Before there were any large-scale clinical or retrospective studies, basic science groups investigated the potential effects of surgical decompression to improve neurological outcomes in clinically relevant animal models. From rat to beagle models, there is a plethora of laboratory evidence indicating significant benefits of acute surgical decompression with a varying postinjury time frame. For example, Dimar et al.\textsuperscript{91} showed that longer periods of spinal cord compression worsened the prognosis of neurologic recov-
Fig. 1. Acute surgical interventions for spinal cord injury (SCI). Interventions were broken down into 3 primary areas: timing of acute decompression, anterior versus posterior approach, and hemodynamic stability. Key aspects from each category are highlighted. The Oxford Center for Evidence Based Medicine Level of Evidence (I–V) for each key point is shown in parentheses followed by corresponding references. AIS, American Spinal Injury Association Impairment Scale; CTJ, cervico-thoracic junction; MAP, mean arterial pressure; SCPP, spinal cord perfusion pressure.

er in their rat model. Carlson et al.92 found that the degree of early hematologic reperfusion after decompression was inversely proportional to the duration of spinal cord compression and proportional to neurologic recovery in dogs. Further, Carlson et al.93 showed in the same dog model, longer durations of spinal cord compression produced larger lesions, which also corresponded to decreased long-term functional outcome. Consistent with these results, small single institution cohort reviews revealed similar results in patients who had undergone urgent decompression after SCI.94,95 These initial studies showed mixed results, none of which were standardized across institutions. However, La Rosa et al.96 showed in their systematic review that early decompression resulted in better outcome compared with both conservative and surgical treatment after 24 hours.

In 2012, Fehlings et al.97 performed a large, multi-institutional retrospective study evaluating 313 patients across 6 hospital systems. Every patient in their cohort received both decompression and instrumented fusion procedures of their cervical spine either within an early (<24 hours) or late (>24 hours) time frame following self-reported SCI. Measurements of postoperative neurological improvement were based on the change in American Spinal Injury Association Impairment Scores (AIS) from baseline (within 24 hours of presentation). The main statistically significant result showed that patients in the early surgery group were almost 3 times more likely to have a 2 grade AIS improvement at the 6-month postoperative follow-up mark. Since that article was published, there have been a multitude of other corroborating cohort studies indicating that patients undergoing early surgery after SCI have a significantly better neurological outcome as compared with patients who underwent surgery after 24 hours.98-101

Despite the clinical evidence suggesting that early surgical intervention is associated with improved outcomes, there remain a number of poorly defined issues regarding optimal timing. For example, the 24-hour cutoff point in some studies is somewhat arbitrary, and other studies have evaluated postsurgical intervention at 8 hours, 72 hours, or even 4 days.102-104 Why then, if the animal models and surgeon preferences clearly show a time-dependent effect on the postoperative neurological benefits, would studies not aim to have their cutoff at less than 24 hours?105 Multiple studies have addressed this discrepancy to show that only between about 20% to 50% of SCI patients can
feasibly undergo an emergency decompression within the first 24 hours after injury due to practical factors like transportation and other life-saving measures.\textsuperscript{97,106,107} A more recent study by Aarabi et al.\textsuperscript{108} revealed that in patients with postoperative MRI confirmation of a complete acute decompression following cervical SCI, preoperative intramedullary lesion length, not the timing of surgery, was the only significant determinant for long-term neurological outcome. Their study also looked at ultra-early (less than 12 hours), early (between 12 and 24 hours), and late (after 24 hours) decompressive surgeries. In total, the relevance of acute decompression as a surgical management for SCI has quickly evolved over the past decades and has shown significant promise towards improving postoperative neurological function in patients across many studies. At the same time, there are still questions that need further investigation to prepare the most accurate, efficient, and beneficial guidelines for treating individuals with SCI.

3. Anterior Versus Posterior Approach for Acute Cervical Decompression

For cervical injuries, surgical technique can vary depending on the nature of the injury, patient factors, surgeon skill level.\textsuperscript{109} The anterior approach generally offers easier access to any anterior compression or disc herniation while also utilizing a safer supine patient position. It is also less invasive when compared to the posterior or combined approaches, but there are limitations and contraindications. Johnson et al.\textsuperscript{110} reported a 13% failure rate for superior endplate compression fractures following an anterior approach. These cases then require a switch to a posterior approach which extends time under anesthesia and increased risk for neurologic deterioration.\textsuperscript{111} Wang et al.\textsuperscript{112} further corroborated these results by showing increased risk for graft migration for patients who only underwent anterior fixation with posterior hardware. If a posterior approach is chosen for addition stability, it brings its own set of potential pitfalls. For one, pedicle screw placement in the cervical spine has been associated with increased rates of vertebral artery injury given its close proximity.\textsuperscript{113} Mainly, studies have also focused on the relative instability at the cervicothoracic junction. If fixation does not cross C7 into T1, Nagashima et al.\textsuperscript{114} noted up to 40% risk of hardware failure. However, Huang et al.\textsuperscript{115} demonstrated that crossing the cervicothoracic junction during posterior decompression and fusion was associated with increased surgical time, estimated blood loss, and rates of wound dehiscence. These counteracting results further illustrate the need for larger cohort studies to clearly elucidate the necessity of crossing the junction.

Of note, situations exist where a combined approach may be beneficial, especially if a ventral decompression is needed or the anterior column’s integrity is compromised.\textsuperscript{116} Recent case reports have even proposed a 3-staged surgical approach consisting of cervical laminectomy, posterior fixation, and anterior corpectomy and fusion.\textsuperscript{117} While these singular demonstrations are intriguing and require further testing, the combined approach may increase surgical trauma via positional changes, nerve injuries, and incidence of emergency airway management.\textsuperscript{118-120} Therefore, anterior alone and posterior alone approaches have dominated the current management of SCI.

In the setting of a SCI, only a handful of studies have directly examined the short and long-term outcomes of each approach for cervical decompression. The most recent study was conducted by Ren et al.\textsuperscript{121} in 2020, in which almost 200 patients underwent either anterior reduction with interbody fusion or posterior reduction with short-segmental pedicle screw fixation. They followed these patients for 10 to 17 years and concluded that the posterior approach was associated with greater loss of alignment by 2 years and at final follow-up. The posterior approach group also had significantly more blood loss, longer operation times, increased risk for infection, and longer hospital stays.\textsuperscript{122} In comparison, the anterior approach was associated with better long-term neurological recovery and preserved cervical alignment.\textsuperscript{123} However, the majority of the current literature have come to conflicting conclusions. In the review of Verlaan et al.,\textsuperscript{124} the posterior pedicle screw fixation method was preferred over both anterior and combined posteroanterior approaches.\textsuperscript{125-127} Looking forward, the debate between which surgical approach is superior will likely depend on timing and individual patient presentation. For example, the role of MRI in surgical decision-making is still under investigation. Imaging can prove crucial when planning either approach, but generally, an MRI is only required for the anterior technique to visualize any impeding structures along the way to the spine.\textsuperscript{128} Importantly, getting an MRI requires substantial cost and time. As mentioned previously, timing of surgery is vital for patient recovery, so every second that can be saved, should be saved. Additionally, with recent innovations in robotic navigation and advancements in minimally invasive surgeries, there will be more data on the safety and efficacy of these enabling technologies. For these reasons, more large cohort prospective studies will be needed to accurately differentiate the benefits of each approach.
4. Anterior Versus Posterior Approach for Acute Thoracolumbar Decompression

There are a variety of causes for SCI in the thoracic and lumbar region including distraction, burst, compression, rotational, and tension band each of which requiring a slightly different surgical approach.\(^{127}\) However, this discussion will focus primarily on fracture dislocations since they are by far the most common cause of SCI in the acute emergency setting given their high-impact nature.\(^{128}\) Fracture dislocations are generally associated with severe neurological dysfunction on presentation and require immediate surgical decompression via posterior pedicle screw fixation after the patient has been medically stabilized.\(^{129}\) Unlike in the cervical region, the posterior approach is considered the primary choice for acute thoracolumbar decompression for a number of reasons: less vascular/abdominal structures to navigate around when approaching posteriorly, better visualization of the spine, and surgeons generally are trained more in this approach compared to anteriorly.\(^{130,131}\) Recent studies have begun examining whether the anterior approach is actually inferior to the posterior. They have shown no neurologic recovery difference between anterior and posterior approaches.\(^{124,132}\) Other studies have implemented a sole anterior approach in patients that do not have any neurologic deficit on presentation; their results have been promising but still have not been tested in cohorts with severe high-impact injuries.\(^{133,134}\)

5. Hemodynamic Stability for Spinal Cord Injuries

As described above, there can be multiple barriers that could prohibit a patient from receiving an early acute decompression surgery in the setting of a SCI. Therefore, it is crucial for medical management to also be part of the treatment protocol. Initially, multiple studies revealed that corticosteroids were thought to be beneficial if given within 8 hours of the injury.\(^{135-137}\) The pathophysiology behind this hypothesis had been studied prior and showed 2 possible pathways by which methylprednisolone may improve neurological recovery. First, methylprednisolone likely suppresses membrane degradation by inhibiting lipid peroxidation and hydrolysis at the site of injury. Additionally, the breakdown of cellular membranes peak within 8 hours of injury, which correlated with the literature at the time.\(^{138,139}\) The second pathway is that vasoactive by-products of arachidonic acid metabolism are reduced when treated with corticosteroids, which improve blood circulation to the injury site.\(^{140}\) Over time, however, new data showed that continuous treatment of steroids increased risk for severe sepsis, infection, respiratory distress, and mortality. Sultan et al.\(^{141}\) showed in their meta-analysis that there was not only a nonsignificant improvement in the neurological recovery but also a significant increased risk for pneumonia. Therefore, corticosteroids are no longer first line agents in the setting of an acute SCI.

Interestingly, the second pathway by which corticosteroids were hypothesized to help with SCI was the basis for the more recent approach to the medical management of SCI: hemodynamic stability and the impact of mean arterial pressure (MAP). The importance of MAP, blood flow, and perfusion relate back to the secondary effects of SCI, which have been thoroughly studied in the literature.\(^{142-144}\) The 2013 guidelines for SCI management indicated that an ideal MAP was between 85–90 mmHg and should be targeted for the first 7 days following a SCI via supplementation of vasopressors and intravenous fluids.\(^{145}\) Following suit, other studies began putting the guidelines into play, and the results were mostly positive. For instance, Hawryluk et al.\(^{146}\) examined a cohort of 100 patients and showed that higher average MAP values correlated with improved recovery in the first 2–3 days after a SCI. Dakson et al.\(^{147}\) showed that there was an 11x better chance for neurologic recovery in patients with MAP > 85 mmHg. The next steps for researchers were to elucidate potential methods to accurately monitor MAP continuously, discover the mechanisms by which MAP actually leads to improved outcomes, and refine the technique of maintaining a constant blood pressure range.

Recently, Brian Kwon and his laboratory addressed these questions and expanded the idea of hemodynamic stability for SCI.\(^{148}\) In his work, Kwon discusses measuring intraparenchymal blood flow and oxygenation using laser Doppler blood flow/oxygen probes. Using this technique, they were also able to show that decompressive surgeries in combination with MAP augmentation significantly increase PO\(_2\) levels close to or above preinjury values, thereby preventing ischemia. They also looked for downstream metabolic changes when using decompression and MAP augmentation, discovering a decrease in the lactate/pyruvate ratio, which is a surrogate for decreased tissue damage. Lastly, they drew more attention to the importance of the previously studied intraspinal pressure (ISP) and spinal cord perfusion pressure (SCPP; SCPP = MAP – ISP).\(^{149-151}\) Along with the other recent literature, SCPP seems to be almost, if not more important than the MAP range. Squair et al.\(^{152}\) showed that a SCPP within 60–65 mmHg, not MAP, was the best indicator of improved neurologic function in humans.

Of note, the literature has also described limitations to maintaining hemodynamic stability in older patients with more extensive neurologic injury. Even when the ideal SCPP and MAP
are controlled for, confounding and uncontrollable variables can affect recovery chances for patients. For instance, Coleman and Geisler\textsuperscript{133} found that among 760 patients, AIS score was the strongest predictor for positive outcomes. Furthermore, the World Federation of Neurosurgical Societies Spine Committee stated in their 2020 guidelines that factors such as older age and more severe neurological damage are associated with a lower likelihood of neurological recovery.\textsuperscript{154} Much of the literature is in agreement with these statements, recommending surgery and medical management for the majority of acute SCI.\textsuperscript{130} Studies have yet to prove that nonoperative management for any severity of acute SCI with boney injury or spinal instability is better than surgery. Interestingly, although elderly patients are at greater risk for deterioration, they generally wait longer for surgery and have higher inpatient mortality rates than younger patients.\textsuperscript{156} More research is needed to fully elucidate the difference in surgical recommendations for patients with only instability, mild or severe deficits. However, based on the current literature, medical management followed by early decompression is recommended as the standard of care for all patients with signs of boney instability.

In total, the medical management of SCI has continued to evolve over the past decade. From corticosteroids to measuring the oxygenation of spinal cord blood flow, the treatment guidelines will continue to reflect the basic science, pharmacological, and clinical research breakthroughs being made.\textsuperscript{157} Of note, a recent study in 2022 has begun to test the feasibility of not only measuring the oxygen tension of the acute SCI site, but also attempting to alter that tension by increasing the fraction of inspired oxygen, or FIO\textsubscript{2}.\textsuperscript{138} With the combination of both surgery and innovative medical treatment, neurological recovery following a SCI is more of a possibility than ever before (Fig. 1).

**CONCLUSION**

Acute traumatic SCI can leave a lasting impact on the overall well-being of an individual. For urgent cases associated with severe neurological dysfunction, it is crucial to provide emergency, rapid, and specialized therapies to minimize secondary injuries. After initial evaluation, surgical candidates should undergo timely decompression, ideally within 24 hours of injury. For both surgical and nonsurgical candidates, medical management with an emphasis on hemodynamic stability and optimizing cord perfusion should be started regardless of surgical status to maximize chances of recovery.

Informed by the numerous preclinical and clinical research studies evaluating the pathophysiology and treatment of SCI, management strategies are constantly evolving, with promising interventions just on the horizon. As described in this review, there are still numerous unanswered questions, new drugs funneling through clinical trials, and fluid protocols hinging on the results of breakthrough studies. In particular, the ongoing debate between ultra-early versus early decompression and when to begin intensive rehabilitation should be significant areas of focus for large-scale trials moving forward. Just like with the effects of initiating rehabilitation after SCI, timing of interventions is clearly important, and researchers have yet to fully define the complete pathophysiological impact of decompression timing on outcomes. Along the same line, are there additional preoperative patient variables that need to be considered when deciding on the most appropriate management plan? These factors could potentially include genetic factors, comorbidities, demographics, imaging, or inflammatory biomarkers – all of which require better understanding.

Looking ahead, we hope this review of the current literature surrounding the acute management of SCI brings to light not only how far treatment has progressed, but also the gaps of knowledge that remain unfilled. With the continuous introduction of neuroregenerative therapeutics like stem cell targeting, hydrogel scaffolding, and monoclonal antibodies, surgical/medical management will need to be tested ethically both alone and in conjunction with pharmacologic treatment to determine which methodology yields the best outcomes for patients. With more comparative data and large-scale cohorts, universal guidelines will begin to reflect these novel treatments once they have been thoroughly tested in the clinical setting.

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A Review of Functional Restoration From Spinal Cord Stimulation in Patients With Spinal Cord Injury

Alice Lin¹, Elias Shaaya², Jonathan S. Calvert³, Samuel R. Parker¹, David A. Borton³,⁴,⁵, Jared S. Fridley²
¹Warren Alpert Medical School, Providence, RI, USA
²Department of Neurosurgery, Brown University, Rhode Island Hospital, Providence, RI, USA
³School of Engineering, Brown University, Providence, RI, USA
⁴Center for Neurorehabilitation and Neurotechnology, Department of Veterans Affairs, Providence, RI, USA
⁵Carney Institute for Brain Science, Brown University, Providence, RI, USA

Traumatic spinal cord injury often leads to loss of sensory, motor, and autonomic function below the level of injury. Recent advancements in spinal cord electrical stimulation (SCS) for spinal cord injury have provided potential avenues for restoration of neurologic function in affected patients. This review aims to assess the efficacy of spinal cord stimulation, both epidural (eSCS) and transcutaneous (tSCS), on the return of function in individuals with chronic spinal cord injury. The current literature on human clinical eSCS and tSCS for spinal cord injury was reviewed. Seventy-one relevant studies were included for review, specifically examining changes in volitional movement, changes in muscle activity or spasticity, or return of cardiovascular pulmonary, or genitourinary autonomic function. The total participant sample comprised of 327 patients with spinal cord injury, each evaluated using different stimulation protocols, some for sensorimotor function and others for various autonomic functions. One hundred eight of 127 patients saw improvement in sensorimotor function, 51 of 70 patients saw improvement in autonomic genitourinary function, 32 of 32 patients saw improvement in autonomic pulmonary function, and 32 of 36 patients saw improvement in autonomic cardiovascular function. Although this review highlights SCS as a promising therapeutic neuromodulatory technique to improve rehabilitation in patients with SCI, further mechanistic studies and stimulus parameter optimization are necessary before clinical translation.

Keywords: Spinal cord injury, Spinal cord stimulation, Electrical stimulation

INTRODUCTION

Spinal cord injury (SCI) is a destructive neurological state with complex pathophysiologic consequences. SCI often occurs secondary to trauma that leads to loss of sensory, motor, and/or autonomic functions.¹,² The initial mechanical injury to the spinal cord causes damage to neural parenchyma, disruption of axonal networks, and glial membrane disruption, collectively known as primary injury.¹ Following this initial insult, secondary damage to the injured spinal cord may occur via apoptotic signaling, ischemia, excitotoxicity, inflammation, and axonal demyelination. Glial scar formation often develops as a result of these local events, which can impair axonal regeneration and synaptic neuroplasticity across the injury site.³ Although there have been several improvements in the understanding of SCI pathophysiology and clinical care, there is no cure for SCI, and the current standard of treatment focuses on teaching compensation strategies to mitigate losses of function.

Recent research has demonstrated novel methods to improve post-SCI recovery and reverse the deleterious outcomes of SCI. Most cases of SCI have an intervening gap of intact tissue at the site of injury; while this tissue is anatomically intact, it is functionally silent due to disruptions to the flow of information within the spinal cord.⁴ Upper motor neurons lose the feedback of
afferent signals and the descending efferent signals terminate at the level of the SCI lesion, though in some cases, propriospinal connections can still provide indirect access to afferent signals. Recent research has indicated that functional recovery can be achieved by taking advantage of the remaining neural connections to re-enable sensorimotor function. In mouse models, Courtine et al. show functional recovery of propriospinal relay connections can only occur when spatially separated lateral hemisections are also separated temporally (i.e., when spinal hemisections were delivered 10 weeks apart), indicating the “rewiring” of connections following SCI via neural plasticity. Circuit reconstruction involves not just the growth of new nerves, but also synaptic regeneration and axonal regrowth to strengthen pre-existing sensorimotor networks. The spontaneous formation of new synapses from local surviving terminals or distant axons occurs in neural tissue that has been spared but is responding to injury. Appropriate axonal growth can be stimulated by growth factors or genetic activation; in rats, growth cone formation and axon regeneration may improve with changes to the axonal cytoskeleton. By modulating the microenvironment of an injury to increase synaptic regeneration or axonal regrowth, damaged neural circuits can potentially be reconstructed with variable functionality.

One technique that has recently grown in prominence for functional recovery in chronic SCI patients is the use of chronic electrical stimulation of the spinal cord. Use of spinal cord stimulation (SCS) on the lumbosacral spinal cord of individuals clinically diagnosed with chronic, motor complete SCI has demonstrated restoration of a wide range of functions. The impact of long-term implantation remains unknown and requires further study along with factors such as injury level and grade, stimulation parameters, and associated pharmacology and physical therapy, which may lead to greater efficacy. The restorative power of adjunctive SCS is likely enabled by the remaining propriospinal fibers that support plasticity by enabling communication across the spinal cord lesion. Animal and computational models have suggested that SCS may recruit nearby Group I and II afferent fibers which excite myelinated motor neurons through monosynaptic and/or polysynaptic pathways. In rodent models, transformation from dormant to active tissue at the injury site occurs through increasing the general level of excitability, allowing sensory information to become a source of control for voluntary movement; using sensory information as a source of control requires an extensive amount of physical training to allow for appropriate remodeling of supraspinal and intraspinal pathways. Further study of electrical stimulation for functional recovery in human patients with chronic SCI is necessary to determine the efficacy of such treatments and to translate electrical stimulation from basic research to effective clinical use.

The aim of this review is to discuss the efficacy and safety of SCS as a neuromodulatory strategy for restoration of neurologic function in patients with chronic SCI. Previous work has been performed to survey the scientific literature regarding the effects of SCS in SCI, however these reviews have focused on either eSCS or tSCS and their effects on a limited number of physiological systems. Here, we discuss the reported effects of SCS, both epidural spinal cord stimulation (eSCS) and transcutaneous spinal cord stimulation (tSCS), on sensory, motor, autonomic, cardiovascular, and pulmonary systems. The limitations of the current literature, and future directions for research in this promising area. This review indicates that eSCS and tSCS are efficacious and safe treatments for chronic SCI, with the potential to improve motor and autonomic function following SCI, but further work needs to be performed to define what patients will respond most efficaciously to either eSCS or tSCS therapy.

**METHODS**

1. Search Strategy

To undertake this review, we followed a protocol in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A search was made of the following electronic databases: PubMed, Cochrane Registry, Embase, and OVID. For the search, we used keywords *spinal cord injury*, *spinal cord stimulation*, *epidural stimulation*, *transcutaneous magnetic stimulation*, *motor control*, *movement*, and *rehabilitation*, combined in the databases as follows: ("spinal cord injury") AND ("spinal cord stimulation" OR "epidural stimulation" OR "spinal cord stimulator" OR "Electrodes, Implanted" OR "paddle spinal cord stimulator" OR “implantable electrodes” OR "transcutaneous magnetic stimulation" OR "Spinal Cord Injuries/therapy*" OR "Spinal Cord Stimulation/methods") AND ("motor control" OR "movement" OR "rehabilitation"). The search was conducted from the start dates of each respective database until January 1st, 2022. Additionally, we carried out an inverse search of the references cited by any relevant articles.

2. Selection Criteria

Using the PICOS structure (Patients, Intervention, Comparison, Outcome, and Study design), we established the following criteria...
inclusion criteria, requiring (1) human patients to have SCI, (2) electrical spinal stimulation to be applied, and (3) outcomes to include assessment of response. We excluded articles that (1) used spinal stimulation for chronic pain treatment and (2) present secondary data, such as literature reviews. Studies performing retrospective analysis on data collected while routinely conducting clinical protocols for evaluation of SCS for spasticity or chronic pain treatment were included. The selection of articles was decided by 2 independent researchers (AL and ES) working in parallel with no points of disagreement.

3. Study Selection
The process for selecting articles was as follows: (1) any duplicates of studies found in the various databases were eliminated; (2) after an initial screening of titles, the abstracts were read to identify articles that fulfilled the pre-established inclusion criteria; and (3) the full text of the remaining studies was read, with any studies meeting the exclusion criteria being ruled out. Researchers worked in parallel to extract data, including subject demographics and injury information as well as SCS stimulation parameters and post-SCS outcomes. Given the possibility of enrollment in multiple studies, for the sake of our review, we treated each patient enrolled in a study to be independent of other patients and other studies. For clinical trials including control groups, we excluded patients in the control groups from our analyses.

4. Bias Assessment
The risk of bias was assessed by 2 independent researchers (AL and ES) using the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool by the Cochrane Scientific Committee for nonrandomized studies of effects of interventions. A detailed description of the process can be found in the Supplementary Table 1.

RESULTS
A total of 503 research reports were located in the above databases. After eliminating duplicates and screening of titles and abstracts, 50 reports were selected for a full reading of the text. After full reading, 12 articles were excluded, and 33 additional studies were identified through the review of bibliographic references. Finally, 71 studies were included in the review. The study selection process can be seen in Fig. 1.

The study design and characteristics of participants are shown in Table 1. Of the reports included in the review, 50 were case or case-series studies and 21 were clinical trials. The total study sample comprised of 327 patients with SCI, 257 males, 54 females, and 16 participants where sex was not specified. Patient age ranged from 18 to 66 years old. The time since injury ranged from 0.1 to 41.1 years. The majority of patients had injury levels in the cervical (n = 174 patients) and thoracic (n = 106 patients) regions. The highest reported level of injury was at C1
Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Subjects(n)</th>
<th>Sex</th>
<th>Age (yr), mean ± SD</th>
<th>Age (yr), range</th>
<th>Level of injury</th>
<th>AIS</th>
<th>Time (yr), mean ± SD</th>
<th>SCI length (yr), range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barolat et al. (1986)</td>
<td>Case report</td>
<td>Philadelphia, PA, USA</td>
<td>1</td>
<td>M</td>
<td>22</td>
<td>22</td>
<td>C5</td>
<td>C</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Herman et al. (2002)</td>
<td>Case report</td>
<td>Phoenix, AZ, USA</td>
<td>1</td>
<td>M</td>
<td>43</td>
<td>43</td>
<td>C6</td>
<td>C</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Carhart et al. (2004)</td>
<td>Case report</td>
<td>Phoenix, AZ, USA</td>
<td>1</td>
<td>M</td>
<td>43</td>
<td>43</td>
<td>C5–C6</td>
<td>C</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Jilge et al. (2004)</td>
<td>Case series</td>
<td>Vienna, Austria</td>
<td>5</td>
<td>2M, 3F</td>
<td>27.6 ± 3.4</td>
<td>24–34</td>
<td>C4–T10</td>
<td>4A, 1B</td>
<td>4.8 ± 3.4</td>
<td>2–8</td>
</tr>
<tr>
<td>Ganley et al. (2005)</td>
<td>Case series</td>
<td>Tempe, AZ, USA</td>
<td>2</td>
<td>2M</td>
<td>45.4 ± 2.5</td>
<td>43–48</td>
<td>C6–T8</td>
<td>C</td>
<td>5.8 ± 2.3</td>
<td>3.5–8.0</td>
</tr>
<tr>
<td>DiMarco et al. (2006)</td>
<td>Case report</td>
<td>Cleveland, OH, USA</td>
<td>1</td>
<td>M</td>
<td>52</td>
<td>52</td>
<td>C5–C6</td>
<td>C</td>
<td>7</td>
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<tr>
<td>Huang et al. (2006)</td>
<td>Case series</td>
<td>Tempe/Phoenix, AZ, USA</td>
<td>2</td>
<td>2M</td>
<td>45.5 ± 3.5</td>
<td>43–48</td>
<td>C5–T8</td>
<td>C</td>
<td>5.8 ± 3.2</td>
<td>3.5–8</td>
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<tr>
<td>DiMarco et al. (2009)</td>
<td>Clinical trial</td>
<td>Cleveland, OH, USA</td>
<td>9</td>
<td>8M, 1F</td>
<td>41 ± 11.5</td>
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<td>C3–C6</td>
<td>-</td>
<td>13.1 ± 11.3</td>
<td>1–34</td>
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<tr>
<td>Harkema et al. (2011)</td>
<td>Case report</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>1</td>
<td>M</td>
<td>23</td>
<td>23</td>
<td>C7</td>
<td>B</td>
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<tr>
<td>Moshonkina et al. (2012)</td>
<td>Case series</td>
<td>St. Petersburg, Russia</td>
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<td>1M, 3F</td>
<td>42 ± 15.7</td>
<td>22–58</td>
<td>C5–L1</td>
<td>2A/B, 1B, IB/C</td>
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<td>-</td>
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<tr>
<td>Hofstoetter et al. (2013)</td>
<td>Case report</td>
<td>Vienna, Austria</td>
<td>1</td>
<td>F</td>
<td>29</td>
<td>29</td>
<td>T9</td>
<td>D</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Angeli et al. (2014)</td>
<td>Case series</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>4</td>
<td>4M</td>
<td>26.9 ± 4</td>
<td>23–32</td>
<td>C6–T6</td>
<td>2A, 2B</td>
<td>3.0 ± 1</td>
<td>2.2–4.2</td>
</tr>
<tr>
<td>Hofstoetter et al. (2014)</td>
<td>Case series</td>
<td>Vienna, Austria</td>
<td>3</td>
<td>2M, 1F</td>
<td>32.7 ± 4.1</td>
<td>28–38</td>
<td>C5–T9</td>
<td>D</td>
<td>10.6 ± 1.5</td>
<td>9–12</td>
</tr>
<tr>
<td>Sayenko et al. (2014)</td>
<td>Case series</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>3</td>
<td>3M</td>
<td>26.3 ± 4.9</td>
<td>23–32</td>
<td>C7–T4</td>
<td>1A, 2B</td>
<td>3.3 ± 1.0</td>
<td>2.2–4.2</td>
</tr>
<tr>
<td>Bedi and Arumugam (2015)</td>
<td>Case report</td>
<td>Punjab, India</td>
<td>1</td>
<td>M</td>
<td>25</td>
<td>25</td>
<td>L1</td>
<td>C</td>
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<tr>
<td>Gerasimenko et al. (2015)</td>
<td>Case series</td>
<td>St. Petersburg, Russia/Los Angeles, CA, USA</td>
<td>5</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>Hofstoetter et al. (2015)</td>
<td>Case series</td>
<td>Vienna, Austria</td>
<td>3</td>
<td>2M, 1F</td>
<td>32.6 ± 5.0</td>
<td>28–38</td>
<td>C5–T9</td>
<td>D</td>
<td>10.6 ± 1.5</td>
<td>9–12</td>
</tr>
<tr>
<td>Rejc et al. (2015)</td>
<td>Case series</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>4</td>
<td>4M</td>
<td>27 ± 4.2</td>
<td>24–33</td>
<td>C7–T4</td>
<td>2A, 2B</td>
<td>3.0 ± 1</td>
<td>2.2–4.2</td>
</tr>
<tr>
<td>Bedi and Arumugam (2016)</td>
<td>Case report</td>
<td>Punjab, India</td>
<td>1</td>
<td>M</td>
<td>25</td>
<td>25</td>
<td>T12</td>
<td>C</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Lu et al. (2016)</td>
<td>Case series</td>
<td>Los Angeles, CA, USA</td>
<td>2</td>
<td>2M</td>
<td>19 ± 1</td>
<td>18–20</td>
<td>C5–C6</td>
<td>B</td>
<td>2.3 ± 0.4</td>
<td>2–2.5</td>
</tr>
<tr>
<td>Minassian et al. (2016)</td>
<td>Case series</td>
<td>Vienna, Austria</td>
<td>4</td>
<td>3M, 1F</td>
<td>39.5 ± 17.1</td>
<td>26–64</td>
<td>C8–T8</td>
<td>A</td>
<td>3.5 ± 1.7</td>
<td>1.7–4.8</td>
</tr>
<tr>
<td>Gad et al. (2017)</td>
<td>Case report</td>
<td>Los Angeles, CA, USA</td>
<td>1</td>
<td>M</td>
<td>40</td>
<td>40</td>
<td>T9</td>
<td>A</td>
<td>4</td>
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</table>

(Continued)
Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Subjects (n)</th>
<th>Sex</th>
<th>Age (yr), mean ± SD</th>
<th>Age (yr), range</th>
<th>Level of injury</th>
<th>AIS</th>
<th>Time (yr), mean ± SD</th>
<th>SCI length (yr), range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grahn et al. [41] (2017)</td>
<td>Case report</td>
<td>Rochester, MN, USA</td>
<td>1</td>
<td>M</td>
<td>26</td>
<td>26</td>
<td>T6</td>
<td>A</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rejc et al. [42] (2017)</td>
<td>Case report</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>1</td>
<td>M</td>
<td>32</td>
<td>32</td>
<td>C7</td>
<td>B</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Rejc et al. [43] (2017)</td>
<td>Case series</td>
<td>Louisville, KY/Los Angeles, CA, USA</td>
<td>4</td>
<td>4M</td>
<td>27±4.2</td>
<td>24–33</td>
<td>C7–T4</td>
<td>2A, 2B</td>
<td>3.0±1</td>
<td>2.2–4.2</td>
</tr>
<tr>
<td>Angeli et al. [44] (2018)</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>4</td>
<td>3M, 1F</td>
<td>25.8±4.5</td>
<td>22–32</td>
<td>C5–T4</td>
<td>2A, 2B</td>
<td>3.1±0.4</td>
<td>2.2–3.3</td>
</tr>
<tr>
<td>Aslan et al. [45] (2018)</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>7</td>
<td>7M</td>
<td>26.7±4.1</td>
<td>-</td>
<td>C5–T4</td>
<td>2A, 2B</td>
<td>2.7±0.5</td>
<td>2.0–3.5</td>
</tr>
<tr>
<td>DiMarco et al. [46] (2018)</td>
<td>Case report</td>
<td>Cleveland, OH, USA</td>
<td>1</td>
<td>M</td>
<td>50</td>
<td>50</td>
<td>C4</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Formento et al. [47] (2018)</td>
<td>Case series</td>
<td>Lausanne, Switzerland</td>
<td>3</td>
<td>3M</td>
<td>36.7±9.6</td>
<td>28–47</td>
<td>C4–C7</td>
<td>2C, 1D</td>
<td>5.3±1.2</td>
<td>4–6</td>
</tr>
<tr>
<td>Freyvert et al. [48] (2018)</td>
<td>Clinical trial</td>
<td>Los Angeles, CA, USA</td>
<td>6</td>
<td>4M, 2F</td>
<td>19.1±1.3</td>
<td>18–21</td>
<td>C2–C6</td>
<td>B</td>
<td>2.3±0.9</td>
<td>1.5–3.8</td>
</tr>
<tr>
<td>Gad et al. [49] (2018)</td>
<td>Clinical trial</td>
<td>Los Angeles, CA, USA</td>
<td>6</td>
<td>5M, 1F</td>
<td>40.2±16.6</td>
<td>20–62</td>
<td>C4–C8</td>
<td>2B, 1C</td>
<td>10.0±7.1</td>
<td>1.1–21</td>
</tr>
<tr>
<td>Harkema et al. [51] (2018a)</td>
<td>Clinical trial</td>
<td>Louisville, KY, USA</td>
<td>4</td>
<td>3M, 1F</td>
<td>30.8±4.1</td>
<td>24–35</td>
<td>C4</td>
<td>3A, 1B</td>
<td>6.5±1.6</td>
<td>3.8–8</td>
</tr>
<tr>
<td>Harkema et al. [52] (2018b)</td>
<td>Clinical trial</td>
<td>Louisville, KY, USA</td>
<td>4</td>
<td>3M, 1F</td>
<td>30.8±4.1</td>
<td>24–35</td>
<td>C4</td>
<td>3A, 1B</td>
<td>6.5±1.6</td>
<td>3.8–8</td>
</tr>
<tr>
<td>Herrity et al. [53] (2018)</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>5</td>
<td>5M</td>
<td>-</td>
<td>-</td>
<td>C4–C5, T4</td>
<td>3A, 2B</td>
<td>5.9±1.9</td>
<td>-</td>
</tr>
<tr>
<td>Inanici et al. [54] (2018)</td>
<td>Clinical trial</td>
<td>Seattle, WA, USA</td>
<td>1</td>
<td>M</td>
<td>62</td>
<td>62</td>
<td>C3–C4</td>
<td>D</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Niu et al. [55] (2018)</td>
<td>Clinical trial</td>
<td>Los Angeles, CA, USA</td>
<td>5</td>
<td>5M</td>
<td>31±10.6</td>
<td>22–43</td>
<td>C5–T4</td>
<td>A, B</td>
<td>8.8±7.5</td>
<td>5–13</td>
</tr>
<tr>
<td>Phillips et al. [56] (2018)</td>
<td>Case series</td>
<td>Los Angeles, CA, USA</td>
<td>5</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>C5–T2</td>
<td>3A, 2B, 2C</td>
<td>&gt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Powell et al. [57] (2018)</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>6</td>
<td>4M, 2F</td>
<td>45.8±14</td>
<td>26–59</td>
<td>C6–L1</td>
<td>4C, 2D</td>
<td>15.7±13.4</td>
<td>4.6–41.1</td>
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<tr>
<td>Rath et al. [58] (2018)</td>
<td>Case series</td>
<td>Los Angeles, CA, USA</td>
<td>8</td>
<td>7M, 1F</td>
<td>29.4±7.7</td>
<td>23–47</td>
<td>C4–T9</td>
<td>6A, 2C</td>
<td>7.3±3.3</td>
<td>2–13</td>
</tr>
<tr>
<td>Wagner et al. [59] (2018)</td>
<td>Case series</td>
<td>Lausanne, Switzerland</td>
<td>3</td>
<td>3M</td>
<td>36.7±9.6</td>
<td>28–47</td>
<td>C4–C8</td>
<td>2C, 1D</td>
<td>5.3±1.2</td>
<td>4–6</td>
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<tr>
<td>Walter et al. [60] (2018)</td>
<td>Case report</td>
<td>Vancouver, BC, Canada</td>
<td>1</td>
<td>M</td>
<td>32</td>
<td>32</td>
<td>C5</td>
<td>B</td>
<td>6</td>
<td>6</td>
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<tr>
<td>West et al. [61] (2018)</td>
<td>Case report</td>
<td>Vancouver, BC, Canada</td>
<td>1</td>
<td>M</td>
<td>Early 30s</td>
<td>Early 30s</td>
<td>C5</td>
<td>B</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Cheng et al. [63] (2019)</td>
<td>Case series</td>
<td>Pasadena, CA/Louisville, KY, USA</td>
<td>2</td>
<td>M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>-</td>
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<tr>
<td>Darrow et al. [64] (2019)</td>
<td>Clinical trial</td>
<td>Minneapolis, MN, USA</td>
<td>2</td>
<td>2F</td>
<td>50±2.8</td>
<td>49–52</td>
<td>T4–T8</td>
<td>A</td>
<td>7.5±3.5</td>
<td>5–10</td>
</tr>
<tr>
<td>Nightingale et al. [66] (2019)</td>
<td>Clinical trial</td>
<td>Vancouver, BC, Canada</td>
<td>1</td>
<td>M</td>
<td>33</td>
<td>33</td>
<td>C5</td>
<td>B</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Sayenko et al. [67] (2019)</td>
<td>Clinical trial</td>
<td>Los Angeles, CA, USA</td>
<td>15</td>
<td>12M, 3F</td>
<td>31.2±8.7</td>
<td>23–53</td>
<td>C4–T12</td>
<td>1A, 1B, 3C</td>
<td>6.0±3.2</td>
<td>2–13</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Study designs, demographic and clinical characteristics of patients with spinal cord injury enrolled in studies evaluating spinal cord stimulation for restoration of function (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Subjects (n)</th>
<th>Sex</th>
<th>Age (yr), mean ± SD</th>
<th>Age (yr), range</th>
<th>Level of injury</th>
<th>AIS</th>
<th>Time (yr), mean ± SD</th>
<th>SCI length (yr), range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terson de Paleville et al.</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>4</td>
<td>4M</td>
<td>27.3 ± 3.7</td>
<td>22.7–31.6</td>
<td>C5–T5</td>
<td>3A, 1B</td>
<td>2.6 ± 0.3</td>
<td>2.3–2.9</td>
</tr>
<tr>
<td>Alam et al.</td>
<td>Clinical trial</td>
<td>Hong Kong, China</td>
<td>1</td>
<td>F</td>
<td>48 ± 12.1</td>
<td>27–58</td>
<td>C7</td>
<td>-</td>
<td>21 ± 2</td>
<td>21</td>
</tr>
<tr>
<td>DiMarco et al.</td>
<td>Case series</td>
<td>Cleveland, OH, USA</td>
<td>10</td>
<td>10M</td>
<td>40.4 ± 12.1</td>
<td>27–58</td>
<td>C2–T1</td>
<td>-</td>
<td>7.1 ± 10.7</td>
<td>3–37</td>
</tr>
<tr>
<td>Gad et al.</td>
<td>Case report</td>
<td>Los Angeles, CA, USA</td>
<td>1</td>
<td>M</td>
<td>39 ± 7.8</td>
<td>26–37</td>
<td>C5</td>
<td>A</td>
<td>9 ± 1</td>
<td>9</td>
</tr>
<tr>
<td>Gill et al.</td>
<td>Clinical trial</td>
<td>Rochester, MN, USA</td>
<td>2</td>
<td></td>
<td>31.5 ± 7.8</td>
<td>26–37</td>
<td>T3–T6</td>
<td>A</td>
<td>4.5 ± 2.1</td>
<td>3–6</td>
</tr>
<tr>
<td>Gorgey et al.</td>
<td>Clinical trial</td>
<td>Richmond, VA, USA</td>
<td>1</td>
<td>1M</td>
<td>26 ± 8.1</td>
<td>26–37</td>
<td>C7</td>
<td>C</td>
<td>2 ± 1</td>
<td>2</td>
</tr>
<tr>
<td>Peña Pino et al.</td>
<td>Clinical trial</td>
<td>Minneapolis, MN, USA</td>
<td>7</td>
<td>4M</td>
<td>42 ± 11.4</td>
<td>30–60</td>
<td>T4–T8</td>
<td>6A, 1B</td>
<td>7.7 ± 4.8</td>
<td>3–17</td>
</tr>
<tr>
<td>Wiesener et al.</td>
<td>Case series</td>
<td>Berlin, Germany</td>
<td>2</td>
<td></td>
<td>49 ± 12.7</td>
<td>40–58</td>
<td>T5–T6</td>
<td>A</td>
<td>23 ± 18.4</td>
<td>10–36</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Clinical trial</td>
<td>Bronx, NY, USA</td>
<td>9</td>
<td>7M</td>
<td>45.9 ± 13.7</td>
<td>22–64</td>
<td>C2–C8</td>
<td>1B, 4C, 4D</td>
<td>10.8 ± 5.9</td>
<td>1–17</td>
</tr>
<tr>
<td>Beck et al.</td>
<td>Case series</td>
<td>Rochester, MN, USA</td>
<td>2</td>
<td>2M</td>
<td>31.5 ± 5.5</td>
<td>26–37</td>
<td>T3–T6</td>
<td>A</td>
<td>4.5 ± 1.5</td>
<td>3–6</td>
</tr>
<tr>
<td>Calvert et al.</td>
<td>Case series</td>
<td>Los Angeles, CA/Rochester, MN, USA</td>
<td>9</td>
<td>8M, 1F</td>
<td>27.1 ± 4.1</td>
<td>22–36</td>
<td>C5–T6</td>
<td>5A, 1B, 3C</td>
<td>6.1 ± 3.1</td>
<td>2–13</td>
</tr>
<tr>
<td>DiMarco et al.</td>
<td>Clinical trial</td>
<td>Cleveland, OH, USA</td>
<td>5</td>
<td>5M</td>
<td>-</td>
<td>30–50</td>
<td>C3–T1</td>
<td>A</td>
<td>-</td>
<td>2–4</td>
</tr>
<tr>
<td>Estes et al.</td>
<td>Clinical trial</td>
<td>Atlanta, GA, USA</td>
<td>8</td>
<td>6M</td>
<td>44.4 ± 15.7</td>
<td>18–63</td>
<td>C1–C7</td>
<td>2C, 6D</td>
<td>0.3 ± 0.1</td>
<td>0.1–0.5</td>
</tr>
<tr>
<td>Herrity et al.</td>
<td>Clinical trial</td>
<td>Louisville, KY, USA</td>
<td>10</td>
<td>8M</td>
<td>27.9 ± 4.7</td>
<td>20–51</td>
<td>C3–T4</td>
<td>6A, 4B</td>
<td>4.4 ± 2.3</td>
<td>1–15</td>
</tr>
<tr>
<td>Ibáñez et al.</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>5</td>
<td>5M</td>
<td>31.9 ± 10.7</td>
<td>24–52</td>
<td>C4–T4</td>
<td>3A, 2B</td>
<td>7.8 ± 5.2</td>
<td>2–16.6</td>
</tr>
<tr>
<td>Inanici et al.</td>
<td>Clinical trial</td>
<td>Seattle, WA, USA</td>
<td>6</td>
<td>4M</td>
<td>42 ± 14</td>
<td>28–62</td>
<td>C3–C5</td>
<td>2B, 2C, 2D</td>
<td>4.6 ± 3.8</td>
<td>1.5–12</td>
</tr>
<tr>
<td>Linde et al.</td>
<td>Clinical trial</td>
<td>Rochester, MN, USA</td>
<td>2</td>
<td>2M</td>
<td>31.5 ± 5.5</td>
<td>26–37</td>
<td>T3–T6</td>
<td>A</td>
<td>4.5 ± 1.5</td>
<td>3–6</td>
</tr>
<tr>
<td>Mesbah et al.</td>
<td>Case series</td>
<td>Louisville, KY, USA</td>
<td>20</td>
<td>15M</td>
<td>31.0 ± 9.6</td>
<td>19.9–60.6</td>
<td>C3–T4</td>
<td>14A, 6B</td>
<td>6.3 ± 3.4</td>
<td>2.4–16.6</td>
</tr>
<tr>
<td>Squair et al.</td>
<td>Case report</td>
<td>Calgary, Alberta, Canada</td>
<td>1</td>
<td>M</td>
<td>38 ± 7.8</td>
<td>38</td>
<td>-</td>
<td>C5</td>
<td>6A, 5B</td>
<td>5.1 ± 2.2</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>Clinical trial</td>
<td>Louisville, KY, USA</td>
<td>11</td>
<td>8M</td>
<td>-</td>
<td>21–45</td>
<td>C2–T1</td>
<td>6A, 5B</td>
<td>5.1 ± 2.2</td>
<td>2.4–8.6</td>
</tr>
</tbody>
</table>

SD, standard deviation; AIS, American Spinal Injury Association Impairment Scale.
### Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Lead placement</th>
<th>No. of electrodes/lead</th>
<th>Stimulation type</th>
<th>Location</th>
<th>Stimulation frequency</th>
<th>Stimulation pulse width</th>
<th>Stimulation amplitude</th>
<th>Stimulation pattern</th>
<th>Stimulation optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barolat et al.19 (1986)</td>
<td>eSCS</td>
<td>Clinical technology corporation</td>
<td>Percutaneous</td>
<td>1</td>
<td>Tonic stimulation</td>
<td>T1–T2</td>
<td>75 Hz</td>
<td>250 μs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Katz et al.20 (1991)</td>
<td>eSCS</td>
<td>Medtronic Paddle</td>
<td>Paddle</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Parameters optimized for spasticity</td>
</tr>
<tr>
<td>Herman et al.21 (2002)</td>
<td>eSCS+BWST therapy</td>
<td>Medtronic Percutaneous</td>
<td>Lumbar enlargement</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>Lumbar enlargement</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>A variety of electrical parameter sets were examined</td>
</tr>
<tr>
<td>Carhart et al.22 (2004)</td>
<td>eSCS+PWBFT therapy</td>
<td>Medtronic Percutaneous</td>
<td>-</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>T10–T12</td>
<td>40–60 Hz</td>
<td>800 μs</td>
<td>Amplitude at mid-point between sensory and motor threshold values</td>
<td>Continuous, charge-balanced, monophasic pulse trains</td>
<td>-</td>
</tr>
<tr>
<td>Jilge et al.23 (2004)</td>
<td>eSCS</td>
<td>Medtronic Percutaneous</td>
<td>-</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>T12–L1</td>
<td>5–60 Hz</td>
<td>210–450 μs</td>
<td>1-10 V</td>
<td>Pulse trains</td>
<td>-</td>
</tr>
<tr>
<td>Minassian et al.24 (2004)</td>
<td>eSCS</td>
<td>Medtronic Percutaneous</td>
<td>-</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>T10–T12</td>
<td>2.2–50 Hz</td>
<td>-</td>
<td>1-10 V</td>
<td>Single pulse, paired pulses, and pulse trains</td>
<td>-</td>
</tr>
<tr>
<td>Ganley et al.25 (2005)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Percutaneous</td>
<td>-</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>T10–T12</td>
<td>20–60 Hz</td>
<td>800 μs</td>
<td>Amplitude between sensory and motor thresholds in S1 and at motor threshold for S2</td>
<td>-</td>
<td>Adjusted on an individual basis</td>
</tr>
<tr>
<td>DiMarco et al.26 (2006)</td>
<td>eSCS</td>
<td>NeuroControl Percutaneous</td>
<td>-</td>
<td>1</td>
<td>Tonic stimulation</td>
<td>T9, T11, L1</td>
<td>53 Hz</td>
<td>150 μs at T9, 200 ms at T11 and L1</td>
<td>40 V</td>
<td>Pulse train with stimulation trigger controlled by patient</td>
<td>-</td>
</tr>
<tr>
<td>Huang et al.27 (2006)</td>
<td>eSCS+ partial weight bearing treadmill therapy</td>
<td>Medtronic Percutaneous</td>
<td>-</td>
<td>4</td>
<td>Tonic stimulation</td>
<td>T10–L2</td>
<td>20–40 Hz</td>
<td>800 μs</td>
<td>3-8.5 V</td>
<td>Pulse train</td>
<td>-</td>
</tr>
<tr>
<td>DiMarco et al.28 (2009)</td>
<td>eSCS</td>
<td>Medtronic Percutaneous</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T9, T11, L1</td>
<td>30–40 Hz</td>
<td>150–200 μs</td>
<td>30–40 V</td>
<td>Pulse train</td>
<td>-</td>
</tr>
<tr>
<td>Harkema et al.29 (2011)</td>
<td>eSCS+ stand training</td>
<td>Medtronic Paddle</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>30–40 Hz</td>
<td>210 or 450 μs</td>
<td>7.5 V</td>
<td>Different stimulation protocols for different activities: both involve tonic stimulation.</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continued)
### Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Lead placement</th>
<th>No. of electrodes/lead</th>
<th>Stimulation type</th>
<th>Location</th>
<th>Frequency</th>
<th>Pulse width</th>
<th>Amplitude</th>
<th>Pattern</th>
<th>Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moshonkina et al. (2012)</td>
<td>eSCS+ locomotor training</td>
<td>Cooner Wire Co.</td>
<td>Percutaneous</td>
<td>2-4</td>
<td>Tonic stimulation</td>
<td>L2–L4, S2</td>
<td>1–12 Hz</td>
<td>-</td>
<td>-</td>
<td>Carried out 2 times for 30 min in addition to the routine pharmacotherapy</td>
<td></td>
</tr>
<tr>
<td>Angeli et al. (2014)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>25–30 Hz</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Stimulation parameters optimized to target primary motor pool activation areas.</td>
</tr>
<tr>
<td>Sayenko et al. (2014)</td>
<td>eSCS</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S2</td>
<td>2 Hz</td>
<td>210 μs</td>
<td>0.5-10 V</td>
<td>-</td>
<td>Spatially selective, rectangular, biphasic pulse waveform</td>
<td></td>
</tr>
<tr>
<td>Rejc et al. (2015)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>25–60 Hz</td>
<td>-</td>
<td>1.0-9.0 V</td>
<td>-</td>
<td>-</td>
<td>Adjustments made to electrode configurations to activate specific motor neuron pools</td>
</tr>
<tr>
<td>Lu et al. (2016)</td>
<td>eSCS</td>
<td>Boston Scientific Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>C4/C5–T1</td>
<td>2–40 Hz</td>
<td>210 μs</td>
<td>0.1-10.0 mA</td>
<td>-</td>
<td>Biphasic stimulation</td>
<td>Optimized for greatest hand motor responses</td>
</tr>
<tr>
<td>Grahn et al. (2017)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>Lumbar enlargement</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Active electrode configurations and stimulation parameters were adjusted to allow volitional control.</td>
</tr>
<tr>
<td>Rejc et al. (2017)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>Starting stimulation parameters of frequency 2 Hz</td>
<td>-</td>
<td>0.1–5 V</td>
<td>-</td>
<td>-</td>
<td>Parameters modulated synergistically to find stimulation frequency that elicited continuous (non-rhythmic) EMG pattern.</td>
</tr>
<tr>
<td>Angeli et al. (2018)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1/S2</td>
<td>2 Hz</td>
<td>450 μs</td>
<td>0.1 V ramping incrementally</td>
<td>-</td>
<td>-</td>
<td>Stimulation configurations selected to promote standing or stepping.</td>
</tr>
</tbody>
</table>

(Continued)
Table 2. Stimulation parameters of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Lead placement</th>
<th>No. of electrodes/lead</th>
<th>Stimulation type</th>
<th>Location</th>
<th>Frequency</th>
<th>Pulse width</th>
<th>Amplitude</th>
<th>Pattern</th>
<th>Optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aslan et al. (^{45}) (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>In standing experiments, voltage, frequency, and configuration of the electrode array were unique to each participant and optimized for over-ground standing.</td>
</tr>
<tr>
<td>DiMarco et al. (^{46}) (2018)</td>
<td>eSCS</td>
<td>-</td>
<td>Percutaneous</td>
<td>2</td>
<td>Tonic stimulation</td>
<td>T9, T11</td>
<td>50 Hz</td>
<td>0.2 ms</td>
<td>40 V</td>
<td>-</td>
<td>Pulse train with monopolar stimulation at T9 or bipolar stimulation at T9/T11</td>
</tr>
<tr>
<td>Formento et al. (^{47}) (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>Lumbosacral</td>
<td>40 Hz</td>
<td>-</td>
<td>3–9 mA</td>
<td>-</td>
<td>Spatially specific stimulation parameters optimized to target primary motor pool activation areas that were key in movement.</td>
</tr>
<tr>
<td>Gill et al. (^{48}) (2018)</td>
<td>eSCS + locomotor training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>15–40 Hz</td>
<td>210 μs</td>
<td>-</td>
<td>Biphasic, charge-balanced pulses</td>
<td>Parameters modified to enable voluntary control.</td>
</tr>
<tr>
<td>Harkema et al. (^{49}) (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>450 μs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Harkema et al. (^{50}) (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>450 μs</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Herrity et al. (^{51}) (2018)</td>
<td>eSCS + activity-based recovery training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>30 Hz</td>
<td>450 μs</td>
<td>Voltage was ramped up slowly (0.1 V increments)</td>
<td>All stimulation at the lower end of the stimulator array optimized for a single patient, then carried over to other patients.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Stimulator type</td>
<td>Lead placement</td>
<td>No. of electrodes/lead</td>
<td>Stimulation parameters</td>
<td>Location</td>
<td>Stimulation frequency</td>
<td>Stimulation pulse width</td>
<td>Stimulation amplitude</td>
<td>Stimulation pattern</td>
<td>Stimulation optimization</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Wagner et al.2 (2018)</td>
<td>eSCS+ locomotor training+ gravity assist device</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Spatiotemporal modulation</td>
<td>T11–L1</td>
<td>20–60 Hz</td>
<td>-</td>
<td>-</td>
<td>Trains of spatially selective stimulation with timing that coincided with intended movement</td>
<td></td>
</tr>
<tr>
<td>Walter et al.5 (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Trains of spatially selective stimulation with timing for specific actions pre-programmed</td>
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<tr>
<td>West et al.28 (2018)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>35 Hz</td>
<td>300 μs</td>
<td>3.5 V</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Calvert et al.25 (2019)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>40 Hz</td>
<td>210 μs</td>
<td>-</td>
<td>Trains of spatially selective stimulation with timing for specific actions</td>
<td></td>
</tr>
<tr>
<td>Cheng et al.26 (2019)</td>
<td>eSCS+ stand training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>25 Hz</td>
<td>200 μs</td>
<td>-</td>
<td>Stimuli optimized with machine learning algorithm</td>
<td></td>
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<tr>
<td>Darrow et al.26 (2019)</td>
<td>eSCS</td>
<td>Abbott</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S2</td>
<td>16–400 Hz</td>
<td>200–500 μs</td>
<td>2.0–15 mA</td>
<td>Optimization for specific locations and activities depending on positionality</td>
<td></td>
</tr>
<tr>
<td>Nightingale et al.27 (2019)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>Abdominal program: 40 Hz. Cardiovascular program: 35 Hz.</td>
<td>Abdominal program: 420 ms. Cardiovascular program: 300 ms.</td>
<td>Abdominal program: 3.5-6.0 V. Cardiovascular program: 3.5-6.0 V.</td>
<td>Spatially directed differences in stimulation configuration.</td>
<td></td>
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<tr>
<td>Terson de Paleville et al.28 (2019)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>L1–S1</td>
<td>Simulation for standing (10–40 Hz) vs stepping (25–45 Hz)</td>
<td>-</td>
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<tr>
<td>DiMarco et al.29 (2020)</td>
<td>eSCS</td>
<td>-</td>
<td>Percutaneous</td>
<td>2</td>
<td>Tonic stimulation</td>
<td>T9–T11</td>
<td>50 Hz</td>
<td>0.2 ms</td>
<td>40 V</td>
<td>-</td>
<td></td>
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<tr>
<td>Gill et al.30 (2020)</td>
<td>eSCS + body weight supported treadmill training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>20–30 Hz</td>
<td>200–450 μs</td>
<td>2.0–4.1 V</td>
<td>Activity-specific spatially directed stimulation</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Lead placement</th>
<th>No. of electrodes/lead</th>
<th>Stimulation parameters</th>
<th>Location</th>
<th>Stimulation frequency</th>
<th>Stimulation pulse width</th>
<th>Stimulation amplitude</th>
<th>Stimulation pattern</th>
<th>Stimulation optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorgey et al.60</td>
<td>eSCS+ exoskeletal-assisted walking training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T12–S2</td>
<td>40 Hz</td>
<td>-</td>
<td>4–8 V</td>
<td>Spatially selective stimulation</td>
<td>Modified based on patient performance</td>
</tr>
<tr>
<td>Peña Pino et al.61</td>
<td>eSCS</td>
<td>Abbott</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T12–L1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Activity-specific spatially directed stimulation based on patient selection of pre-programmed settings</td>
<td></td>
</tr>
<tr>
<td>Beck et al.63 (2021)</td>
<td>eSCS+task-specific training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>Lumbo-sacral</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Parameters were adjusted to enhance motor performance for standing or stepping</td>
</tr>
<tr>
<td>Calvert et al.65 (2021)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Electrode configurations enabled specific motor activation</td>
</tr>
<tr>
<td>DiMarco et al.68</td>
<td>eSCS</td>
<td>-</td>
<td>Percutaneous</td>
<td>2</td>
<td>Tonic stimulation</td>
<td>T9–T11</td>
<td>50 Hz</td>
<td>-</td>
<td>20–30 V</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Herrity et al.69</td>
<td>eSCS+activity-based recovery training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>-</td>
<td>L1–S1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Parameters optimized based on individualized maps of motor pools activation</td>
</tr>
<tr>
<td>Ibáñez et al.64 (2021)</td>
<td>eSCS+activity-based recovery training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T11–L1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Linde et al.67 (2021)</td>
<td>eSCS+ locomotor training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>Lumbo-sacral</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Stimulation parameters optimized for movement (determined by participants)</td>
</tr>
<tr>
<td>Mesbah et al.68</td>
<td>eSCS+ activity-based recovery training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T12–L2</td>
<td>2 Hz or 30 Hz</td>
<td>450 or 1,000 µs</td>
<td>-</td>
<td>Bipolar electrode stimulation using a single adjacent anode and cathode as well as wide field configurations</td>
<td>Further optimization for individual joint movement</td>
</tr>
<tr>
<td>Squair et al.66 (2021)</td>
<td>eSCS</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>T10–T12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Parameters optimized to recruit the lower thoracic spinal segments and increase blood pressure</td>
</tr>
<tr>
<td>Smith et al.68 (2022)</td>
<td>eSCS+activity-based recovery training</td>
<td>Medtronic</td>
<td>Paddle</td>
<td>16</td>
<td>Tonic stimulation</td>
<td>Lumbo-sacral</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Stimulation parameter optimized to activate specific motor neuron pools</td>
</tr>
</tbody>
</table>

eSCS, epidural spinal cord stimulation; BWST, body weight supported treadmill training; PWBT, partial body weight bearing treadmill training.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Stimulation parameters</th>
<th>Location</th>
<th>Stimulation frequency</th>
<th>Stimulation pulse width</th>
<th>Stimulation amplitude</th>
<th>Stimulation pattern</th>
<th>Stimulation optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofstoetter et al. (2013)</td>
<td>tSCS + treadmill stepping</td>
<td>Schwa-Medico</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>30 Hz</td>
<td>2-ms width (1 ms per phase)</td>
<td>18 V</td>
<td>Charge-balanced, symmetric, biphasic rectangular pulses</td>
<td>-</td>
</tr>
<tr>
<td>Hofstoetter et al. (2014)</td>
<td>tSCS</td>
<td>Schwa-Medico</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>50 Hz</td>
<td>2 ms</td>
<td>Intensities producing paresthesias but no motor responses in lower limbs</td>
<td>Biphasic pulses for 30 min</td>
<td>-</td>
</tr>
<tr>
<td>Bedi et al. (2015)</td>
<td>tSCS + locomotor training</td>
<td>-</td>
<td>Tonic stimulation</td>
<td>T10–L1</td>
<td></td>
<td></td>
<td>Amplitude raised to elicit sensory stimulation</td>
<td>Carrier modulated to “beat” frequency</td>
<td>-</td>
</tr>
<tr>
<td>Gerasimenko et al. (2015)</td>
<td>tSCS</td>
<td>NeuroRecovery</td>
<td>Tonic stimulation</td>
<td>C5, T11, L1</td>
<td>Carrier frequency of 10 kHz at 5–40 Hz</td>
<td>0.5–1.0 ms</td>
<td>30–200 mA</td>
<td>Biphasic rectangular bursts with carrier frequency administered at beat frequency with spatial specificity for different motor neuron pool activation</td>
<td>-</td>
</tr>
<tr>
<td>Hofstoetter et al. (2015)</td>
<td>tSCS + treadmill stepping</td>
<td>Schwa-Medico</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>30 Hz</td>
<td>1 ms</td>
<td>Target intensities defined as to produce paresthesias covering most of the lower limb dermatome yet sub-threshold for leg muscle activation</td>
<td>Charge-balanced, symmetric, biphasic rectangular pulses</td>
<td>-</td>
</tr>
<tr>
<td>Bedi et al. (2016)</td>
<td>tSCS</td>
<td>-</td>
<td>Tonic stimulation</td>
<td>T10–L1</td>
<td></td>
<td></td>
<td>Raised to elicit sensory stimulation</td>
<td>Carrier modulated to “beat” frequency</td>
<td>-</td>
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<tr>
<td>Minassian et al. (2016)</td>
<td>tSCS + robotic-driven gait orthosis</td>
<td>Schwa-Medico</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>30 Hz stimulation</td>
<td>1 ms</td>
<td>-</td>
<td>Rectangular, monophasic paired pulses (interstimulus interval 30 ms, 50 ms, 100 ms) or single pulses</td>
<td>-</td>
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<tr>
<td>Gad et al. (2017)</td>
<td>tSCS + exoskeleton + buspirone</td>
<td>-</td>
<td>Tonic stimulation</td>
<td>T11–T12, Co1</td>
<td>30 Hz at T11 and/or 5 Hz at Co1</td>
<td>-</td>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Stimulation parameters</th>
<th>Location</th>
<th>Stimulation frequency</th>
<th>Stimulation pulse width</th>
<th>Stimulation amplitude</th>
<th>Stimulation pattern</th>
<th>Stimulation optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freyvert et al.⁹⁹</td>
<td>tSCS + buspirone</td>
<td>-</td>
<td>Tonic stimulation</td>
<td>CS</td>
<td>5–30 Hz</td>
<td>-</td>
<td>20–100 mA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gad et al.⁷⁰</td>
<td>tSCS + functional task training</td>
<td>NeuroRecovery Technologies Inc.</td>
<td>Tonic stimulation</td>
<td>C3–C4, C6–C7</td>
<td>30 Hz with carrier frequency of 10 kHz</td>
<td>1 ms</td>
<td>70–210 mA</td>
<td>Carrier modulated to “beat” frequency with biphasic waveform or monophasic waveform</td>
<td>-</td>
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<tr>
<td>Inanici et al.⁷³</td>
<td>tSCS + PT</td>
<td>NeuroRecovery Technologies Inc.</td>
<td>Tonic stimulation</td>
<td>C3–C4, C6–C7</td>
<td>Pules at frequency of 30 Hz with carrier frequency of 10 kHz</td>
<td>1 ms</td>
<td>80–120 mA</td>
<td>Carrier frequency modulated to “beat” frequency</td>
<td>-</td>
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<tr>
<td>Niu et al.⁷⁴</td>
<td>tSCS</td>
<td>MagVenture</td>
<td>Tonic stimulation</td>
<td>T11–L3/L4</td>
<td>1 Hz or 30 Hz</td>
<td>250 μs</td>
<td>-</td>
<td>Trains of biphasic single pulse, continuous stimulation for sessions of three periods of 4 min continuous stimulation with a 30s break in between</td>
<td>-</td>
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<tr>
<td>Phillips et al.⁵⁰</td>
<td>tSCS</td>
<td>ValuTrode</td>
<td>Tonic stimulation</td>
<td>T7–T8</td>
<td>30 Hz</td>
<td>1 ms</td>
<td>10–70 mA</td>
<td>Monophasic pulses for at least 1 min</td>
<td>-</td>
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<tr>
<td>Powell et al.⁵¹</td>
<td>tSCS</td>
<td>NeuroConn</td>
<td>Tonic stimulation</td>
<td>T10–T11</td>
<td>-</td>
<td>-</td>
<td>2.5 mA</td>
<td>5 pulses for 20 min with interstimulus interval of 5 sec</td>
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<tr>
<td>Rath et al.⁵²</td>
<td>tSCS</td>
<td>ValuTrode</td>
<td>Tonic stimulation</td>
<td>T11–T12, L1–L2</td>
<td>“Beat” frequency of 30 Hz over T11 and 15 Hz during stimulation over L1, with each pulse filled with a carrier frequency of 10 kHz</td>
<td>1 ms</td>
<td>10–150 mA</td>
<td>Monophasic, rectangular pulses with carrier frequency modulated to “beat” frequency</td>
<td>-</td>
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<tr>
<td>Knikou et al.⁵⁶</td>
<td>tSCS</td>
<td>Digitimer</td>
<td>Tonic stimulation</td>
<td>T10–L1/L2</td>
<td>0.2 Hz</td>
<td>1 ms</td>
<td>Subthreshold and suprathreshold intensities</td>
<td>Monophasic stimuli for 16+ sessions of 60 min</td>
<td>-</td>
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<tr>
<td>Sayenko et al.⁷⁷</td>
<td>tSCS + locomotor training</td>
<td>ValuTrode</td>
<td>Tonic stimulation</td>
<td>T11–T12, L1–L2</td>
<td>0.2–30 Hz with each pulse filled by a carrier frequency of 10 kHz</td>
<td>1 ms</td>
<td>Up to 150 mA</td>
<td>Monophasic pulses with each pulse filled by a carrier frequency</td>
<td>-</td>
</tr>
<tr>
<td>Alam et al.⁷⁹</td>
<td>tSCS + locomotor training</td>
<td>Digitimer</td>
<td>Tonic stimulation</td>
<td>T11, L1</td>
<td>9.4 kHz burst signal delivered at 0.5–30 Hz</td>
<td>100 μs to 1 ms</td>
<td>Dependent on activity (90–120 mA)</td>
<td>Biphasic stimulation with burst duration at T11 and L1</td>
<td>-</td>
</tr>
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</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Stimulator type</th>
<th>Stimulation parameters</th>
<th>Location</th>
<th>Stimulation frequency</th>
<th>Stimulation pulse width</th>
<th>Stimulation amplitude</th>
<th>Stimulation pattern</th>
<th>Stimulation optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gad et al. (^{60})</td>
<td>tSCS</td>
<td>SpineX</td>
<td>Tonic stimulation</td>
<td>C3–C4, C5–C6, T1–T2</td>
<td>Carrier pulse (10 kHz)</td>
<td>1 ms</td>
<td>-</td>
<td>High frequency biphase carrier pulse combined with a low frequency (30 Hz) burst pulse</td>
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</tr>
<tr>
<td>Wiesener et al. (^{61}) (2020)</td>
<td>tSCS + FES + swim training</td>
<td>RehaMove</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>50 Hz</td>
<td>1 ms</td>
<td>-</td>
<td>Biphasic pulses</td>
<td></td>
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<tr>
<td>Wu et al. (^{65})  (2020)</td>
<td>tSCS</td>
<td>Digitimer</td>
<td>Tonic stimulation</td>
<td>T2–T4 (posteriorly), C4–C5 (anteriorly)</td>
<td>0.2 Hz</td>
<td>-</td>
<td>-</td>
<td>Pulses delivered in pseudo-random order or in pairs with 40 ms interstimulus intervals</td>
<td></td>
</tr>
<tr>
<td>Calvert et al. (^{63}) (2021)</td>
<td>tSCS</td>
<td>Digitimer</td>
<td>Tonic stimulation</td>
<td>T11–L2</td>
<td>0.2 and 2 Hz</td>
<td>1 ms</td>
<td>0–150 mA</td>
<td>Monophasic rectangular pulses</td>
<td></td>
</tr>
<tr>
<td>Estes et al. (^{84}) (2021)</td>
<td>tSCS + locomotor training</td>
<td>Empi Continuum</td>
<td>Tonic stimulation</td>
<td>T11–T12</td>
<td>50–Hz pulse</td>
<td>-</td>
<td>Highest intensity tolerated by patients or upon reporting paresthesias</td>
<td>Biphasic pulse for 30 min</td>
<td></td>
</tr>
<tr>
<td>Inanici et al. (^{86}) (2021)</td>
<td>tSCS + functional task training</td>
<td>NeuroRecovery Technologies Inc.</td>
<td>Tonic stimulation</td>
<td>C2+C4 or C4+C6, anterior iliac crests of pelvis</td>
<td>30-Hz base with 10 kHz overlapping frequency</td>
<td>1 ms</td>
<td>0–120 mA</td>
<td>Carrier modulated to “beat” frequency</td>
<td></td>
</tr>
</tbody>
</table>

tSCS, transcutaneous spinal cord stimulation; PT, physical therapy; FES, functional electrical stimulation.
in a study by Estes et al. The most studied American Spinal Cord Injury Association (ASIA) scores were ASIA A (n = 132), followed by ASIA B (n = 67), ASIA C (n = 40), and ASIA D (n = 29).

The main stimulation parameters of the eSCS studies are shown in Table 2. The main stimulation parameters of the tSCS studies are shown in Table 3. Of these studies, 48 used eSCS and 24 used tSCS. Of the studies using eSCS, most studies used a Medtronic stimulator (31 of 48) with 16-electrode paddle leads. The locations of lead placement for both eSCS and tSCS studies are shown in Fig. 2. The highest level of lead placement was C2 via tSCS reported by Inanici et al. The lowest level of lead placement was Co1 via tSCS by Gad et al. The most common and effective level of lead placement for volitional movement of lower extremities was in the range of T10–L2. The most common and effective level of lead placement for volitional movement of upper extremities was in the range of C4–6. For genitourinary function, the most common and effective level of lead placement was L1-S1. Lead placement for pulmonary function studies was most common and most effective at T9–11. The most common level of lead placement for cardiovascular function was T11–L1, which has been shown to be effective in reducing orthostatic hypotension. However, lead placement at T7–8 and L1–S1 were also found to be effective for addressing cardiovascular function. The range of stimulus locations can be seen in Fig. 2. Stimulation parameters varied across the studies. We categorized stimulation parameters into 2 major categories: tonic stimulation, where uniform pulses or pulse trains were fired, or spatiotemporal modulation, where spatially selective stimulation was optimized to induce intended movements. Only one study included spatiotemporal modulation of stimulation, though Rowald et al. (a study published outside of our search parameters) used spatiotemporal modulation as well. Pulse widths ranged from 150 μsec to 2 msec. Current intensities ranged from 0.1–15 mA/1–40 V in eSCS studies and

Fig. 2. Range of stimulation locations.
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Type of outcome studied</th>
<th>Measured outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barolat et al.19</td>
<td>eSCS</td>
<td>Volitional: EMG, spasticity</td>
<td>Complete abolition of the spasms, voluntary contraction and relaxation of left quadriceps with eSCS, augmentative effect on deep tendon reflexes in the lower extremities</td>
<td>None noted</td>
</tr>
<tr>
<td>Katz et al.20</td>
<td>eSCS</td>
<td>GU: EMG, bladder volume, peak urinary flow</td>
<td>Postoperative changes in the lower urinary tract function were noted in 6 patients. Urodynamic parameters did not change significantly following implantation in the remaining 17 patients.</td>
<td></td>
</tr>
<tr>
<td>Herman et al.21</td>
<td>eSCS + BWST therapy</td>
<td>Volitional: gait analysis, whole body metabolic rate, BWS, TSW, OGW, HCA, IWS, sense of effort, spasticity</td>
<td>Immediate improvement in the subject's gait rhythm. After months of training, performance in speed, endurance, and metabolic responses gradually converged with/without eSCS at short distances. Performance with eSCS was superior at long distances.</td>
<td>None noted</td>
</tr>
<tr>
<td>Carhart et al.22</td>
<td>eSCS + PWBT therapy</td>
<td>Volitional: EMG, gait analysis, BWS, TSW, IWS, Borg scale for sense of effort</td>
<td>Reduction in sense of effort for over ground walking from 8/10 to 3/10 (Borg scale) and doubled walking speed</td>
<td>Discomfort at 100Hz stimulation</td>
</tr>
<tr>
<td>Jilge et al.23</td>
<td>eSCS</td>
<td>Volitional (changes in muscle activity): EMG, induced movement</td>
<td>Enabled initiation and retention of lower-limb extension, elicited posterior root muscle-reflex responses</td>
<td>None noted</td>
</tr>
<tr>
<td>Minassian et al.24</td>
<td>eSCS</td>
<td>Volitional (changes in muscle activity): EMG, induced movement</td>
<td>Recruitment of lower-limb muscles in segmental-selective way, characteristic of posterior root stimulation; stimulation at 5–15 and 25–50 Hz elicited sustained tonic and rhythmic activity respectively.</td>
<td>None noted</td>
</tr>
<tr>
<td>Ganley et al.25</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, TSW, OGW, HCA, IWS, sense of effort</td>
<td>Both patients were able to walk faster and further with stimulation than without stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>DiMarco et al.26</td>
<td>eSCS</td>
<td>Pulmonary: airway pressure, air flow rate, volume of respiratory secretions</td>
<td>Combined T9+L1 stimulation increased airway pressure and expiratory flow rate to 132 cm H2O and 7.4 L/s respectively</td>
<td>None noted</td>
</tr>
<tr>
<td>Huang et al.27</td>
<td>eSCS + partial weight bearing treadmill therapy</td>
<td>Volitional: EMG, gait analysis, BWS, TSW, OGW, IWS, Borg scale for sense of effort</td>
<td>Acute modulations in muscle activities of both patients with stimulation but differences in observed pattern, magnitude, and spectral content of EMGs.</td>
<td>None noted</td>
</tr>
<tr>
<td>DiMarco et al.28</td>
<td>eSCS</td>
<td>Pulmonary: airway pressure, air flow rate, volume of respiratory secretions</td>
<td>During stimulation, mean maximum airway pressure generation and peak airflow rates 137± 30 cm H2O and 8.6 ± 1.8 L/s respectively.</td>
<td>One nonfunctional lead in each subject, skin breakdown and infection near receiver in one subject, mild leg jerks during SCS (well tolerated), temporary asymptomatic autonomic dysreflexia in three subjects which abated completely with continued SCS</td>
</tr>
<tr>
<td>Harkema et al.29</td>
<td>eSCS + stand training</td>
<td>Volitional and GU: EMG, gait analysis, BWS, A/I stand, A/I step, proprioception, bladder storage and voiding</td>
<td>Recovery of supraspinal control of some leg movements only during epidural stimulation 7 months after implantation.</td>
<td>None noted</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Type of outcome studied</th>
<th>Measured outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moshonkina et al.(^{29}) (2012)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, BWS, IWS</td>
<td>Thresholds of muscle responses were significantly lower with bipolar stimulation than the thresholds determined with monopolar stimulation of a single segment.</td>
<td>None noted</td>
</tr>
<tr>
<td>Angeli et al.(^{2}) (2014)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, TSW, ASIA score</td>
<td>Achieved recovery of intentional movement of legs during epidural stimulation</td>
<td>None noted</td>
</tr>
<tr>
<td>Sayenko et al.(^{32}) (2014)</td>
<td>eSCS</td>
<td>Volitional: EMG, BWS</td>
<td>Selective topographical recruitment of proximal and distal leg muscles during rostral and caudal stimulation of lumbar spinal cord</td>
<td>None noted</td>
</tr>
<tr>
<td>Rejc et al.(^{36}) (2015)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, BWS, A/I stand</td>
<td>Achieved full weight-bearing standing with continuous EMG patterns in lower limbs during stimulation</td>
<td>Discomfort (abdominal contractions) caused by stimulation</td>
</tr>
<tr>
<td>Lu et al.(^{30}) (2016)</td>
<td>eSCS</td>
<td>Volitional: EMG, handgrip force</td>
<td>Improved hand strength (approximately three-fold) and volitional hand control with stimulation</td>
<td>None noted</td>
</tr>
<tr>
<td>Grahn et al.(^{41}) (2017)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, A/I stand</td>
<td>eSCS with activity-specific training enabled (1) volitional control of task-specific muscle activity, (2) volitional control of rhythmic muscle activity to produce steplike movements while side-lying, and (3) independent standing.</td>
<td>None noted</td>
</tr>
<tr>
<td>Rejc et al.(^{32}) (2017a)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, A/I stand, STS</td>
<td>Progressive recovery of voluntary leg movement and standing without stimulation, re-emergence of muscle activation patterns sufficient for standing</td>
<td>None noted</td>
</tr>
<tr>
<td>Rejc et al.(^{33}) (2017b)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, A/I stand, STS</td>
<td>Improved standing (4/4) and stepping (3/4) ability with stimulation and stand/step training.</td>
<td>None noted</td>
</tr>
<tr>
<td>Angeli et al.(^{44}) (2018)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, I. sit, BWS, A/I stand, TSW, OGW, IWS, proprioception</td>
<td>All (4/4) achieved independent standing and trunk stability with stimulation after 287 sessions, some (2/4) achievement of over ground walking with stimulation</td>
<td>One hip fracture during training, one mild drainage from surgery site, one ankle edema</td>
</tr>
<tr>
<td>Aslan et al.(^{45}) (2018)</td>
<td>eSCS</td>
<td>Cardiovascular: EMG, plethysmography, BP, BP regulation during orthostasis, HR</td>
<td>In three patients with arterial hypotension, eSCS applied while supine and standing maintained blood pressure at 119/72 ± 7/14 mmHg compared to 70/45 ± 5/7 mmHg without eSCS.</td>
<td>None noted</td>
</tr>
<tr>
<td>DiMarco et al.(^{46}) (2018)</td>
<td>eSCS</td>
<td>Pulmonary: airway pressure, air flow rate, volume of respiratory secretions</td>
<td>Paw increased from 20 cm H(_2)O (8.6% predicted) during spontaneous efforts to 84 cm H(_2)O at FRC and 103 cm H(_2)O at TLC during bipolar (T9–T11) SCS and 61 cm H(_2)O at FRC and 86 cm H(_2)O at TLC with monopolar (T9) SCS.</td>
<td>Temporary development of asymptomatic autonomic dysreflexia resolving after 5–6 weeks</td>
</tr>
<tr>
<td>Formento et al.(^{47}) (2018)</td>
<td>eSCS</td>
<td>Volitional: EMG, gait analysis, proprioception</td>
<td>Continuous eSCS prevented 2/3 participants from detecting leg movements.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gill et al.(^{48}) (2018)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, A/I stand, TSW, A/I step, OGW, HCA, IWS, spasticity</td>
<td>Achieved independent bilateral stepping with stimulation</td>
<td>None noted</td>
</tr>
</tbody>
</table>
Table 4. Outcomes of selected studies for epidural spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Type of outcome studied</th>
<th>Measured outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harkema et al.</td>
<td>eSCS</td>
<td>Cardiovascular: EMG, BP, BP during orthostasis, HR, plethysmography</td>
<td>Persistent hypotension was resolved in four individuals.</td>
<td>None noted</td>
</tr>
<tr>
<td>Harkema et al.</td>
<td>eSCS</td>
<td>Cardiovascular: EMG, BP, BP during orthostasis, HR, plethysmography</td>
<td>Orthostatic hypotension was alleviated in 4 individuals. Improved cardiovascular response was observed after daily eSCS without stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Herrity et al.</td>
<td>eSCS + activity-based recovery training</td>
<td>GU: EMG, storage and voiding, urodynamic parameters via cystometry</td>
<td>All 5 patients showed improvements in bladder emptying.</td>
<td>None noted</td>
</tr>
<tr>
<td>Wagner et al.</td>
<td>eSCS + locomotor training + gravity assist device</td>
<td>Volitional: EMG, gait analysis, EEG, BWS, STS, A/I step, OGW, HCA, IWS, cycling, proprioception, ASIA score</td>
<td>Re-established adaptive control of paralyzed muscles during overground walking stimulation within one week, regained voluntary control over paralyzed muscles without stimulation, regained walking and cycling ability</td>
<td>None noted</td>
</tr>
<tr>
<td>Walter et al.</td>
<td>eSCS</td>
<td>GU: EMG, EKG, external anal sphincter/ pelvic floor muscle tone and detrusor pressure, Neurogenic Bowel Dysfunction Score, orgasm</td>
<td>Reduced time needed for bowel management, modulated detrusor pressure and external anal sphincter/pelvic floor muscle tone</td>
<td>None noted</td>
</tr>
<tr>
<td>West et al.</td>
<td>eSCS</td>
<td>Cardiovascular: EMG, plethysmography, BP, BP regulation during orthostasis, cardiac function (contractility, stroke volume, cardiac output), MCA via transcranial doppler</td>
<td>Stimulation resolved the orthostatic hypotension.</td>
<td>None noted</td>
</tr>
<tr>
<td>Calvert et al.</td>
<td>eSCS + locomotor training</td>
<td>Volitional: EMG, induced movement</td>
<td>Enabled intentional control of step-like activity in both subjects within first 5 days of testing</td>
<td>None noted</td>
</tr>
<tr>
<td>Cheng et al.</td>
<td>eSCS + stand training</td>
<td>Volitional: EMG</td>
<td>Spatiotemporal modulation during SCI patient standing leads to activation of an additional neural circuit, which significantly improves patient standing ability.</td>
<td>None noted</td>
</tr>
<tr>
<td>Darrow et al.</td>
<td>eSCS</td>
<td>Volitional, cardiovascular, and GU: EMG, EKG, BP, BP regulation during orthostasis, HR, cardiac function (contractility, stroke volume, cardiac output), MCA, bladder function (storage and voiding, incontinence, synergy), bowel synergy, orgasm</td>
<td>Restoration of cardiovascular function in one patient, achieved orgasm in one patient with and immediately after stimulation, improved bowel-bladder synergy in both patients while restoring volitional urination in one patient</td>
<td>None noted</td>
</tr>
<tr>
<td>Nightingale et al.</td>
<td>eSCS</td>
<td>Cardiovascular and pulmonary: body composition, metabolic rate, oxygen consumption</td>
<td>Increased absolute and relative peak oxygen consumption (15%–26%) during exercise with stimulation; peak oxygen pulse increased with stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Terson de Paleville et al.</td>
<td>eSCS + locomotor training</td>
<td>Cardiovascular and pulmonary: body composition, metabolic rate, oxygen consumption</td>
<td>Increases in lean body mass with decreases on percentage of body fat, particularly android body fat, and android/gynoid ratio from baseline to post training</td>
<td>None noted</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Type of outcome studied</td>
<td>Measured outcome</td>
<td>Complications</td>
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<tr>
<td>DiMarco et al.⁹⁰ (2020)</td>
<td>eSCS</td>
<td>Pulmonary: airway pressure, air flow rate, volume of respiratory secretions</td>
<td>Following daily use of SCS, mean inspiratory capacity improved from 1,636 ± 229 to 1,932 ± 239 mL (127% ± 8% of baseline values) after 20 weeks. Mean maximum inspiratory pressure increased from 40 ± 7 to 50 ± 8 cm H₂O (127% ± 6% of baseline values) after 20 weeks.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gill et al.⁹³ (2020)</td>
<td>eSCS + body weight supported treadmill training</td>
<td>Volitional: EMG, gait analysis, BWS, TSW, A/I step, proprioception</td>
<td>During eSCS-enabled BWST stepping, the knee extensors exhibited an increase in motor activation during trials in which stepping was passive compared to active or during trials in which 60% BWS was provided compared to 20% BWS.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gorgey et al.⁹⁰ (2020)</td>
<td>eSCS + exoskeleton-assisted walking training</td>
<td>Volitional: EMG, A/I stand, A/I step, OGW, IWS</td>
<td>After 24 sessions (12 weeks) of exoskeleton-assisted walking with eSCS, swing assistance decreased from 100% to 35%, accompanied by 573 unassisted steps.</td>
<td>None noted</td>
</tr>
<tr>
<td>Peña Pino et al.⁹¹ (2020)</td>
<td>eSCS</td>
<td>Volitional: EMG, cycling, modified Ashworth scale</td>
<td>In one participant, we observed an increase in episodes of urinary incontinence with worsening bladder compliance and pressures at the end of the study.</td>
<td>None noted</td>
</tr>
<tr>
<td>Beck et al.⁶² (2021)</td>
<td>eSCS + task-specific training</td>
<td>GU: EMG, incontinence, storage and voiding, urinary complications, Neurogenic Bladder Symptom Score</td>
<td>eSCS decreased the amplitude of evoked responses of both patients when instructed to perform a full leg flexion.</td>
<td>None noted</td>
</tr>
<tr>
<td>Calvert et al.⁶³ (2021)</td>
<td>eSCS</td>
<td>Volitional: EMG</td>
<td>Mean pressure during spontaneous efforts was 30 ± 8 cm H₂O. After a period of reconditioning, SCS resulted in pressure of 146 ± 21 cm H₂O.</td>
<td>None noted</td>
</tr>
<tr>
<td>DiMarco et al.⁹³ (2021)</td>
<td>eSCS</td>
<td>Pulmonary and GU: airway pressure generation, bowel management, orgasm</td>
<td>There was also a significant improvement change in bladder capacity at post-training (70 ± 83 mL, p &lt; 0.05) and at follow-up (102 ± 120 mL, p &lt; 0.05).</td>
<td>None noted</td>
</tr>
<tr>
<td>Herrity et al.⁰⁵ (2021)</td>
<td>eSCS + activity-based recovery training</td>
<td>GU: storage and voiding, urodynamic parameters via cystometry</td>
<td>Human spinal circuitry receiving eSCS can promote both orderly (according to motor neuron size) and inverse trends of motor neuron recruitment.</td>
<td>None noted</td>
</tr>
<tr>
<td>Ibáñez et al.⁶⁴ (2021)</td>
<td>eSCS + activity-based recovery training</td>
<td>Volitional: EMG, A/I stand, STS</td>
<td>Two participants, both with sensorimotor complete SCI graded AIS-A, were able to improve independence of the stance.</td>
<td>None noted</td>
</tr>
<tr>
<td>Linde et al.⁶⁷ (2021)</td>
<td>eSCS + locomotor training</td>
<td>Volitional: Force sensitive resistors, gait analysis, TSW</td>
<td>All individuals with chronic and clinically motor complete SCI that participated in the study (n = 20) achieved lower extremity voluntary movements post-eSCS implant and prior to any training.</td>
<td>None noted</td>
</tr>
<tr>
<td>Mesbah et al.⁶⁵ (2021)</td>
<td>eSCS + activity-based recovery training</td>
<td>Volitional: EMG</td>
<td>eSCS led to real-time hemodynamic stabilization during orthostatic challenges.</td>
<td>None noted</td>
</tr>
<tr>
<td>Squair et al.⁹⁰ (2021)</td>
<td>eSCS</td>
<td>Cardiovascular: plethysmography, BP, BP regulation during orthostasis, HR</td>
<td>Participants with spared spinal cord tissue (7/11) achieved some knee independence with eSCS.</td>
<td>None noted</td>
</tr>
<tr>
<td>Smith et al.⁹⁰ (2022)</td>
<td>eSCS + activity-based recovery training</td>
<td>Volitional: EMG, A/I stand, STS</td>
<td></td>
<td>None noted</td>
</tr>
</tbody>
</table>

eSCS, epidural spinal cord stimulation; EMG, electromyogram; BWST, body weight supported treadmill training; BWS, body weight support; TSW, treadmill step/walk; OGW, over-ground walking; HCA, home and community access; IWS, increased walking speed; PWBT, partial body weight bearing treadmill training; GU, genitourinary; A/I, assisted/independent; STS, sit to stand transition; BP, blood pressure; HR, heart rate; FRC, functional residual capacity; TLC, total lung capacity; SCS, spinal cord stimulation; EKG, electrocardiogram; AIS-A, American Spinal Injury Association Impairment Scale grade A.
### Table 5. Outcomes of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Type of outcome studied</th>
<th>Measured outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofstoetter et al. (2013)</td>
<td>tSCS + treadmill stepping</td>
<td>Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk</td>
<td>Enhanced voluntary lower limb EMG activities in a step-phase appropriate manner with stimulation, modified coordination of hip and knee movements</td>
<td>None noted</td>
</tr>
<tr>
<td>Hofstoetter et al. (2014)</td>
<td>tSCS</td>
<td>Volitional (changes in muscle activity): EMG, gait analysis, IWS, spasticity</td>
<td>Increased index of spasticity from pendulum test, increased gait speed during stimulation in two subjects by 39%</td>
<td>None noted</td>
</tr>
<tr>
<td>Bedi et al. (2015)</td>
<td>tSCS + locomotor training</td>
<td>Volitional: EMG, ASIA score</td>
<td>Improvement in ASIA score of lower limb by 2 points on right side and by 1 point on left side.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gerasimenko et al. (2015)</td>
<td>tSCS</td>
<td>Volitional: EMG</td>
<td>Induced rhythmic leg movements and corresponding coordinated movement EMG activity in leg muscles with stimulation</td>
<td>None noted</td>
</tr>
<tr>
<td>Hofstoetter et al. (2015)</td>
<td>tSCS + treadmill stepping</td>
<td>Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk</td>
<td>Motor outputs augmentative and step-phase dependent during stimulation, increased hip flexion during swing by 11.3° ± 5.6° across all subjects</td>
<td>None noted</td>
</tr>
<tr>
<td>Bedi et al. (2016)</td>
<td>tSCS</td>
<td>Volitional: EMG, ASIA score</td>
<td>Increased number of rhythmically responding muscles, augmented thigh muscle activity, and suppressed donus with stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Minassian et al. (2016)</td>
<td>tSCS + robotic-driven gait orthosis</td>
<td>Volitional (changes in muscle activity): EMG, gait analysis, treadmill step/walk</td>
<td>Increased number of rhythmically responding muscles, augmented thigh muscle activity, and suppressed donus with stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gad et al. (2017)</td>
<td>tSCS + exoskeleton + buspirone</td>
<td>Volitional and cardiovascular: EMG, gait analysis, BP, HR</td>
<td>Increased patient generation of level of effort, improved coordination patterns of the lower limb muscles, smoother stepping motion, increased blood pressure and heart rate</td>
<td>None noted</td>
</tr>
<tr>
<td>Freyvert et al. (2018)</td>
<td>tSCS + buspirone</td>
<td>Volitional: EMG, handgrip strength, ASIA score, spasticity</td>
<td>Increased mean hand strength by 300% with stimulation and buspirone, some functional improvements persisted after interventions discontinued</td>
<td>None noted</td>
</tr>
<tr>
<td>Gad et al. (2018)</td>
<td>tSCS + functional task training</td>
<td>Volitional: EMG, handgrip strength</td>
<td>Improved voluntary hand function occurred within a single session in every subject tested.</td>
<td>None noted</td>
</tr>
<tr>
<td>Inanici et al. (2018)</td>
<td>tSCS + PT</td>
<td>Volitional: EMG, handgrip force, GRASSP score, ASIA score</td>
<td>Graded Redefined Assessment of Strength, Sensation, and Prehension (GRASSP) test score increased 52 points and upper extremity motor score improved 10 points. Sensation recovered on trunk dermomes, and overall neurologic level of injury improved from C3 to C4.</td>
<td>Mild, painless hyperemia under electrode, self-resolved</td>
</tr>
<tr>
<td>Niu et al. (2018)</td>
<td>tSCS</td>
<td>GU: EMG, storage and voiding</td>
<td>Bladder function improved in all five subjects, but only during and after repeated weekly sessions of 1 Hz TMS. All subjects achieved volitional urination.</td>
<td>None noted</td>
</tr>
<tr>
<td>Phillips et al. (2018)</td>
<td>tSCS</td>
<td>Cardiovascular: BP, cardiac function (contractility, stroke volume, cardiac output), MCA and PCA velocity</td>
<td>During orthostatic challenge, electrical stimulation completely normalized BP, cardiac contractility, cerebral blood flow, and abrogated all symptoms.</td>
<td>None noted</td>
</tr>
</tbody>
</table>

(Continued)
### Table 5. Outcomes of selected studies for transcutaneous spinal cord stimulation facilitation of outcomes following spinal cord injury (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Type of outcome studied</th>
<th>Measured outcome</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powell et al.³⁵ (2018)</td>
<td>tSCS</td>
<td>Volitional: EMG</td>
<td>No significant differences in change of MEP amplitudes but indication of laterality of response.</td>
<td>None noted</td>
</tr>
<tr>
<td>Rath et al.³² (2018)</td>
<td>tSCS</td>
<td>Volitional: EMG, gait analysis, BWS</td>
<td>During spinal stimulation, the center of pressure displacements decreased to 1.36 ± 0.98 mm compared with 4.74 ± 5.41 mm without stimulation in quiet sitting.</td>
<td>None noted</td>
</tr>
<tr>
<td>Knikou et al.³⁶ (2019)</td>
<td>tSCS</td>
<td>Volitional: EMG</td>
<td>Repeated stimulation increased homosynaptic depression in all SCI subjects. Stimulation decreased the severity of spasms and ankle dorsus.</td>
<td>None noted</td>
</tr>
<tr>
<td>Sayenko et al.²⁷ (2019)</td>
<td>tSCS + locomotor training</td>
<td>Volitional: EMG, BWS, A/I stand</td>
<td>All participants could maintain upright standing with stimulation, some (7/15) without external assistance applied to the knees or hips, using their hands for upper body balance as needed.</td>
<td>One case of skin breakage due to electrode defect, resolved after a week without stimulation</td>
</tr>
<tr>
<td>Alam et al.³⁸ (2020)</td>
<td>tSCS + locomotor training</td>
<td>Volitional: EMG, gait analysis, BWS, A/I stand</td>
<td>After 32 training sessions with tSCS, the patient regained significant left-leg volitional movements and improved pinprick sensation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Gad et al.³⁹ (2020)</td>
<td>tSCS</td>
<td>Pulmonary: EMG, airway pressure, air flow rate, volume of respiratory secretions</td>
<td>Improved breathing and coughing ability both during and after stimulation.</td>
<td>None noted</td>
</tr>
<tr>
<td>Wiesener et al.⁴¹ (2020)</td>
<td>tSCS + FES + swim training</td>
<td>Volitional: EMG, swim analysis, increased swimming speed, cycling, spasticity</td>
<td>tSCS support yielded mean decreases of swimming pool lap times by 19.3% and 20.9% for Subjects A and B, respectively.</td>
<td>None noted</td>
</tr>
<tr>
<td>Wu et al.⁴² (2020)</td>
<td>tSCS</td>
<td>Volitional: EMG</td>
<td>Resting motor threshold at the abductor pollicis brevis muscle ranged from 5.5 to 51.0 mA. As stimulus intensity increased, response latencies to all muscles decreased.</td>
<td>Asymptomatic sustained 20% or greater change in mean arterial pressure, self-resolved</td>
</tr>
<tr>
<td>Calvert et al.⁶³ (2021)</td>
<td>tSCS</td>
<td>Volitional: EMG</td>
<td>All 4 AIS-B/C participants tested with tSCS demonstrated a reduction in the evoked responses amplitude during stimulation compared to the normalized relaxed value in at least 3 out of 4 of the recorded muscles.</td>
<td>None noted</td>
</tr>
<tr>
<td>Estes et al.⁶⁴ (2021)</td>
<td>tSCS + locomotor training</td>
<td>Volitional: gait analysis, IWS, spasticity</td>
<td>Significant improvements in walking outcomes following the intervention period.</td>
<td>Discomfort, tightness in the abdomen and lower back near electrodes</td>
</tr>
<tr>
<td>Inanici et al.⁶⁵ (2021)</td>
<td>tSCS + functional task training</td>
<td>Volitional, cardiovascular, and GU: GRASSP lateral pinch force, spasticity, HR, storage and voiding</td>
<td>Rapid and sustained recovery of hand and arm function. Muscle spasticity reduced and autonomic functions including heart rate, thermoregulation, and bladder function improved.</td>
<td>Mild allergic skin rash</td>
</tr>
</tbody>
</table>

tSCS, epidural spinal cord stimulation; EMG, electromyogram; IWS, increased walking speed; AIS, American Spinal Cord Injury Association; BP, blood pressure; HR, heart rate; GU, genitourinary; PCA, posterior cerebral artery; MCA, middle cerebral artery; BWS, body weight support; A/I, assisted/independent; AIS-B/C, American Spinal Injury Association Impairment Scale grade B/C.
2.5–210 mA/18 V in tSCS studies, though most studies used high intensities close to the subjects’ tolerance threshold. The most common and most effective stimulation settings for lower extremity volitional movement were spatially directed based on settings optimized for individual patients performing specific activities (based on muscle group activation). Upper extremity volitional movement was most commonly studied using 0.5–1.0 ms bursts of stimulation at 0.2–90 Hz with carrier frequencies of 2.5–10 kHz, which was found to be effective, though Lu et al.\textsuperscript{36} found that spatially directed stimulation optimized for individual patients and activities were also effective. For genitourinary function, the most common stimulation settings were spatially directed and optimized for specific patients and specific activities but optimization for volitional activity of lower extremities was ineffective in improving genitourinary outcomes. Instead, tonic stimulation at 2–60 Hz was effective in improving bladder storage and voiding. Stimulation settings for pulmonary function studies were most common and effective with tonic stimulation at 2–60 Hz. The most common stimulation settings for cardiovascular function were spatially directed, an effective setting for improving cardiovascular outcomes.

The main outcomes of the eSCS studies are shown in Table 4. The main outcomes of the tSCS studies are shown in Table 5. Positive volitional outcomes were measured in terms of electromyography (EMG) activity consistent with activities such as stepping, gait analysis consistent with more fluid movements, increased muscle strength, achievement of independent sitting, increased body weight support, achievement of A/I step, achievement of A/I stand, increased fluidity of sit to stand transition, improved treadmill step/walk, improved overground walking, increased home and community access, increased walking speed, decreased spasticity, decreased sense of effort, or improved ASIA score. Positive genitourinary outcomes were measured in terms of EMG activity consistent with better muscle control, decreased incontinence, increased storage and voiding volume, decreased urinary complications, improved urodynamic parameters via cystometry, decreased time and effort used in bowel management, achievement of orgasm, and decreased Neurogenic Bladder Symptom Score. Positive cardiovascular outcomes were measured in terms of stable blood pressure, improved blood pressure regulation during orthostasis, improved cardiac function, stable heart rate, normal middle cerebral artery blood flow, increased metabolic rate, and increased oxygen consumption. Positive pulmonary outcomes were measured in terms of increased airway pressure, increased ability to cough, increased air flow rate, and decreased volume of respiratory secretions. All but one study reported positive outcomes—Beck et al.\textsuperscript{82} reported worsening genitourinary function when using eSCS parameters optimized for volitional movement. Of the 51 studies examining sensorimotor function, 45 studies evaluated lower extremity function and 6 studies evaluated hand function. With regards to autonomic function, 10 studies examined genitourinary function, 8 studies examined pulmonary function, and 11 studies examined cardiovascular function. Four studies reported the return of volitional movement without stimulation.\textsuperscript{2,42,78,81} Physical training was described preimplantation in 24 studies and postimplantation in 33 studies, though number of sessions ranged from none to 160 sessions and duration of sessions ranged from 0.5–3 hours. Six studies reported the return of autonomic function during stimulation.\textsuperscript{50,59,74,76} One study reported the experience of orgasm for the first time since injury in a patient.\textsuperscript{76} Out of 327 patients with varying stimulation and evaluation protocols, 118/127 patients saw improvement in sensorimotor function during stimulation, 51 of 70 patients saw improvement in autonomic genitourinary function during stimulation, 32 of 32 patients saw improvement in autonomic pulmonary function during stimulation, and 32 of 36 patients saw improvement in autonomic cardiovascular function during stimulation. Most patients with improvements in sensorimotor function underwent extensive physical training, ranging from one month to almost 4 years. Of the 127 patients studied for changes in sensorimotor function, 8 patients did not see improvement in motor function, potentially due to lower spasticity scores prior to treatment.\textsuperscript{68,81} Seventy-one of 127 patients saw return of volitional movement during stimulation. After months of physical training with adjunctive SCS, 7 of 127 patients saw lasting return of volitional movement in the absence of stimulation for months. In general, there was good tolerability of the intervention by patients with few significant complications.

**DISCUSSION**

The use of electricity to modulate the nervous system has existed throughout history with variable efficacy. Though use of electricity for neuromodulation has existed since the Ancient Egyptians, studies of electrical stimulation of the spinal cord began in the late 1900s.\textsuperscript{89,90} Electrical stimulation of the spinal cord was first tested in 1967 when Norman Shealy applied electrical stimulation subdurally to the dorsal column of cats and found prolonged after-discharge upon electrical stimulation.\textsuperscript{90} Based on these findings, Shealy partnered with a graduate engineering student, Thomas Mortimer, to develop an implantable
spinal cord stimulator by modifying cardiovascular stimulators. Subsequently, use of spinal electrical stimulation was applied in a human patient for temporary severe pain management. More recent approaches to SCS for management of chronic pain include burst stimulation to deliver square waves (5 spikes at 40-Hz bursts with each burst at 500 Hz) or high frequency stimulation (10 kHz) via the Senza system. Although the exact mechanism of pain relief during SCS remains unclear, the Gate Control Theory has prevailed as the main explanation for decreased pain perception with stimulation. As hypothesized by the Gate Control Theory, the analgesic effects of SCS are achieved due to greater sensory information being carried by large diameter (touch, vibration, pressure) fibers relative to sensory information being carried by small diameter (pain) fibers to the dorsal horn of the spinal cord. SCS has improved over time, first with the transition of electrode placement from subdural to epidural, then with technological advancements allowing for fully implanted systems with battery-powered pulse generators. These advancements have led to further mechanistic rodent studies on the effect of SCS on functional recovery following SCI, such as return of motor, sensory, or autonomic function below the injury site.

The mechanism of action for return of function with SCS after SCI is not fully understood, though current mouse models suggest that SCS transforms dormant tissue to active tissue at the injury site by increasing general excitability. Central pattern generators (CPGs) are dedicated spinal circuits that elicit coordinated rhythmic activity of multiple muscles—CPGs also control reflex influences on alpha motor neurons by facilitating or inhibiting these neurons during specific phases of motion. In rats, stimulation of CPGs in a regular pattern, with the fixed time periods between each stimulation, has been shown to induce adaptive plasticity, promoting spinal cord learning, whereas unsynchronized stimulation has been shown to generate maladaptive spinal plasticity, increasing nociceptive hyperreactivity. Coupled with extensive physical training, modulation of excitability allows sensory information to be used as a source of control for voluntary movement through appropriate remodeling of supraspinal and intraspinal pathways in mouse models. However, it should be noted that there are notable anatomical differences between rodents, larger animal models, and humans. For example, rhesus monkeys are more comparable to humans in the projection of the corticospinal tracts. In primates, the corticospinal tract projects through the dorsolateral column, and contains axons originating from both the left and right motor cortex. In contrast, in rodents the corticospinal tract is primarily located in the dorsal column, and these axons exclusively originate from the contralateral motor cortex. A substantial number of corticospinal axons decussate along the spinal cord midline in monkeys, but not in rodents. These anatomical considerations should be taken into account when comparing mechanistic studies with clinical outcomes.

The majority of the functional improvements shown with SCS have been paired with periods of intense motor training. On average, 5.4 months of physical training was required for improvements in volitional movement, such as EMG activity consistent with step-like activity, gait analysis consistent with more fluid movements, increased muscle strength or improved ASIA score—most patients did not completely regain volitional movement. Innovations in approach, such as spatiotemporally modulated dorsal root targeted stimulation, enables activity-based movement within 1 day of stimulation. By pairing stimulation and physical training, plastic changes can be achieved, leading to return of volitional movement in the absence of stimulation. On average, 6.48 months of physical training was required for return of volitional movement in the absence of stimulation in patients—Alam et al. demonstrated the return of volitional movement in the absence of stimulation after 3 months of physical training whereas Rejc et al. demonstrated return of volitional movement in the absence of stimulation after 5.5 years of physical training including 21 months of training prior to stimulator implantation. The remodeling of supraspinal and intraspinal pathways of these patients likely occurs using the same mechanisms underlying learning and memory in the hippocampus—in response to stimulation, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors mediate long-term potentiation and long-term depression. Current studies using electricity to treat chronic SCI in rodent models as well as human patients show that electricity is an efficacious neuromodulator for recovery from SCI when paired with physical training, but the optimal amount of training is likely subject dependent and requires further study.

Recently, eSCS and tSCS have both emerged as electricity-based neuromodulation that target the spinal cord, and have shown impressive results in the restoration of function in individuals with SCI. eSCS is defined by the delivery of electricity to the dorsal surface of the dura mater of the spinal cord. Though most commonly used for chronic pain management, eSCS has been shown to improve motor strength and voluntary motor function in patients with SCI. tSCS, much like eSCS, elicits spinal cord reflex activity but has electrodes placed on the skin instead of on the dura. Through utilizing unique
waveforms, tSCS permits high-current electrical stimulation to reach spinal networks without causing discomfort. The differences in electrode placement between epidural SCS and tSCS in stimulation location are visualized in Fig. 3. Both techniques activate the dorsal roots, though tSCS stimulation of the skin may contribute to elevated neural activity as well. The dorsal roots are comprised of primary afferent fibers—these large diameter proprioceptive sensory fibers have the lowest activation threshold and are preferentially recruited during stimulation. eSCS produces a localized electric field resulting in higher segmental selectivity of the recruited dorsal roots, a feature that allows induction of nonvolitional movements. tSCS produces a more distant and unfocused electric field with less segmental selectivity—by providing uniform bilateral coverage of several spinal cord segments, tSCS can increase the general excitability of the spinal cord to induce volitional movement in conjunction with physical training. Though eSCS and tSCS differ in application, both have been shown to be efficacious in eliciting functional recovery following SCI, and further research should be performed to compare and contrast outcomes with these techniques.

1. Sensorimotor Function

Both eSCS and tSCS have been shown to restore sensorimotor function, most notably measured in return of volitional movement and changes in EMG activity. Of the 127 patients studied for sensorimotor function, 71 patients regained volitional movement during SCS, 51 using eSCS and 20 using tSCS. Of the 51 patients to regain volitional movement during eSCS, 28 patients were noted to have complete SCI (ASIA A) and 23 patients were noted to have incomplete SCI. Of the 20 patients to regain volitional movement during tSCS, none were noted to have complete SCI (ASIA A) and 19 patients were noted to have incomplete SCI, with one patient’s SCI injury grade not reported. Usage of eSCS in conjunction with months of physical training induced return of volitional movement without eSCS in 7 patients. Usage of tonic tSCS at T11 and L1 in conjunction with extensive physical training also induced return of volitional leg movements without stimulation in a single patient, as well as increased pin-point sensation. These studies examine volitional movement, which requires a descending depolarizing input to reach motor threshold, activating motor neurons involved in movement. Immediate improvements in muscle strength and sensation may be explained by modulation of spinal networks into a physiologic state that enables greater access of supraspinal control to sensorimotor networks. In individuals with complete SCI, stimulation is postulated to access local spinal circuitry via dorsal root primary afferent fibers. For individuals with an incomplete SCI, SCS is postulated to increase the descending activation of spinal inhibitory circuitry through brainstem-spinal cord loops (orthodromic conduction), as well as activating dorsal column fibers to modulate activity of segmental circuitry involved in regulation of afferent inputs and motor neuron excitability (antidromic conduction). The tonic activation of the dorsal root afferent fibers elevates spinal network excitability and brings both interneurons and motor neurons closer to motor threshold, making the circuit more likely to respond to limited post-injury descending drive.
preclinical and clinical studies have examined the usage of SCS with targeted spatiotemporal eSCS to activate discrete somatomotor networks during locomotion and other pattern-based activities. By developing software to support rapid configuration of stimulation programs that reproduced natural activity-specific activation of motor neurons, Rowald et al. were able to use spatiotemporally modulated eSCS on SCI patients to enable activity-dependent movements such as walking and cycling. Due to the heterogeneity of SCI and differences in spinal anatomy, intensive stimulation optimization or computational modeling for individual subjects may be necessary to increase the efficacy of spatiotemporal stimulation. The studies reviewed show great potential for therapeutic applications of eSCS in restoring motor function in patients with severe SCI, especially with optimized and targeted approaches.

2. Genitourinary Function

Both eSCS at T11–L1 and L1–L2 and tSCS at T11–L3/L4 have been shown to improve bowel-bladder function in patients with SCI. Usage of spatially directed eSCS, specifically on the caudal end of a T11–L1 array or on the rostral end of a L1–S2 array, improved bowel-bladder function. Stimulation using the caudal end of a T11–L1 array (pulse width of 390–450 μsec, frequency 25–45 Hz, intensity 4–7 V) in a young male patient (32 years old) 5 years after sustaining motor complete, sensory incomplete SCI increased external anal sphincter/pelvic floor muscle tone and detrusor pressure—these effects significantly expedited bowel management (p = 0.039) and decreased the severity of neurogenic bowel dysfunction from severe to minor, as seen in a reduction in neurogenic bowel dysfunction score from 15 to 8 and improvement of general satisfaction scale from 5 to 8. Stimulation using the rostral end of an L1–S2 electrode to excite caudal preganglionic neurons distributed between T1 and L2 in two older female patients in their fifth and sixth decade of life, five and 10 years after sustaining motor and sensory-complete SCI, allowed improvement of bowel-bladder synergy in both patients but recovery of ability to void voluntarily but incompletely with residual volumes in only one patient. Conversely, usage of tonic tSCS to stimulate T11–L3/4 at 1Hz improved bladder function during stimulation in 5/5 patients, increasing the volume of urine produced voluntarily from none to 1,120 mL/day, decreasing the frequency of self-catheterization from 6.6/day to 2.4/day, and increasing bladder capacity from 244 mL to 404 mL. SCS is currently hypothesized to enable genitourinary function via an increase in storage and voiding reflexes as well as volitional sphincter control by allowing the micturition circuitry in the sacral cord to appropriately respond to residual descending input from supraspinal micturition centers. Taken together, these studies indicate that SCS of preganglionic neurons near L1 is safe and effective in improving bowel-bladder function in chronic SCI patients.

3. Pulmonary Function

Both eSCS and tSCS have been used to improve pulmonary function in patients with SCI. Regular use of tonic eSCS at T9–L1 (40 V, 30–55 Hz) can lead to pulmonary function changes, notably an increase over 10 and 20 weeks in positive expiratory pressure generation to restore cough. Additionally, usage of tonic tSCS with a 10-kHz carrier pulse and a 30-Hz burst pulse at the C3–4, C5–6, and T1–12 improved breathing and coughing ability in a patient, with improvements persisting for a few days after tSCS was stopped. Pulmonary function changes in response to SCS are likely due to induction of an excitatory functional state leading to recruitment of respiratory intercostal and trunk muscles. Additionally, dorsal lower thoracic SCS may lead to activation of spinal cord pathways with connections to phrenic motor neuron pools, leading to coactivation of the diaphragm as well. Both eSCS and tSCS hold promise in improving pulmonary function for patients with SCI, though further study of the effects of tSCS are necessary to confirm these findings.

4. Cardiovascular Function

eSCS and tSCS has been demonstrated to restore autonomic cardiovascular function in patients with SCI. Phillips et al. reported return of autonomic cardiovascular function during an orthostatic challenge, noting normalization of blood pressure and heart rate, with tonic monophasic tSCS at 30 Hz at the T7 level. Similar results as discussed with tSCS have been shown with eSCS as well, noting resolution of orthostatic hypotension. Cardiovascular function changes in response to SCS, as measured by normalization of heart rate or blood pressure, are likely due to 2 possible mechanisms involving sympathetic preganglionic neuron excitation: (1) small caliber C-fiber afferents excitation, leading to propriospinal interneuron overactivity associated with autonomic dysreflexia, or (2) propriospinal and sympathetic preganglionic neurons excitation, either directly through electrical stimulation or by preferential excitation of large diameter sensory axons that do not elicit autonomic dysreflexia. As orthostatic hypotension can have a large negative effect on quality of life, further study of the effects of tSCS and eSCS, on cardiovascular function is necessary.
5. Risk of Bias
A detailed list of risk of bias assessments using ROBINS-I is provided in Supplementary Table 1. Within each study, the risk of bias was judged overall as serious for 66 publications. The bias in measurement of outcomes was the primary source of bias due to lack of blinding in the majority of studies. Additionally, though most studies included patients acting as their own controls with “stimulator on” versus “stimulator off” settings, many patients themselves reported being able to discern between on and off states of the stimulator, and therefore cannot be reliably blinded. The judgement of risk of preintervention domains (confounding, selection, and classification biases) ranged from moderate to serious, where moderate was the lowest possible risk of bias for intervention studies. Most studies were considered low risk for deviation from intended interventions (n = 53) and low risk for missing data (n = 65). Studies ranged from low to moderate with regards to risk of bias for selective reporting.

6. Safety of SCS
SCS is well-documented as a safe treatment for chronic pain due to its reversible and minimally invasive characteristics. Catastrophic complications, such as life-threatening infections or new neurological deficits, are incredibly rare, noting only one reported case of death due to infection and one reported case of paralysis from epidural abscess prior to 2007. The incidence of minor complications with SCS has been reported to be around 30%–40%, though these minor complications occur within 12 months of implantation and are generally resolved. Complications of mechanical origin (rate of 24%–50%), such as lead fracture or disconnection (rate of 5%–9%), lead migration (rate of 0%–27%), or implantable pulse generator failure (rate of 1.7%), are far more common than complications of biological origin (rate of 7.5%), including events like infection (rate of 3%–8%) or dural puncture (rate of 0.3%–2%). However, the possibility of adverse events in the use of SCS in patients with SCI, particularly with regards to infection, needs further study. Though not present in the studies listed above, there have been a number of patients with surgical site infections after epidural SCS placement. The results of this review indicate that both epidural and transcutaneous SCS are viable options for increasing voluntary motor response of the upper and lower limbs, trunk stability, and autonomic function in patients with SCI. The limited number of complications suggest that both forms of SCS are safe and well tolerated. Both epidural and transcutaneous SCS had cases of dermatologic issues that resolved with time. The 2 reports of potential autonomic dysreflexia self-resolved, one caused by epidural SCS and the other by transcutaneous SCS. Across the studies listed above, there was a 4% complication rate, noting 5 potential cases of autonomic dysreflexia, 3 cases of skin breakage or infection, 1 case of mild drainage from the surgery site, 1 case of a mild skin allergy, 2 cases of a single nonfunctional lead, and 1 case of ankle edema. Stimulation parameters were adjusted to lower levels of patient discomfort, though discomfort at increased frequencies of stimulation (~100 Hz) was more prevalent with epidural SCS.

While research has shown using SCS is a safe and effective option in treating patients with SCI, many steps are necessary for SCS to become a standard treatment for return of motor and autonomic function in SCI patients. The number of clinical trials examining SCS use in SCI has increased over the past 5 years, especially with regards to volitional and nonvolitional movement. A search of ongoing clinical trials pertaining to SCS use in SCI patients was conducted using the publicly available trial registry, ClinicalTrials.gov (https://clinicaltrials.gov/). This search was conducted on March 12th, 2022 and included the search terms “spinal cord injury” and “spinal cord stimulation.” After screening for trials specifically using eSCS or tSCS, 60 active trials were identified, with 23 studies using eSCS, 35 studies using tSCS, and 2 studies using eSCS as well as tSCS. 4 studies are currently examining the use of SCS on children with SCI. Forty studies are examining SCS effects on sensorimotor function (both volitional and nonvolitional), 7 studies are examining effects of SCS on autonomic cardiovascular function, 9 studies are examining effects of SCS on pulmonary function, and 9 studies are examining effects of SCS on the genitourinary system. Additionally, 3 studies are examining effects of SCS on muscle electrical activity and 4 studies are examining effects of SCS on muscle spasticity. Additionally, many new clinical trials are studying different stimulation parameters as well as concurrent pharmacologic treatments. To move towards further clinical translation, further clinical trials should adopt more robust research designs to reduce bias, such as including control groups, incorporating randomization before implantation, and adding further blinding to patients and assessors, as well as developing the framework for multicenter studies in an effort to include more patients and make data accessible for external analysis.

The use of SCS to induce functional recovery after SCI is still a fairly new technique—the data gathered across the studies listed in this paper are mostly from case or case-series studies with no appropriate control groups to assess if SCS is a better treatment than placebo or the current standard of care. The patients in the reviewed studies were mostly male (n = 257), indi-
cating a gender bias—though males are more commonly injured, these results suggest that more females should be included in SCS studies to identify potential gender differences. Additionally, age ranged from 18 to 66 years, but the age recommended for implantation may differ based on the indication for SCS.\textsuperscript{126,127} Time between injury and enrollment ranged from 0.1 to 41.1 years, indicating that delayed implantation was not contraindicated. The patients studied had a wide range of injury levels, demonstrating the effectiveness of SCS in treating diverse patient populations, but making it difficult to draw conclusions on the most suitable patient population for SCS. Our review of the literature reveals that further standardization of optimal stimulation frequency and location to elicit specific outcomes, such as bladder control or autonomic cardiovascular response, are necessary. Currently, stimulators used in SCS are designed for chronic pain treatment rather than return of sensorimotor or autonomic function—given that the optimal stimulation parameters differ greatly both between individuals and between specific functions, both sensorimotor and autonomic, stimulators with greater programmability would be greatly beneficial for further studies. Given rat model data has shown that SCS amplifies pre-existing signals in the remaining intact tissue after SCI, individuals with anatomically intact tissue at the injury site may be good candidates for treatment.\textsuperscript{4} However, further research needs to be done to assess which subjects will respond most efficaciously to neuromodulation therapy, and whether eSCS or tSCS will be of greatest utility for each individual.

**CONCLUSION**

The results of this review indicate that epidural and transcutaneous spinal cord stimulation are active areas of study holding promise for improving motor and autonomic function following SCI. Although the results of these studies are positive, significant research still needs to be performed to transition the use of SCS in the restoration of function following SCI from basic research to clinical use. Further mechanistic studies are needed to define optimal stimulation parameters and develop a greater understanding of how SCS interacts with residual connections across the SCI lesion. Based on the current reported results, it is likely that restoration of different functions require optimization by delivering stimulation at distinct spinal levels and with specific parameters. Additionally, structured clinical trials with increased number of subjects need to be performed to evaluate the parameters necessary for greatest efficacy in eSCS and tSCS treatment of patients with chronic SCI.

**NOTES**

**Supplementary Materials:** Supplementary Table 1 can be found via https://doi.org/10.14245/ns.2244652.326.

**Conflict of Interest:** The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: AL, ES; Data curation: AL, ES; Formal analysis: AL, ES; Writing - original draft: AL, ES; Writing - review & editing: AL, ES, JSC, SRP, DAB, JSF.

**ORCID**

Alice Lin: 0000-0002-2526-477X
Elias Shaaya: 0000-0002-2243-7954
Jonathan S. Calvert: 0000-0001-7197-9082
Samuel R. Parker: 0000-0001-9552-3354
David A. Borton: 0000-0003-0710-3005
Jared S. Fridley: 0000-0002-6336-5950

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## Supplementary Table 1. ROBINS-I risk of bias analyses of SCS studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Confounding</th>
<th>Selection</th>
<th>Classification</th>
<th>Deviations from intended interventions</th>
<th>Missing data</th>
<th>Measurement of outcomes</th>
<th>Selection of reported results</th>
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### Supplementary Table 1. ROBINS-I risk of bias analyses of SCS studies (continued)

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ROBINS-I, Risk of Bias in Non-Randomized Studies of Interventions; SCS, spinal cord stimulation.
In this systematic review, Lin et al. comprehensively assess the functional restoration from spinal cord stimulation in 327 patients with chronic, traumatic spinal cord injury identified in 50 case or case-series studies and 21 clinical trials. During stimulation, an overwhelming majority of patients had improvement in sensorimotor function and autonomic genitourinary, pulmonary, and cardiovascular function. Volitional movement lasting for months in the absence of stimulation was seen in some patients. The majority of functional improvements in volitional movement were paired with intense motor training and most patients did not completely regain volitional movement. There was a 4% complication rate with autonomic dysreflexia and skin breakdown or infection reported as the most common complications.

The limitations of the current research were clearly discussed including the heterogeneity of this patient population, the varied stimulation parameters of transcutaneous and epidural spinal cord stimulation, the numerous locations of the lead placements, and the wide range of functional outcomes evaluated. The authors appropriately suggest that future studies decrease the bias in outcome measurements due to lack of control groups and lack of blinding to patients and assessors. Moreover, they encouraged multicenter studies to increase patient enrollment, as well as the development of greater programmability of the stimulators to allow determination of optimal stimulation frequency and modalities.

The functional improvement demonstrated during transcutaneous and epidural spinal cord stimulation in patients with chronic, traumatic spinal cord injury has generated tremendous excitement around the possibility of meaningful functional recovery and neuro-modulation of previously “dormant” neural pathways. These findings have stimulated numerous clinical trials and industry funding to develop programmable stimulators that enable targeted spinal cord stimulation. Once these devices are deemed safe and efficacious, then regulatory clearance in Asia, Europe and the United States will allow further access to these devices so that more patients can be enrolled in more robust multicenter, clinical trials. It is probable that these studies will demonstrate that targeted, transcutaneous and epidural spinal cord stimulation will promote meaningful functional gains for patients with chronic, traumatic spinal cord injury.

Conflict of Interest: The author has nothing to disclose.
REFERENCE

Effects of D-Serine and MK-801 on Neuropathic Pain and Functional Recovery in a Rat Model of Spinal Cord Injury

Dongwoo Yu1,*, Seul Ah Mun2,*, Sang Woo Kim1,*, Dae-Chul Cho2, Chi Heon Kim1, Inbo Han1, Subum Lee5, Sang-Woo Lee2, Kyoung-Tae Kim2

1Department of Neurosurgery, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu, Korea
2Department of Neurosurgery, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
3Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea
4Department of Neurosurgery, CHA University, School of medicine, CHA Bundang Medical Center, Seongnam, Korea
5Department of Neurosurgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

Objective: Neuropathic pain is a common secondary complication of spinal cord injury (SCI). N-methyl-D-aspartate (NMDA) receptor activation is critical for hypersensitivity in neuropathic pain. This activation requires the binding of both glutamate and the D-serine co-agonist to the NMDA glycine site. We evaluated the effects of D-serine on neuropathic pain after SCI and explored the underlying molecular mechanisms.

Methods: Anesthetized rats underwent T9 spinal cord contusion (130 kdyn). D-serine (500 and 1,000 mg/kg) and MK-801 hydrogen maleate (2.0 mg/kg) were injected daily for 2 weeks, starting the day after SCI. Functional outcomes were assessed according to the Basso, Beattie, and Bresnahan scale, while histological outcomes were evaluated based on lesion volume and spared tissue area. Mechanical allodynia and thermal hyperalgesia were evaluated by measuring the withdrawal threshold of a von Frey filament and hot/cold plate latency. Western blotting was performed to determine the expression levels of Trpv1, Nav1.9, calcitonin gene-related peptide (CGRP), and β-actin in damaged tissue.

Results: The withdrawal threshold values and latency of the D-serine group were significantly lower than those of the noninjection group. The MK-801 group showed higher threshold values and latencies than the other groups. Western blotting showed increased Nav1.9 and Trpv1 levels and lower CGRP levels in the D-serine group, whereas the MK-801 group showed the opposite results.

Conclusion: D-serine increases neuropathic pain after traumatic SCI by mediating the NMDA receptor. NMDA receptor antagonists alleviate neuropathic pain after traumatic SCI.

Keywords: Serine, MK-801, NMDA, Spinal cord injuries, Neuropathic pain

INTRODUCTION

Neuropathic pain is a common complication of traumatic spinal cord injury (SCI) occurring in 37.8% to 60.7% of cases following acute SCI.1-3 In peripheral neuropathy, the peripheral terminals of pain-processing unmyelinated C fibers and thinly myelinated Aδ-fibers can spur the development of neuropathic pain after being affected by metabolic damage, toxins, medications, cytokines, and other inflammatory mediators, resulting in fiber density changes and neuronal hyperexcitability.4,5
Peripheral nerve damage provides an opportunity for maladaptation at every point in the pain pathway. After peripheral nerve injury, subsequent central nervous system changes contribute to central sensitization. In central neuropathy, SCI causes direct and indirect spinal damage that leads to changes in neurochemical features in the nervous system, including sodium ion channels; voltage-gated calcium channels; glutamate and gamma-aminobutyric acid metabolism; and serotonergic, noradrenergic, opioid, and N-methyl-d-aspartate (NMDA) receptors. Neurochemical and excitotoxic changes can cause the release of excitatory amino acids such as glutamate, produce free radicals and reactive oxygen species, and cause an imbalance in ionic gradients. These maladaptive changes in neurons along the nociceptive pathway can lead to neuropathic pain following SCI.

NMDA receptor activation causes the spinal cord neurons to become more responsive to all inputs, including those from damaged or sensitized nociceptors and low-threshold mechanoreceptors, resulting in central sensitization. Central sensitization plays a fundamental role in the development of neuropathic pain, in which NMDA receptor activation is a key mechanism. This activation requires the binding of not only glutamate but also the coagonist D-serine for efficient receptor opening. D-serine plays an important role as a gliotransmitter released from astrocytes and contributes to the development of neuropathic pain. Evidence to date supports the hypothesis that D-serine is involved in neuropathic pain. However, most studies reported so far have focused on peripheral neuropathy induced in animal models.

Based on these previous results, we hypothesized that D-serine plays an important role in the development of neuropathic pain after traumatic SCI. It is possible that D-serine-induced pain after SCI was caused by activation of NMDA receptor and calcium inflammation of nociceptors and neuronal calcification. However, few studies have reported that D-serine causes neuropathic pain following traumatic SCI. Thus, this study analyzed whether D-serine induces neuropathic pain after traumatic SCI and tested whether the mechanism is mediated by NMDA receptors (Fig. 1A).

MATERIALS AND METHODS

1. Animals and Cord Injury Model

All animal testing in this study was conducted at our university, which follows the National Institute of Health Guide for the Care and Use of Laboratory Animals (KNU-2020-0024). The animals were randomly assigned to 5 groups (n = 30 per group): sham group, SCI group, SCI with D-serine 500 group (intraperitoneal [i.p.] injection of 500 mg/kg D-serine for 14 days beginning 1 day after SCI), SCI with D-serine 1000 group (i.p. injection of 1,000 mg/kg D-serine for 14 days beginning 1 day after SCI), and SCI with MK-801 group (i.p. injection of 2.0 mg/kg MK-801 for 14 days beginning 1 day after SCI). The rats were anesthetized via i.p. injection of a mixture of ketamine (90 mg/kg) and xylazine (10 mg/kg). After anesthesia, the spinal column was exposed from T8 to T10 and damaged at T9 with a 130 kdyn force applied using an infinite horizon impactor. Sham surgery was performed by exposing the spinal column in the same manner but without cord injury. Postoperatively, the urine was expelled by applying pressure to the abdomen twice daily for 6 weeks.

2. Drug Administration

The following drugs were injected i.p.: D-serine (500 mg/kg, 1,000 mg/kg) and MK-801 hydrogen maleate (MK-801; 2.0 mg/kg, a selective antagonist that binds to sites located within NMDA-associated ion channels) purchased from Sigma-Aldrich (St. Louis, MO, USA). The drugs were injected at the same time every day for 2 weeks, starting from the day after surgery. Thirty minutes before the evaluation of functional outcomes, all compounds were administered intraperitoneally. The choice of dose and pretreatment time for each drug were derived from previously reported studies. The experimental design is illustrated in Fig. 1B.

3. Behavioral Assessments

At 1, 7, 14, 21, 28, 35, and 42 days following cord injury or sham surgery, the functional outcome of the rats was assessed using the Basso, Beattie, and Bresnahan’s open-field locomotor rating scale (BBB score, 0–21 points). The functional scores of the hind limbs observed for each animal for 1 minute were recorded and averaged by 2 investigators who were blinded to the group assignments. The ladder rung test was performed simultaneously with the BBB test. This test assesses the animal’s ability to accurately position itself on a step with its hind foot on a metal bar placed at 1.5 cm within a total length of 1.2 m while crossing the ladder. The test also evaluates fore- and hindlimb coordination. The animals were videotaped at 3 intersections. The video data were analyzed by counting the positions of the correct hind paws on the bar. Each item was scored out of 10. In all experiments assessing functional outcomes, the rats underwent stabilization and training for 2 weeks before surgery. During the follow-up behavioral assessments, a blinded experi-
Fig. 1. (A) Experimental animal design. The rat spinal cord is damaged at the T9 site using 130 kdyn of force on an infinite horizon impactor. Intraperitoneal D-serine (500 or 1,000 mg/kg) or MK-801 hydrogen maleate (MK-801; 2.0 mg/kg) is injected at the same time every day for 2 weeks, starting 1 day after surgery. (B) Schematic diagram of the proposed mechanisms for neuropathic pain after spinal cord injury. Increased D-serine production after the injury contributes to the development of neuropathic pain by inducing N-methyl-D-aspartate (NMDA) receptor activation. Exogenous MK-801 administration attenuates the spinal cord injury-induced development of neuropathic pain by inactivation of NMDA receptors. i.p., intraperitoneal; SCI, spinal cord injury.

4. Processing of Spinal Cord Tissue
We prepared 3 sections per animal and sacrificed a total of 3 rats for each target. All animals used in this study were deeply
anesthetized, perfused with phosphate-buffered saline (PBS) through the left ventricle to remove blood, and then perfused with 4% paraformaldehyde dissolved in 0.1 M PBS (pH 7.4) solution and fixed. After fixation, the spinal cord, approximately 15 mm above and below the epicenter, was collected, immersed in paraffin, and cut into 4-μm-thick sections. The cut tissue was deparaffinized and rehydrated for hematoxylin and eosin (H&E) and alizarin red S (ARS) staining. H&E staining was performed according to the manufacturer’s instructions (ab245880; Abcam). For calcium staining, the slides were incubated in 2% ARS (Sigma A-5533) at pH 4.3 (adjusted with ammonium hydroxide) and stained to remove excess dye. The slides were then soaked 20 times in acetone and 20 times in acetone-citrate solution. Section images taken with a Nikon Eclipse 80i were traced using ImageJ software ver. 1.53 (National Institutes of Health, Bethesda, MD, USA) to delineate and quantify the lesions. We identified the lesion site based on the results of H&E staining and confirmed it after merging the 3 based on the lesion site. Targets are merged with different colors by differentiating the 2nd antibody to proceed with fluorescent staining, and then quantification is performed after classifying the colors in which each target in the specified area appears in the Image J program, and then merging again. We performed ARS staining to highlight and detect calcium deposits in tissues or vasculature by binding to calcium through a chelation process, primarily to visualize the results at the cellular level.

5. Nociceptive Behavioral Tests
Von Frey filament and hot and cold plate experiments were performed every week to measure the degree of mechanical allodynia and thermal hyperalgesia after the development of the animal model. In this study, the hot plate test was based on methods in published paper.23 Before proceeding with the von Frey filament experiments, the rats were placed in an acrylic box installed on a wire mesh test bench measuring 2 × 2 mm and allowed to acclimatize for at least 15 minutes. When rat movements quieted, a medium-thick von Frey filament (Stoelting Co., Wood Dale, IL, USA) was used to make vertical contact with the affected sole and held in place for 5–6 seconds. A positive reaction was defined as avoidance, flinching, or licking of the sole. The stimulation was performed using a weak filament if a positive reaction was observed; otherwise, the stimulation was performed with a strong filament, and the continuous response was evaluated using the up-down method. The hot plate test is another classic test in the field and is typically set up to observe a response between 5 and 15 seconds. The temperature is often set at 52°C or 55°C and rarely at 48°C. A baseline latency of 5–15 seconds for paw licking is generally observed at 52°C or 55°C. In contrast to tail flick test and other tests that apply thermal stimulation to the hind paws, rats with SCI cannot remove their hind limbs from the stimulation. So, the results were limitingly gathered the nociceptive response time of the rat from the upper spinal pathway by placing on a metal surface maintained at a constant temperature.23,24

6. Western Blot Analysis
Under anesthesia, the rats were bled through transcardial perfusion with warm 1× PBS. The thoracic spinal cords of the
rats were then rapidly dissected and immediately homogenized on ice in cold RIPA buffer (Cell Signaling) containing a protease inhibitor cocktail (GenDEPOT). The homogenate was centrifuged at 13,000 rpm and 4°C for 30 minutes. Protein quantification of the homogenates was performed using the BCA Protein Assay (Thermo Scientific, Rockford, IL, USA). The proteins were separated by molecular weight by sodium dodecyl sulfate-polyacrylamide gel electrophoresis using a 10% gel and transferred to a nitrocellulose membrane. The membrane was blocked using 5% nonfat milk powder in Tris-buffered saline containing 0.1% Tween-20 and incubated at room temperature for 1 hour. To determine the expression levels of Trpv1, Nav1.9 (Alomone Labs, 1:200), calcitonin gene-related peptide (CGRP; Cloud-Clone Corp, 1:200), and β-actin (Sigma-Aldrich, 1:1,000) in the damaged tissue, the membrane was incubated overnight at 4°C in a buffer with diluted antibody and then incubated with a secondary antibody (all Cell Signaling) bound to horseradish peroxidase for 1 hour at room temperature. The proteins were detected on a LAS 4000 instrument (GE Healthcare, Chicago, IL, USA) using a chemiluminescent reagent (Thermo Fisher Scientific Inc., Waltham, MA, USA) and quantified using ImageJ software (National Institute Health, Bethesda, MD, USA).

Fig. 3. (A) Histologic outcomes after spinal cord injury. (B, C) Graphs showing the areas of spared tissue from 5 mm rostral to 5 mm caudal to the lesion epicenter and quantitative lesion volumes for all groups. SCI, spinal cord injury. *p < 0.05. **p < 0.01.
7. Statistical Analysis

All values are presented as means ± standard error of the mean. The statistical significance of the differences between groups was assessed using 1-way analysis of variance (ANOVA), followed by a post hoc least-significant difference range test. The differences in behavioral scores between the groups at each time point were analyzed using repeated-measures ANOVA with post hoc Tukey and Kruskal–Wallis tests. A p-value of <0.05 and p < 0.01 were considered statistically significant. All statistical comparisons were performed using IBM SPSS ver. 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Effects of Drugs on Functional Outcomes in the SCI Rat Model

The rats in the sham operation group showed normal gait (score 21) after surgery. The MK-801 group showed significant functional recovery 21 days postinjury (dpi) compared to the SCI and D-serine groups. The mean BBB scores did not differ significantly at any time point in the SCI, D-serine 500, and D-serine 1,000 groups (Fig. 2A). In ladder rung test conducted at 21, 28, 35, and 42 dpi, D-serine group had significantly more foot faults than MK-801 group (Fig. 2B).

2. Histopathological Evaluations of the Spinal Cord

To investigate the effects of D-serine and MK-801 on the spared tissue area and lesion volume in the spinal cord after SCI, the rats were euthanized. The MK-801 group showed a lower lesion volume and a higher spared tissue area compared to those in the SCI and D-serine groups (Fig. 3). These results were consistent with the functional outcomes.

3. Effects of Drugs on Mechanical and Thermal Allodynia

The results showed that cord injury-induced mechanical allodynia and thermal hyperalgesia postoperatively. At 14, 21, and 35 dpi, rats with SCI in the D-serine 500 group showed a significant decrease in the withdrawal threshold to mechanical stimulation compared to rats in the SCI group. The withdrawal thresholds in the MK-801 group were significantly higher than those in the SCI, D-serine 500, and D-serine 1,000 groups at 7, 14, 21, 35, and 42 dpi, respectively (Fig. 4A). We observed significant increases in the withdrawal latency of the D-serine 1,000 group compared to those in the SCI group at 14, 21, 28, and 42 dpi. However, the MK-801 group showed a significant increase in withdrawal latency compared to those in the SCI, D-serine 500, and D-serine 1,000 groups at 7, 14, 21, 35, and 42 dpi (Fig. 4B).

4. Expression Levels of Nav1.9, Trpv1, and CGRP

We examined the expression levels of members of the pain signaling pathways, including Nav1.9, Trpv1, and CGRP, in Western blot assays of samples collected at 1, 7, 14, and 42 days after SCI (Fig. 5A). The expression levels of Nav1.9 and Trpv1 in the spinal cord were significantly higher in the D-serine group than those in the MK-801 group (Fig. 5B, C). Conversely, CGRP lev-
els in the spinal cord were significantly higher in the MK-801 group than those in the D-serine group (Fig. 5D).

5. Calcium Deposition in Injured Spinal Cords

ARS staining was performed to investigate calcium deposition in the spinal cord after SCI. The D-serine group showed a larger area stained with alizarin S compared to that in the MK-801 group (Fig. 6).

DISCUSSION

The 2 important results of this study were as follows: first, the i.p. administration of D-serine significantly increased neuropathic pain in the SCI rat model. Second, rats that received an i.p. injection of MK-801, an NMDA receptor antagonist, showed significantly decreased neuropathic pain compared to the SCI and D-serine groups. In addition, i.p. injection of MK-801 promoted functional recovery. Although the estimated incidence of neuropathic pain after traumatic SCI is up to 60%, few stud-

Fig. 5. (A) Expression levels of Nav1.9, Trpv1, and calcitonin gene-related peptide (CGRP) at 1-, 7-, 14-, and 42-day postinjury. (B–D) The bar graphs show these expression levels in the spinal cord for all groups. SCI, spinal cord injury. *p < 0.05. **p < 0.01.
ies have reported on neuropathic pain after traumatic SCI, especially on the effects of D-serine and MK-801. Thus, this study investigated the effects of D-serine and MK-801 on neuropathic pain after traumatic SCI in a rat model.

NMDA are heteromeric protein complexes. The 3 families of NMDA subunits are NR1, NR2, and NR3. The pathological role of NMDA receptors in neuropathic pain has been primarily studied in animal models of peripheral nerve injury. Isaev et al. reported that the bath application of NMDA induced a greater increase in whole-cell currents and calcium influx in spinal lamina II neurons in nerve-ligated rats compared to that in control rats. Ultenius et al. reported a significantly increased phosphorylation rate of the NR1 subunit of the NMDA receptor in the dorsal horn of the spinal cord after sciatic nerve ligation in rats. NMDA receptors in the dorsal horn play a critical role in nociceptive transmission and synaptic plasticity. The activation of NMDA receptors requires the simultaneous binding of glutamate and the coagonists D-serine or glycine, which increases the affinity of glutamate binding and facilitates excitatory transmission. D-serine is a potent coagonist of the NMDA glutamate receptor and appears to play a major modulatory role in NMDA receptor-mediated neurotransmission, neurotoxicity, synaptic plasticity, and cell migration. Choi et al. reported that D-serine increased glutamate receptor phosphorylation in a protein kinase C-dependent manner, contributing to the development of mechanical allodynia. Our results showed that the i.p. administration of D-serine significantly increased glutamate receptor phosphorylation and activate NMDA receptors, leading to spinal neuron sensitization. Thus, we propose that D-serine plays a role in the aggravation of mechanical allodynia and thermal hyperalgesia in a rat model of SCI.

MK-801 is a noncompetitive antagonist of NMDA receptors.
In the present study, the i.p. administration of MK-801 significantly reduced established mechanical and thermal allodynia in SCI rats. Thus, the exogenous administration of MK-801 may prevent pain perception by decreasing NMDA receptor activation to prevent the development of central sensitization. Our results regarding mechanical allodynia are consistent with those of other reports on the role of NMDA antagonist administration in a neuropathic pain model but discordant with those on thermal hyperalgesia. Thus, the role of NMDA receptors in thermal hyperalgesia remains controversial. Bennett et al. reported that the intrathecal application of D-AP5, a competitive NMDA receptor antagonist, attenuated mechanical allodynia, but not thermal hyperalgesia, in a rodent spinal hemisection model of SCI. Ren et al. reported that intrathecal administration of MK-801 significantly attenuated thermal hyperalgesia in a carrageenan model of acute inflammation. The effectiveness of NMDA receptor antagonists differs in various neuropathic pain models. In this study, both mechanical allodynia and thermal hyperalgesia increased after the i.p. administration of D-serine. Therefore, exogenous administration of an NMDA antagonist attenuated the SCI-induced development of mechanical and thermal allodynia.

In this study, the i.p. administration of MK-801 was effective in the functional recovery of SCI in rats. Traumatic SCI causes an excessive accumulation of glutamate outside cells and leads to an increased flux of calcium ions into the cells via NMDA receptors. Excessive glutamate release may damage oligodendrocytes in SCI. Calcium dysregulation is a key step in the secondary injury cascade after SCI. Therefore, NMDA receptors may be effective therapeutic targets for preventing secondary injury in SCI. Esposito et al. reported that the i.p. administration of MK-801 in SCI rats significantly improved the recovery of locomotor function. Gaviria et al. reported that gacyclidine, a noncompetitive NMDA receptor antagonist, attenuated spinal cord damage in rats with contusive SCI. Our results are consistent with those of other studies on the effectiveness of NMDA antagonists in functional recovery after traumatic SCI.

In this study MK-801 was administered systemically, it could be affected off-target effects about cognitive function or behavior. It is well known that systemic administration of MK-801 causes enhanced locomotion in rodents. Wisnewski and Lauwereyns reported that systemic administration of a relatively small dosage of MK-801 facilitates performance. Similarly, systemic administration of MK-801 may have affected functional recovery due to the off-target effect in this study.

This study had some limitations. First, we did not study about the neuropathic pain and functional recovery by a specific D-serine antagonist. Because of MK-801 is not a specific D-serine antagonist, to determine whether the D-serine participate in excitotoxic neurotransmitter-induced central sensitization needs additional study. Second, we did not assess the differences in effects according to the dose of MK-801 administered. As we only administered a dose of 2.0 mg/kg, additional experiments on the effects of different doses are needed. Also, since the concentration was not measured at each time point, the difference in the result value depending on the concentration could not be explained. Third, we only administered drugs via intraperitoneal injection. Systemic injections may interfere with peripheral mechanisms. Fourth, there is a lack of a definite mechanism for the effect of NMDA antagonists on thermal hyperalgesia in the rat model of SCI. In many rat models of peripheral neuropathy, the administration of an NMDA receptor antagonist reduces mechanical allodynia but does not affect thermal hyperalgesia. However, in the present study, MK-801 inhibited both SCI-induced mechanical allodynia and thermal hyperalgesia. Further studies are needed to characterize the discordant results between SCI and peripheral nerve injury models.

**CONCLUSION**

In our study, D-serine injection increased neuropathic pain following traumatic SCI. This mechanism was mediated by the NMDA receptor, and NMDA receptor antagonist alleviated neuropathic pain after traumatic SCI.

**NOTES**

Conflict of Interest: The authors have nothing to disclose.

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**ORCID**

Dongwoo Yu: 0000-0003-2100-5452
Seul Ah Mun: 0000-0002-4447-7930
Sang Woo Kim: 0000-0002-1439-7964
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Dae-Chul Cho: 0000-0002-2899-8015
Chi Heon Kim: 0000-0003-0497-1130
Inbo Han: 0000-0002-0834-9325
Subum Lee: 0000-0003-4732-8137
Sang-Woo Lee: 0000-0002-1751-2163
Kyoung-Tae Kim: 0000-0003-4867-6854

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Meta-Analysis on the Effect of Hypothermia in Acute Spinal Cord Injury

Hong Kyung Shin, Jin Hoon Park, Sung Woo Roh, Sang Ryong Jeon
Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Objective: Acute spinal cord injury (SCI) can result in debilitating motor, sensory, and autonomic dysfunction. As a treatment option, therapeutic hypothermia has been researched to inadequate pharmaceutical treatment, except for methylprednisolone. In this article, we systematically meta-analyzed to clarify the effect of hypothermia in acute SCI on neurological outcomes.

Methods: The PubMed, Embase, Web of Science, and Cochrane clinical trial databases were systematically searched until June 30, 2022. The proportion of cases with improved neurological status after hypothermia in acute SCI were pooled with a random-effects model. Subgroup analyses for the method of hypothermia and injury level were conducted.

Results: Eight studies with a total of 103 patients were included. Hypothermia in acute SCI improved neurological function by 55.8% (95% confidence interval [CI]: 39.4%–72.1%). The subgroup analysis revealed that the pooled proportion of cases showing neurological improvement was higher with systemic hypothermia (70.9%) (95% CI, 14.9%–100%) than with local hypothermia (52.5%) (95% CI, 40.4%–64.5%), although the subgroup difference was not statistically significant (p = 0.53). Another subgroup analysis revealed that the proportion of cases with neurological improvement did not differ statistically between the cervical spine (61.4%) (95% CI, 42.2%–80.6%) and thoracic spine injury groups (59.4%) (95% CI, 34.8%–84.0%) (p = 0.90).

Conclusion: This meta-analysis identified that more than 50% of patients showed neurological improvement after hypothermia following acute SCI in general. A multicenter, randomized, double-blind study with larger sample size is necessary to validate the findings further.

Keywords: Acute, Hypothermia, Meta-analysis, Spinal cord injury

INTRODUCTION

Acute spinal cord injury (SCI) is a potentially debilitating neurological disorder that can result in partial or total loss of motor, sensory, and autonomic function. In addition to a poorer quality of life for the patients, SCI also has negative socioeconomic effects on their families and on society. There are currently no effective therapeutic approaches for the treatment of acute SCI, although various potential drugs and treatments are being researched. Surgical treatment with adequate decompression and fixation has the possibility of functional recovery of the neural structures. However, the outcomes of additional therapeutic pharmacological treatment are unsatisfactory, except with methylprednisolone; nevertheless, the evidence in support of methylprednisolone is inconclusive.

Recently, therapeutic hypothermia has emerged as one of the most promising treatments. It has been studied experimentally and clinically for a variety of disorders, including cerebral aneurysm, traumatic brain injury (TBI), aortic arch aneurysm, cardiac arrest, and acute SCI. The purpose of therapeutic hypothermia is to decrease the metabolic rate for oxygen, hence lowering lactate levels and other byproducts of anaerobic metabo-
lism and minimizing cellular acidosis. It is hypothesized that therapeutic hypothermia can inhibit several metabolic pathways, inflammatory responses, and apoptotic processes that occur following an ischemia cascade.²

Studies on animals have consistently demonstrated its effectiveness in functional recovery after SCI.²⁻⁵ Furthermore, clinical trials on therapeutic hypothermia have shown positive outcomes.⁶⁻⁷ It can be induced as local and systemic hypothermia, and each has its pros and cons. While systemic hypothermia can lead to rapid and persistent hypothermic status through surface cooling, endovascular heat exchange catheters, or cold intravenous infusions, local hypothermia has the advantage of direct irrigation to the intradural or extradural space with cold saline without the risk of systemic consequences.⁸ However, human investigations on the effects of hypothermia have yielded inconsistent results, depending on the clinical circumstances and methods of hypothermia, although animal studies have showed usually positive results.

The purpose of present meta-analysis is to assess the effect of hypothermia on acute SCI. We specifically evaluated whether the influence of hypothermia on neurological outcome varies according to the method of hypothermia and the level of injury.

MATERIALS AND METHODS

This research followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.⁷ We conducted a meta-analysis and systematic review of clinical studies on therapeutic hypothermia for the treatment of acute SCI.

1. Search Strategy
We searched records in PubMed, Embase, Web of Science, and Cochrane clinical trial since their inception through June 30, 2022. The following search queries included SCI and hypothermia synonyms and related terms: (spine OR "spinal cord" OR vertebral) AND (injury OR injuries OR injured OR trauma OR traumatic) AND (hypothermia OR hypothermic OR cooling OR cooled). Furthermore, the reference lists of the indicated articles were searched for further relevant studies. Two reviewers worked separately on the literature search and selection. The disagreements between the reviewers were resolved after the discussion.

2. Study Selection
Patients, interventions, outcomes, and study design (PICOS) criteria were used to choose inclusion for the study. PICOS criteria in this article are as follows: (1) "patients” with acute SCI, (2) hypothermia treatment as the “intervention,” (3) no relevant “comparator,” (4) neurological outcomes as the “outcome,” and (5) original articles for “study design.” The following were the exclusion criteria: (1) nonoriginal articles, (2) not in the field of interest, (3) not written in English, (4) overlap in study population, (5) the number of populations is less than five, and (6) insufficient information on study outcomes. When research populations are overlapped, we included the study that had the most extensive data.

3. Extraction of Data and Quality Assessment
Characteristics of included studies were extracted using a standardized form, including author, publication year, country, the number of patients, age, injury level, initial neurological status of American Spinal Injury Association (ASIA) A or complete deficit, method of hypothermia, route of hypothermia, time from injury to hypothermia, duration of hypothermia, target temperature, number of patients with other treatments such as surgery or steroid, follow-up period, and final neurological outcome. The methodologic quality of the included studies was assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.¹⁰ This tool evaluates 7 assessment domains, which include bias due to confounder, subject selection, classification of interventions, deviations in interventions, missing data, biased measurements, and biased reporting. The potential for bias in each individual domain is rated as either low, moderate, serious, or critical, respectively. After combining the results of these domains, an overall risk of bias judgment was determined to be either low, moderate, serious, or critical. Two reviewers separately extracted the data and evaluated its quality; any discrepancies were resolved through discussion.

4. Statistical Analysis
To analyze the relationship regarding pooled outcomes, we calculated the proportion with 95% confidence interval (CI) for studies. The proportions were pooled using meta-analysis utilizing the random-effects model (DerSimonian-Laird technique) with logit transformation for computing weights. The Cochran Q test and the Higgins I² test were used to assess heterogeneity between the outcomes of the various studies. To assess the presence of publication bias, funnel plots and Egger tests were used.¹¹ Stratification by the method of hypothermia and injury level was done for subgroup analyses. Every test was 2-sided, and a p-value of 0.05 or less was regarded as statistically significant. R software was used to conduct the statistical analysis (ver. 4.0.4;

RESULTS

1. Literature Search

A preliminary literature search utilizing the subject headings revealed 769 articles from PubMed, 1,472 studies from Embase, 838 studies from Web of Science, and 46 studies from the Cochrane clinical trial. There were 1,220 duplicates among these 3,125 studies, thus they were eliminated. After evaluating the remaining 1,905 titles and abstracts, 1,888 were deemed ineligible because they did not match the selection criteria. Ten of the remaining seventeen studies were removed based on the following criteria (Supplementary Table 1): overlap in study populations (n = 3), the number of populations was less than five (n = 6), and insufficient information on study outcomes (n = 1). One paper was added during a manual screening of references. Finally, a total of 8 studies were included in the meta-analysis. Fig. 1 presents the detailed selection process.

2. Study Characteristics

Table 1 summarizes the baseline characteristics of the included studies. The included studies were all retrospective. The studies included a total of 103 patients who were provided hypothermia treatment for SCI. Among the 8 articles included, 6 studies used local hypothermia for 63 patients, and 2 studies used systemic hypothermia for 40 patients.

3. Quality Assessment

The overall quality assessment using the 7 domains of the ROBINS-I tool is shown in Fig. 2. Most domains were assessed as a low to moderate risk of overall bias. However, 1 study (12.5%) was evaluated as a serious risk of bias as 2 methods of hypothermia were used. Two studies (25.0%) were evaluated as having...
<table>
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<th>Study</th>
<th>Country</th>
<th>No. of patients</th>
<th>Mean age (yr)</th>
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<th>Initial neurological status of ASIA A or complete deficit (%)</th>
<th>Method</th>
<th>Route</th>
<th>Median injury to hypothermia time (hr)</th>
<th>Median duration (hr)</th>
<th>Target temperature (°C)</th>
<th>No. of patients with other treatments (%)</th>
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ASIA, American Spinal Injury Association; C, cervical; NR, not reported; T, thoracic.
*L1 is classified as thoracic level.
a low risk of overall bias, and 5 studies (62.5%) were judged as having a moderate risk of overall bias. The detailed results of the quality assessment of each study are presented in Supplementary Table 2.

4. Neurological Status According to the Method of Hypothermia

All 8 studies investigated the neurological status after therapeutic hypothermia in patients with SCI. The changes in neurological status after hypothermia in all studies were stratified by the method of hypothermia and are illustrated in Fig. 3. The proportion of patients with neurological improvement across all 8 studies was 55.8% (95% CI, 39.4%–72.1%). Higgins $I^2$ statistics revealed significant heterogeneity ($I^2 = 67$%). The sub-

Fig. 2. Risk of bias assessment using the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) tool.

Fig. 3. Forest plots of neurological improvement in local and systemic hypothermia. CI, confidence interval; df, degrees of freedom.

Fig. 4. Forest plots of neurological improvement in cervical and thoracic injury. CI, confidence interval; df, degrees of freedom.
group analysis revealed that the proportion of systemic hypothermia patients with neurological improvement was greater than that of the local hypothermia group. (proportion, 70.9%; 95% CI, 14.9%–100.0% and proportion, 52.5%; 95% CI, 40.4%–64.5%, respectively); however, the difference between the groups was not statistically significant (p = 0.53). The funnel plot and Egger test showed no publication bias (Supplementary Fig. 1; Intercept = -0.34, p = 0.48).

5. Neurological Status According to the Injury Level

All 8 studies demonstrated the neurological status according to the injury level. The changes in neurological status after hypothermia in the included studies based on the injury level are illustrated in Fig. 4. Higgins I² statistics revealed significant heterogeneity (I² = 58%). The subgroup analysis suggested that the proportion of patients with neurological improvement was not statistically different between groups with cervical and thoracic spine injuries (p = 0.90) (proportion, 61.4%; 95% CI, 42.2%–80.6% and proportion, 59.4%; 95% CI, 34.8%–84.0%, respectively). The funnel plot and Egger test showed no publication bias (Supplementary Fig. 2; Intercept = -0.51, p = 0.18).

DISCUSSION

Acute SCI is a serious neurological event that can have adverse effects on health, finances, relationships, and quality of life. Many studies and guidelines have been researched for the treatment of acute SCI. However, there are no effective treatments to prevent the deleterious consequences of acute SCI; the evidence regarding the efficacy of methylprednisolone is inconclusive, and it is recommended only for specific indications.

In this meta-analysis, we evaluated the impact of therapeutic hypothermia on the outcomes of patients with acute SCI. The pooled proportion of patients in whom hypothermia for acute SCI led to neurological improvement was 55.8%. Analysis of the outcomes based on the method of hypothermia showed that the pooled proportion of patients with neurological improvement was 52.5% with local hypothermia and 70.9% with systemic hypothermia, respectively (p = 0.53). Furthermore, an analysis based on the levels of injury showed that the pooled proportion of patients with neurological improvement was 61.4% in the cervical spine injuries and 59.4% in the thoracic spine injuries group (p = 0.90). These findings suggest that hypothermia for acute SCI showed an improvement in neurological status in more than 50% of the patients in general.

Although the result of an experimental study varies depending on the protocol of the study, hypothermia for acute SCI has shown generally beneficial effects in experimental animal models. Ok et al. reported that both local (28°C for 48 hours) and systemic hypothermia (32°C for 48 hours) had neuroprotective effects after acute SCI in rats, and systemic hypothermia showed a higher neuroprotective effect due to antiapoptotic and anti-inflammatory effects. In another study on local hypothermia, Casas et al. found no significant additive therapeutic effect of local hypothermia (24°C–35°C) in terms of locomotor outcomes or tissue preservation in rats with moderate thoracic spinal cord contusions. In contrast, systemic hypothermia has shown a consistently beneficial effect on neurological function. Kao et al. revealed that moderate systemic hypothermia (33°C for 2 hours) resulted in lower levels of apoptosis, infarction volume, activated inflammation, and hind limb locomotor dysfunction in a rat SCI contusion model. Moreover, Maybhate et al. showed that moderate systemic hypothermia (32°C for 2 hours) produced improvements in somatosensory evoked potentials and motor function in a rat SCI model.

Local hypothermia has been widely performed in acute SCI. Of the 8 studies included in our analysis, 6 used local hypothermia. There were 2 common methods to achieve local hypothermia: intradural irrigation after durotomy or extradural saline cooling. Intradural irrigation was performed in 4 studies for 0.5 to 3 hours with saline at 4°C to 12°C. Intradural irrigation was performed for a shorter duration with a lower temperature of saline compared to extradural cooling. This method was used only until the 1970s as intradural irrigation causes herniation of the injured spinal cord through the durotomy incisions. Extradural saline cooling was performed in 3 studies for 4 to 120 hours with saline at 6°C to 33°C. Recent studies used cooling of the extradural space method, which achieves constant temperature by placing the heat exchanger tubing system in the epidural space.

Before the 2000s, systemic hypothermia was used in the treatment of some conditions such as cerebral aneurysm, TBI, or aortic arch aneurysm, following its use for cardiac arrest in the 1950s. In early 2010, clinical studies for acute SCI were published from the University of Miami group. They used systemic endovascular hypothermia for 48 hours with a target rectal temperature of 33°C. Dididze et al. reported the effect of systemic hypothermia after SCI as 42.9%. After obtaining promising results from their retrospective data, they conducted prospective research and incorporated their findings in this paper. However, as they did not utilize steroids, it is difficult to directly compare the results with those of previous SCI trials that did
use steroids. In addition, Madhavan et al. used systemic hypothermia for iatrogenic SCI after surgery and reported its efficacy as 100% effect. When there was a traumatic event and loss of intraoperative evoked potential during the surgery, which resulted in neurological deterioration, they promptly began systemic hypothermia following the operation. The immediate response to the neurological alteration and previously performed surgery may have contributed to the superior results. Because the time from injury to hypothermia was substantially shorter than in other research, and surgical decompression was accomplished during the initial surgery, recovery may have been reached in all patients. In addition, the initial neurological status of ASIA A patients before hypothermia was present in only one patient (20%), but in another research, this ranged from 71.4% to 100%. As incompletely injured spinal cord has functional reserve for recovery, there might be more opportunity to recover after hypothermia. Although previous studies on systemic hypothermia usually used surface cooling with water-circulating blankets above and below the patient or cold intravenous fluid infusion, recent studies used endovascular cooling, which is superior to other techniques for the maintenance of systemic hypothermia. Endovascular cooling entails percutaneously inserting a catheter into the inferior vena cava, and saline chilled to 4°C to 5°C is pumped into the catheter balloons. The catheter cools the blood and has a temperature probe for blood temperature monitoring.

Existing research indicates that hypothermia is not an innocuous treatment. Complications of hypothermia could include pulmonary, cardiac, and thromboembolic events. These also occur or are aggravated due to SCI itself. The complications might vary based on the methods of hypothermia. Local hypothermia involves risks related to the techniques used to achieve local cooling. Gallagher et al. used an epidural cooling catheter to induce local hypothermia, following which a surgical site infection occurred in 3 of their 5 patients. The trial was prematurely terminated due to the surgical site infection. Deep systemic hypothermia (24°C–30°C), performed previously, had complications such as cardiac arrhythmias, hypotension, coagulopathies, systemic infections, and electrolyte abnormalities. However, modest systemic hypothermia (32°C–34°C) provides the benefits of hypothermia without additional significant morbidity associated with deep systemic hypothermia. Furthermore, a recent prospective multicenter study showed that modest systemic hypothermia was not associated with an increased risk of complications after SCI. A clinical trial on systemic hypothermia (33°C for 48 hours) following acute SCI (≤ 24 hours) is currently underway.

This meta-analysis has some limitations. First, the number of included studies was few, and the number of included patients was small. However, this may be the first meta-analysis to offer a broad overview of this subject. Second, every study that was included was retrospective study. To confirm the outcomes of our meta-analysis, prospective investigations may be required. Third, the neurological change was assessed as only improved or not, rather than the change of specific grades. This may affect the results of the study, as the neurological improvement can be affected by the initial neurological status. Fourth, the follow-up period varies between studies. As the neurological recovery could be acquired in long term follow-up, the difference of follow-up period could affect the evaluation of the neurological status. Fifth, there was no standardization among the included studies about the basic characteristics of hypothermia, including method of hypothermia, route of hypothermia, time from injury to hypothermia, duration of hypothermia, and target temperature. Therefore, caution is necessary while interpreting our pooled estimates. Lastly, combined treatments other than hypothermia were different between the studies. The use of steroid and the surgical intervention were different between the studies.

CONCLUSION

This present meta-analysis and systematic review found that more than half the patients (55.8%) showed neurological improvement after hypothermia following acute SCI in general. In recent times, intradural local hypothermia is no longer performed, and extradural local hypothermia has shown clinical efficacy. In addition, modest systemic hypothermia using the endovascular cooling technique is currently used without an increased risk of complications. Although systemic hypothermia showed higher neurological improvement rates (70.9%) compared to local hypothermia (52.5%), there was no statistical difference, which might be due to the small number of patients included in the study. A multicenter, randomized, double-blind study with a significantly larger number of patients and a standardized defined methodology is necessary.

NOTES

Supplementary Materials: Supplementary Tables 1, 2 and Figs. 1, 2 can be found via https://doi.org/10.14245/ns.2244444.222.
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**Author Contribution:** Conceptualization: HKS, JHP, SWR, SRJ; Data curation: HKS; Formal analysis: HKS; Methodology: HKS, JHP, SWh, SRJ; Visualization: HKS; Writing - original draft: HKS, SRJ; Writing - review & editing: HKS, SRJ

**ORCID**
- Hong Kyung Shin: 0000-0001-8182-3321
- Jin Hoon Park: 0000-0002-0903-3146
- Sung Woo Roh: 0000-0001-6562-4154
- Sang Ryong Jeon: 0000-0002-8340-7978

**REFERENCES**

Hypothermia in Acute Spinal Cord Injury

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Supplementary Table 1. Studies excluded at the full-text articles assessment

<table>
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<td>Cappuccino et al.,⁸ (2010)</td>
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<td>Piastra et al.,⁹ (2016)</td>
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**Supplementary Table 2. Risk of bias using the Cochrane ROBINS-I Tool**

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Overall risk of bias: equal to the most severe level of bias found in any domain.
ROBINS-I, Risk of Bias in Nonrandomized Studies of Interventions.
Supplementary Fig. 1. Funnel plot of the subgroup analysis by the method of hypothermia.
Supplementary Fig. 2. Funnel plot of the subgroup analysis by the injury level.
SUPPLEMENTARY REFERENCES

Transcription Profiling of a Revealed the Potential Molecular Mechanism of Governor Vessel Electroacupuncture for Spinal Cord Injury in Rats

Xingru Xiao1,2,*, Qingwen Deng1,*, Xiang Zeng1,2, Bi-Qin Lai1,2, Yuan-Huan Ma1,3, Ge Li2,4, Yuan-Shan Zeng1,2,5,6,7, Ying Ding1,2

1Department of Histology and Embryology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China
2Key Laboratory for Stem Cells and Tissue Engineering, Ministry of Education, Sun Yat-sen University, Guangzhou, China
3Guangzhou Institute of Clinical Medicine, Guangzhou First People’s Hospital, South China University of Technology, Guangzhou, Guangdong Province, China
4Medical Research Center, Guangdong Cardiovascular Institute, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Science, Guangzhou, Guangdong, China
5Institute of Spinal Cord Injury, Sun Yat-sen University, Guangzhou, China
6Guangdong Provincial Key Laboratory of Brain Function and Disease, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China
7Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

Objective: This study aimed to identify differentially expressed genes (DEGs) by transcriptome analysis to elucidate a potential mechanism by which governor vessel electroacupuncture (GV-EA) promotes neuronal survival, axonal regeneration, and functional recovery after complete transection spinal cord injury (SCI).

Methods: Sham, control, or GV-EA group adult female Sprague Dawley rats underwent a complete transection SCI protocol. SCI area RNA-seq investigated the DEGs of coding and noncoding RNAs 7 days post-SCI. Gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) enrichment analyses were used to classify DEGs functions, to explain a possible molecular mechanism. Immunofluorescence and BBB (Basso, Beattie, and Bresnahan) score were used to verify a GV-EA treatment effect following SCI.

Results: GV-EA treatment could regulate the expression of 173 mRNA, 260 lncRNA, and 153 circRNA genes among these DEGs resulted by SCI. GO enrichment analysis showed that the DEGs were most enriched in membrane, actin binding, and regulation of Toll-like receptor signaling pathway. KEGG pathway analysis showed enriched pathways (e.g., Toll-like receptors, MAPK, Hippo signaling). According to the ceRNA network, miR-144-3p played a regulatory role by interacting with lncRNA and circRNA. GV-EA also promoted the injured spinal cord neuron survival, axonal regeneration, and functional improvement of hind limb locomotion.

Conclusion: Results of our RNA-seq suggest that post-SCI GV-EA may regulate characteristic changes in transcriptome gene expression, potential critical genes, and signaling pathways, providing clear directions for further investigation into the mechanism of GV-EA in subacute SCI treatment. Moreover, we found that GV-EA promotes neuronal survival, nerve fiber extension, and motor function recovery in subacute SCI.

Keywords: Spinal cord injury, Governor vessel electroacupuncture, RNA sequencing, Bioinformatic analysis, CeRNA
INTRODUCTION

Spinal cord injury (SCI) is a destructive trauma that causes a high rate of disability and serious adverse outcomes. Post-SCI pathological changes occur in 2 phases: primary injury and secondary injury, with the latter well established to cause more deleterious impacts. Secondary injury occurs in acute, subacute, and chronic stages, referring to a dynamic, complex cascade of reactions. The acute phase occurs from 2–48 hours post-SCI and leads to axonal injury and cell necrosis. The subacute phase begins on the second day post-SCI and lasts 2 weeks; during this period there is a phagocytic response to clear cellular debris, and early axonal growth occurs. The chronic phase is primarily characterized by glial scar formation and de-myelination, beginning 2 weeks post-SCI and persisting long-term. SCI treatment is often impossible during the acute phase, so treatment during the subacute stage is common. Advancing functional recovery requires that we find effective therapies that improve neuronal survival and promote axon regeneration.

Electroacupuncture (EA) at governor vessel (GV) acupoints (GV-EA), a traditional Chinese treatment in wide use for various SCI problems, has been reported to reduce secondary injury and promote axonal regeneration and functional recovery. The GV route is similar to that of the spinal cord in anatomy and function, so that GV-EA produces a marked effect. In our previous research, we demonstrated that GV-EA may play an important role in neuroprotection by regulating annexin A5, collapsin response-mediated protein 2, and calcitonin gene-related peptide (CGRP) expression in SCI. In particular, CGRP has been shown to promote regeneration of nerve fibers. GV-EA also increases neurotrophin-3 (NT-3) level in the injured spinal cord, ameliorating the microenvironment and protecting nerve cells by binding with corresponding receptor TrkC. NT-3 also has anti-inflammatory effects and reduces muscle atrophy.

However, the concrete mechanisms of GV-EA effects in SCI have yet to be clarified.

RNA sequencing (RNA-seq) is a powerful tool used in many fields to describe comprehensive genomic functions. Investigating differential gene expression is among its most commonly used functions. Thus, this study aimed to identify differentially expressed genes (DEGs) by transcriptome analysis of RNA-seq to elucidate a potential mechanism of GV-EA neuroprotection for SCI, and evaluated the interaction networks among long noncoding RNAs (lncRNAs), circular RNAs (circRNAs) and mRNA with microRNAs (miRNAs) by using competitive endogenous RNA (ceRNA) fundamentals. The results of bioinformatic analysis showed that GV-EA treatment could regulated 173 mRNAs, 260 lncRNAs, and 153 circRNAs among these differential expression genes after SCI. These DEGs are highly related to inflammation, oxidative stress, apoptosis signaling pathways. In addition, GV-EA also promoted the injured spinal cord neuron survival, axonal regeneration, and functional improvement of hind limb locomotion. To our knowledge, our study is the first to provide a comprehensive description of the mechanism underlying the reparative effects of GV-EA in rats with subacute SCI.

MATERIALS AND METHODS

1. Spinal Cord Injury

The complete transection SCI model used adult female Sprague Dawley rats (aged 2 months, 220–250 g), supplied by the Experimental Animal Center of Sun Yat-sen University, China. All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC), Sun Yat-Sen University (SYSU) (approved No. SYSU-IACUC-2019-B086). All procedures were compliant with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals. Rats were divided into 3 groups: control (gelatin sponge [GS] graft only); GV-EA (GS graft plus GV-EA); and sham (laminctomy only, without SCI).

The animals were anesthetized with 1% pentobarbital sodium (40 mg/kg, intraperitoneal). For SCI, we exposed the T10 spinal cord segments via laminectomy by cutting the dura mater with sterile microforceps and microscissors. A pair of angled microscissors was used to completely transect the T10 spinal cord. Next, a thin slice of gelatin sponge (GS, 2 mm × 2 mm × 1 mm) was immediately transplanted into the injury gap. Postsurgical care included penicillin (50,000 U/kg/day, intramuscular) for 3 consecutive days, and manual emiction 3 times daily until the end of the experiment.

2. EA treatment

The EA stimulation method has been previously described. Briefly, we used 2 pairs of GV acupoints: GV9 (Zhi-yang)–GV6 (Jizhong) and GV2 (Yaoshu)–GV1 (Changqiang) (Supplementary Fig. 1). The acupuncture needles were manipulated for insertion into the specific acupoints at a depth of 5 mm, and the needles connected with a purpose-made device (model number G6805-2A, Shanghai Medical Electronic Apparatus Company, Shanghai, China), which provided an alternating pattern of sparse and dense wave pulsed stimulation.
The stimulation frequencies and durations were applied in a repetition period of 2 Hz for 2.85 seconds and 60 Hz for 1.05 seconds. During EA treatments, the current intensity between acupoint pairs across the lesion site was ~5 μA. EA treatments lasted for 20 minutes every other day, beginning on the third postsurgical day.

3. Tissue Extraction and RNA Sequencing

Seven days postsurgery, rats in all groups were anesthetized with 1% pentobarbital sodium (40 mg/kg, intraperitoneal), then perfused with phosphate buffer saline (PBS). Spinal cords (1-cm segment containing the injury epicenter) were then removed from rats in the sham (n = 3), control (n = 5), and GV-EA (n = 5) groups.

Total RNA of each sample was extracted using TRIzol Reagent/RNeasy Mini Kit (Qiagen, Venlo, The Netherlands). Total RNA of each sample was quantified and qualified by Agilent 2100/2200 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA), NanoDrop (Thermo Fisher Scientific Inc., Waltham, MA, USA), and 1% agarose gel. One microgram total RNA was then concentrated by RNeasy Mini Kit (Qiagen, Venlo, The Netherlands). Total RNA of each sample was quantified and qualified by Agilent 2100/2200 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA), NanoDrop (Thermo Fisher Scientific Inc., Waltham, MA, USA), and 1% agarose gel. One microgram total RNA was then enriched with Ribo-Zero Gold Kit. Then the remaining RNA was fragmented and reverse-transcribed. First strand cDNA was synthesized using ProtoScript II Reverse Transcriptase with random primers and Actinomycin D. The second-strand cDNA was synthesized using Second Strand Synthesis Enzyme Mix (include dACG-TP/dUTP). The purified double-stranded cDNA by beads was then treated with End Prep Enzyme Mix (include dACG-TP/dUTP). The purified double-stranded cDNA was synthesized using Second Strand Synthesis Enzyme Mix (include dACG-TP/dUTP). The purified double-stranded cDNA by beads was then treated with End Prep Enzyme Mix to repair both ends and add a dA-tailing in one reaction, followed by a T-A ligation to add adaptors to both ends. Size selection of Adaptor-ligated DNA was then performed using beads, and fragments of ~400 bp (with the approximate insert size of 300 bp) were recovered. The dUTP-marked second strand was digested with Uracil-Specific Excision Reagent enzyme. Each sample was then amplified by polymerase chain reaction (PCR) using P5 and P7 primers and the PCR products were validated. Then libraries with different indexes were multiplexed and loaded on an Illumina NovaSeq 6,000 instrument for sequencing using a 2 × 150 paired-end configuration according to manufacturer’s instructions. The sequences were processed and analyzed by GENEWIZ, Inc. (Suzhou, China).

4. Tissue Processing Immunofluorescence Staining

All rats were then deeply anesthetized with 1% pentobarbital sodium (50 mg/kg, intraperitoneal) and transcardially perfused with normal saline containing 0.002% NaNO₃ and 0.002% heparin, followed by a fixative of 4% paraformaldehyde in 0.1 M PBS (pH, 7.4). The spinal cord was dissected and post-fixed for 24 hours in the same fixative and kept in 30% phosphate-buffered sucrose at 4°C for 48 hours, then frozen and embedded in optimal cutting temperature compound. Successive T8–12 spinal cord segments were cut into longitudinal 25-μm sections. These were then washed with 0.01 M PBS for 5 minutes and blocked with 10% goat serum for 30 minutes at 37°C. The tissue sections were then incubated with primary antibodies diluted with 0.01 M PBS containing 0.3% Triton X-100 at 4°C overnight. After this, they were washed with PBS 3 times for 5 minutes, then incubated with secondary antibodies for 1 hour at 37°C. Cell nuclei were marked with the Hoechst3342 (Hoe). After 3 rinses, the slides were observed with a confocal microscope (Carl Zeiss, Oberkochen, Germany). Primary antibodies included rabbit anti-neurofilament protein 200 (1:200; Sigma-Aldrich, St. Louis, MO, USA) and rabbit polyclonal anti-NeuN (1:500; Abcam, Cambridge, UK). Secondary antibodies included goat anti-rabbit IgG488 (1:1,000; Abcam) and goat anti-rabbit IgG555 (1:1,000; Abcam).

5. Behavioral Assessment

After surgery, hindlimb locomotor function was assessed weekly with the Basso, Beattie, and Bresnahan (BBB) open field locomotor test, on which a score of 0 points indicates severe neurological deficits and 21 points indicates normal performance. Behavioral assessments were performed by 2 experimenters who were blinded to the group information.

6. Computational Analysis for RNA-Seq Data

1) Quality control

To remove technical sequences, including adapters, PCR primers, or fragments thereof, and base quality < 20, pass filter data of fastq format were processed by Cutadapt (v1.9.1) to be high-quality clean data. Then Q20, Q30, and GC contents of cleaning data were calculated. For miRNA, we used the next-generation sequencing data quality statistical software Trimomatic (V0.32) to delete connectors and low-quality sequences in the raw (i.e., pass filter) data for subsequent information analysis. Next, expression data for lncRNA, circRNA, miRNA, and mRNA were analyzed by principal components analysis (PCA) and Pearson correlation coefficient clustering to judge sample repeatability and whether there were remaining abnormal candidates for elimination.
2) Expression analysis and differential expression analysis

We used FPKM method for standardization, which not only normalizes the sequencing depth, but also normalizes the gene length, so that the estimated values of gene expression levels of genes are comparable. The formula is:

$$\text{FPKM} = \frac{\text{total exon Fragments}}{\text{mapped reads(Millions)} \times \text{exon length(Kb)}}$$

Among them, total exon reads/mapped reads (Millions) can be regarded as the percentage of all reads is mapped to this gene, and then divided by the gene length, we can get the percentage of total mapped reads per unit length that is expressed. Then reference genome sequences (version: Rattus norvegicus. Rnor_6.0.9) and gene model annotation files of relative species were downloaded from genome website, such as UCSC, NCBI, ENSEMBL. Hisat2 (v2.0.1) was used to index reference genome sequence and align clean data to reference genome. In the beginning transcripts in FASTA format are converted from known gff annotation file and indexed properly. Then, with the file as a reference gene file, RSEM (v1.2.15) estimated gene and isoform expression levels from the pair-end clean data. At last, differential expression analysis used the DESeq2 Bioconductor package, a model based on the negative binomial distribution. The estimates of dispersion and logarithmic fold changes incorporate data-driven prior distributions, Padj of genes were set < 0.05 and fold change were set ≥1.2 to detect differential expressed ones.

3) GO and KEGG enrichment analysis

Gene ontology (GO) enrichment analysis of DEGs was implemented by the GOseq (v1.34.1), in which gene length bias was corrected. GOseq was used to identify GO terms on an annotated list of enriched genes with a significant Padj < 0.05. GO enrichment analysis identifies the biological process (BP), cellular component (CC), and molecular function (MF) of DEGs. Kyoto encyclopedia of genes and genomes (KEGG) is a collection of databases dealing with genomes, biological pathways, diseases, drugs, and chemical substances (http://en.wikipedia.org/wiki/KEGG). We used in-house scripts to enrich significant DEGs in KEGG pathways.

4) lncRNA/circRNA-miRNA-mRNA interaction analysis

Based on the sample expression data of lncRNA (or circRNA) and mRNA, the Pearson correlation analysis of lncRNA (or circRNA) and mRNA was carried out by using the stats package cor ( ) method of R language, and the results with correlation coefficient greater than 0.95 and p-value of < 0.05 were screened to prepare for the study of regulatory relationship. First, the miranda software (v3.3a) is used to predict the targeting relationship between miRNA and IncRNA (or circRNA), and then miRNA software (v3.3a) is used to predict the targeting relationship between miRNA and mRNA. Finally, miRNA is used as a connecting bridge to build an indirect regulatory relationship between mRNA and IncRNA (or circRNA) with a correlation coefficient greater than 0.95. Using CytoScape software (V3.5.1) to draw the regulation network diagram.

7. Statistical Analyses

All data are presented as mean ± standard deviation and were analyzed using 1-way analysis of variance (ANOVA) or repeated measures ANOVA with IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). When variance analysis was satisfied, the least significant difference method was applied for multiple comparisons of the average number of each group. When variance was not uniform, the Kruskal-Wallis test or Dunnett T3 was applied. BBB score data were analyzed by repeated measures ANOVA for homogeneity of variance, then ANOVA was used for between-groups comparisons. A p-value < 0.05 was considered statistically significant.

RESULTS

1. RNA-seq of Spinal Cord Transcriptome

To determine the possible mechanism of GV-EA in the treatment of subacute SCI, we performed whole-genome sequencing analysis to identify possible key regulatory genes following 7-day EA treatment of the injured spinal cord. First, we analyzed fragments per kilo base of exon model per million mapped fragments with DEG-seq software, and filtered out the low-quality spliced reads in the original sequence to eliminate the influence of gene length and sequencing quantity on gene expression, and obtain high-quality data. Q20 and Q30 values of clean data were obtained after processing. There were ~12 G/sample IncRNA for analysis, with Q20 > 97% and Q30 > 93% (Supplementary Table 1). There were ~350 M/sample miRNA data for analysis, with Q20 > 99% and Q30 > 98% (Supplementary Table 2). There were ~12 G/sample circRNA data for analysis, with Q20 > 97% and Q30 > 93% (Supplementary Table 3). Thus, the data quality and quantity were reliable.

Through the overall correlation analysis of sample expression data, we found no need to remove any sample. For mRNA, PC
Fig. 1. Differential mRNA expression, gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathway analysis. (A) Heatmap of differentially expressed genes (DEGs) between sham (n = 3), control (n = 5), and governor vessel electroacupuncture (GV-EA) (n = 5) groups (p < 0.05) with green and red indicating downregulated and upregulated expression, respectively. (B, C) Venn diagrams show DEGs overlap among experimental groups. Green and red represent downregulated and upregulated expression, respectively. (D) Top 30 GO terms in the enrichment analysis. The abscissa represents numbers of differentially expressed mRNAs and the ordinate represents the function in each GO term. Pink: BP; Green: cellular component; Blue: molecular function. (E) Bubble diagram of top 20 significantly enriched KEGG pathways. The abscissa shows the rich factor and ordinate shows the enrichment to KEGG pathways. The circle size marks the number of genes and the color change from red to blue indicates p-value change from low to high.
score plots showed that the contribution of PC1, PC2, and PC3 were 39.1%, 8.3%, and 6.9%, respectively (Supplementary Fig. 2). The EA5 sample was far from the treatment groups, but the correlation coefficient between the EA5 sample and the other 4 samples in this GV-EA group is higher than 0.95, so this EA5 sample were not excluded. For lncRNA, PC1, PC2, and PC3 were 48.1%, 28.1%, and 10.2%, respectively (Supplementary Fig. 3), and correlation analysis indicated that there were no abnormal samples. For miRNA, PC1, PC2, and PC3 were 15.9%, 10.7%, and 9.5%, respectively (Supplementary Fig. 4); Although the C4 sample in the control group was far from the others, the correlation between them was strong so that this C4 sample was not removed. The PC1, PC2, and PC3 of circRNA were 14.2%, 11.7%, and 10.7%, respectively (Supplementary Fig. 5), and no samples needed to be removed.

2. Identification of DEGs in Injured Spinal Cord following GV-EA Treatment

We analyzed DEGs of mRNA, lncRNA, miRNA, and circRNA between the control and GV-EA group according to foldchange ≥ 2 and Padj < 0.05 and found that there was almost no DEGs difference of mRNA, miRNA, and lncRNA. Therefore, we reanalyzed after adjusting the mRNA, miRNA, and lncRNA parameters for foldchange ≥ 1.2 and Padj < 0.05.

To determine the impact of GV-EA on regulation of mRNA expression in the SCI groups, we performed a cluster analysis of the genes that differed significantly. We used EB-seq algorithm to analyze and screen DEGs to identify those that are upregulated and downregulated. We found that 5266 genes were significantly altered among the experimental groups (Fig. 1A). Venn diagrams showed 4636 dramatically DEGs in the control group relative to sham, with 2431 upregulated and 2205 downregulated. As compared with the control group, 704 genes in the GV-EA group displayed differential expression, with 347 upregulated and 357 downregulated genes (Fig. 1B, C). Among the downregulated DEGs after SCI, 59 genes were upregulated after GV-EA treatment (Fig. 1B); 114 of the upregulated DEGs following SCI were downregulated by GV-EA treatment (Fig. 1C).

To provide more precise insight into the DEG functions and relative pathways, we carried out GO analysis and KEGG en-
richment analysis of the 3 groups. We selected 30 GO terms with the most significant enrichments (Padj ≤ 0.05) for display in a GO enrichment histogram: membrane (GO:0016020), cytoplasm (GO:0005737), and integral component of plasma membrane (GO:0005887) were the most enriched in CC. Actin binding (GO:0003779), protein heterodimerization activity (GO:0046982), and protein kinase binding (GO:0019901) were the highest in MF. Toll-like receptor (TLR) signaling pathway (GO:0034123), cytokine secretion (GO:0050707), and cellular response to lipopolysaccharide (GO:0071222) were significantly enriched in BP (Fig. 1D). To further refine the signaling pathways involved in DEG systems, a KEGG bubble chart was used to show the top 20 pathways with the most significantly differentiated enrichment. Mitogen-activated protein kinase (MAPK) signaling pathway, TLR signaling pathway, and cytokine–cytokine receptor interaction were most strongly related to GV-EA therapy for SCI. Twelve DEGs were involved in MAPK signaling pathway, primarily enriching MAP3K13, NCAM1, RasGRP4, MEF2C, STMN1, CACNA2D2, IL1r, EGF, and others. TLR signaling pathway and others contained 68 DEGs, enriching TLR5, TLR2, TLR8, TLR9, and others (Fig. 1E).

LncRNAs, circRNAs, and miRNAs are all noncoding RNAs (ncRNAs), which lack the protein coding ability and participate in mediating various disease responses. LncRNAs are ncRNAs with > 200 nucleotides which participate in a variety of BPs. In addition to analyzing the DEG transcriptome, we evaluated the differential expression of lncRNA. Using the same method described above, we found that compared with the sham group, 1,597 genes were upregulated, and 1,469 genes were downregulated in the control group. Further, 1,287 genes in the GV-EA group relative to the control group show differential expression, with 587 upregulated and 700 downregulated. Moreover, 260 genes coexisted between the 2 comparison groups, allowing further detailed assessment (Fig. 2A–C).

CircRNA is a newly identified ncRNA, with a stable circular structure. Change in circRNA expression may affect the level of its origin mRNA. DEG enrichment showed that 1,284 genes changed significantly. Compared with the sham group, 380
genes were upregulated and 536 genes were downregulated in the control group. Compared with the control group, 298 genes were upregulated and 323 genes were downregulated in the GV-EA group. Venn analysis showed 153 genes involved in GV-EA repair SCI, including 55 upregulated and 98 downregulated (Fig. 3A–C).

An miRNAs is a short stranded RNA of ~22nt length that can regulate target gene expression. According to the ceRNA theory, competitive binding between sponge RNA and miRNA target genes can regulate miRNA target gene activity. Thus, IncRNAs, or circRNAs can play a considerable role in regulating miRNA levels to change target mRNA expressions. To explore the relations between mRNA expression and ncRNA regulation, miRanda, and RNA hybrid algorithms were used to predict the target miRNAs of circRNA, IncRNA, and mRNA, respectively. Then, the IncRNA, circRNA, and mRNA genes with the same expression trends were extracted by sequence clustering analysis, and combined to form an interactive network. The predicted results revealed 4 target genes related to miRNA–mRNA regulation: TLR2, TPM1, LIMK1, and SCARB1. In the IncRNA-miRNA-mRNA interaction network, 43 IncRNAs and 4 mRNAs had the same expression trend (be-

![Fig. 4. CeRNA network construction. (A) LncRNA-miRNA-mRNA ceRNA network. Red ball, green circle and orange triangle indicate mRNA, miRNA and IncRNA, respectively. (B) CircRNA-miRNA-mRNA ceRNA network. Red ball, green circle, and blue diamond indicate mRNA, miRNA, and circRNA, respectively.]
longing to the increase-decrease type/decrease-increase type). In the circRNA-miRNA-mRNA predicted interaction network, 89 circRNAs and 4 mRNAs had the same expression trend. Further, 9 miRNAs were predicted to act as junctions to interact with lncRNAs and circRNAs to regulate mRNA expressions: rno-miR-338-3p, rno-miR-125a-3p, rno-miR-293-5p, rno-miR-125a-5p, rno-miR-29c-3p, rno-miR-21-5p, rno-miR-144-3p, rno-mir-134-5p, and rno-mir-455-5p (Fig. 4A, B).

3. Effects of Long-term Treatment With GV-EA on Subacute SCI

Based on the RNA-seq results, we further investigated the effect of long-term GV-EA in subacute SCI. Injured rats were treated with GV-EA from post-SCI day 3 for 1 month. We use immunofluorescence to detect neurons (NeuN) and axons (NF200). Four weeks after GV-EA, compared with the control group, the GV-EA group had more surviving NeuN+ neurons (Fig. 5A, C). They also had more NF200+ fibers regenerated into the SCI area (Fig. 5B, D). The hindlimbs of rats were paralyzed after SCI. In the GV-EA group, BBB scores were significantly higher than those of the control group in the period from 2 weeks to 4 weeks post-SCI. At 4 weeks after SCI, the BBB score of GV-EA group reached about 4 points (Fig. 5E). These results indicated that long-term GV-EA may protect neuron survival and promote nerve fiber regeneration in the injured area, facilitating recovery of locomotor function.

![Figure 5](https://doi.org/10.14245/ns.2244452.226)

**Fig. 5.** Governor vessel electroacupuncture (GV-EA) can protect neurons survival, promote axon regeneration and improve function recovery. (A, B) The immunofluorescence staining of NeuN and NF in sham, control, and GV-EA group after spinal cord injury (SCI) 4 weeks, scale bars = 1,000 µm; 40 µm in (a1–a3; b1–b3). (C) Bar chart shows the number of NeuN+ and Hoe+ in the area of spinal cord injury. (D) Bar chart shows the mean fluorescence intensity of NF positive expression in the area of spinal cord injury. (E) Basso, Beattie, and Bresnahan (BBB) behavioral scores in the different stages of sham, control, and GV-EA group after SCI 4 weeks. n = 5/group; *p < 0.05 indicates significant difference when compared with the sham group. #p < 0.05 indicates significant difference when compared with the control group.
DISCUSSION

EA is an ancient, widely used method for treating human disease. It has shown positive effects in SCI, playing a variety of beneficial roles by stimulating special acupoints and conducting them from the meridians and channels to the target site.23 GV-EA can promote neural survival and differentiation of pre-induced mesenchymal stem cells within GS scaffolds at the SCI lesion site.24 Further, GV-EA stimulates the internal growth of spinal cord neurons to improve neuronal survival rate, axonal regeneration, and synaptic function by upregulating the CGRP/α-CaMKII/NT-3 pathway.7 Additionally, GV-EA combined with transplanted stem cells has advantageous anti-inflammatory and neuroprotective effects during early-stage SCI.9 Morphologically, we found that GV-EA effectively protects NeuN+ neurons and enhances NF+ nerve fiber regeneration over a relatively long period. Those results verified that long-term GV-EA treatment of subacute SCI may play a significant role in promoting neuronal survival, nerve fiber extension, and motor function recovery.7-9 However, the specific molecular mechanism by which GV-EA treatment impacts subacute SCI has remained unclear. Therefore, we used high-throughput sequencing technology to conduct RNA-seq analysis of injured spinal cord tissues after 7 days of GV-EA treatment for SCI, screening out the related DEGs for biological analysis.

To our knowledge, this is the first study to use RNA-seq to reveal the impacts of GV-EA on SCI; these results are therefore valuable advances and a basis for subsequent studies. We employed reverse transcription to establish cDNA libraries after removing rRNA from total RNA. Thus, further study of the interaction between coding and ncRNA will help better explain these effects. The Q20 and Q30 values, combined with PCA and correlation cluster analysis results demonstrate that our data are of sufficient quality for use in further analyses.

After 7 days of GV-EA treatment, 173 DEGs were regulated, among which 59 were upregulated and 114 were downregulated. The 5 most altered DEGs after SCI were LIMK1, MOBP, PLXND1, CACNA2D2, and Wnt7a. According to a recent study, LIMK1 deletion elevates cofilin activity to promote spinal motor axon growth, as confirmed using a LIMK1−/− mouse model; and following sciatic nerve injury, modulation of the cofilin/LIMK1 pathway accelerates sciatic nerve growth and improves recovery of some sensory and motor functions.25 Tedeschi et al.26 demonstrated that CACNA2D2 encodes the voltage-gated calcium channel alpha2delta2 subunit, which limits the development and regeneration of axon growth in central nervous system injury, whereas pharmacological blockade of this subunit by pregabalin administration can enhance axonal regeneration in adult mice following SCI. It has been shown that loss of SEMA3E-PLXND1 signaling changes the synaptic connection; specifically, SEMA3E-induced, PLXND1-mediated rejection may block synaptic formation related to sensorimotor connectivity.27

To further explain the function and role of DEG mRNAs, we performed GO enrichment and KEGG pathway analysis. GO enrichment analysis suggested that positive regulation of cell death and regulation of cytokine secretion may be related to neuron survival and inflammation after GV-EA treatment in SCI. Consistent with this, the genes for positive cell death regulation include NOD1, CTGF, and ALOX12. NOD1 can activate caspase-1, leading to cell death.28 Bone marrow mesenchymal-derived exosomes may protect neurons and extend nerve fibers, ultimately accelerating locomotor function recovery by decreasing NOD1.29 SiRNA-induced silencing of CTGF can attenuate astrogliosis and scar formation, facilitating recovery of locomotor function following SCI.30 Transgenic mice with ALOX12 overexpression have promoted inflammation and apoptosis in SCI.31 Furthermore, the GO results for regulation of cytokine secretion included TLR8, TLR2, TLR9, and TLR5, corresponding to the pathway for enrichment of oxidative stress. Pathway enrichment also showed that MAPK signaling and TLR signaling were notable. MAPK signaling pathway not only participated in inflammatory response, but also mediated spinal cord regeneration and inhibit the secondary injury of SCI.32 MAP3K13 that involved in MAPK signaling pathway has been shown to regulate injury signals in damaged neurons to regulate regeneration, while in undamaged neurons to regulate sprouting after SCI.33 NCAM has been demonstrated to promote axonal regeneration as a therapeutic gene.34 TLR signaling pathway is related to oxidative stress. For example, one function of the TLR4/MyD88 signaling pathway is promoting nerve cell death by inducing inflammation. Gut microbiota dysregulation can also deteriorate SCI by activating the TLR/MyD88 signaling pathway.35 We also identified some pathways highly related to neuroprotection and axon regeneration. For instance, yes-associated protein (YAP) was upregulated in male C57BL/6 astrocytes and activated in a Hippo pathway-dependent manner post-SCI. Conditional knockout of YAP in astrocytes can significantly inhibit post-SCI astrocyte proliferation in male C57BL/6, as well as reduce glial scar formation, inhibit axon regeneration, and damage behavior recovery.36 Zhang et al.37 found that overexpression of miR-338-5p in exosomes derived...
from mesenchymal stromal cells provides neuroprotective effects via the Cnr1/Rap1/Akt pathway after SCI in rats. It has also been reported that in vivo grafting of Netrin-1 overexpressing fibroblasts into the dorsal column lesion cavity demonstrates that Netrin-1 inhibits axonal regeneration. Further, Netrin-1 was the first axon guidance molecule to be discovered in vertebrates. Therefore, GV-EA may effectively regulate the BBB scores gradually in rats. Our lncRNA results showed that 91 of the over 8,128 DEGs changed by GV-EA. Additional recent studies have also shown that circRNAs are highly expressed in neural tissues, regulating neuronal and synaptic functions. Our ceRNA regulatory network results indicate that TCONS_00032537, TCONS_00138251, and TCONS_00138251 in upregulated genes, and in TCONS_00125346, TCONS_00236532 and TCONS_00128041 in downregulated genes. Additional recent studies have also shown that circRNAs are highly expressed in neural tissues, regulating neuronal and synaptic functions. Our ceRNA regulatory network results indicate that TCONS_00032537, TCONS_00138251, and TCONS_00138251 in upregulated genes, and in TCONS_00125346, TCONS_00236532 and TCONS_00128041 in downregulated genes. Additional recent studies have also shown that circRNAs are highly expressed in neural tissues, regulating neuronal and synaptic functions. These results suggested that GV-EA treatment promotes the survival of neurons and stimulates axonal growth into the lesion site, and improves partial locomotor functional recovery in the transected spinal cord in rats.

**CONCLUSION**

We explored DEGs and the ceRNA network through RNA-seq to establish a clear direction for further study of the mechanism of GV-EA in subacute SCI treatment. The results of RNA-seq analysis showed that GV-EA treatment could regulated 173 DEGs of mRNA, 260 DEGs of IncRNA, and 153 DEGs of circRNA among these differential expression genes after SCI. The DEGs changed by GV-EA are highly related to inflammation, oxidative stress, apoptosis, neuroprotection signaling pathways (e.g., TLR, MAPK, Hippo signaling pathway), which may warrant further investigation in the future. We also found that novel ceRNA network through RNA sequencing, which provided a clear direction for further study on the mechanism of GV-EA in the treatment of subacute SCI. Moreover, we found that long-term GV-EA beginning during the subacute SCI stage can promote neuronal survival, nerve fiber extension, and motor function recovery.

**NOTES**

Supplementary Materials: Supplementary Tables 1–3 and Figs. 1–5 can be found via https://doi.org/10.14245/ns.2244452.226.

Conflicts of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: XX, QD, XZ, BQL, YHM, GL, YSZ, YD; Data curation: XX, QD, XZ, BQL, YHM, GL, YSZ, YD; Formal analysis: XX, QD, XZ, BQL, YHM, GL, YSZ, YD; Funding acquisition: YD; Methodology: XX, QD, YD; Project administration: YD; Writing - original draft: XX, QD; Writing - review & editing: YD.

ORCID
Xingru Xiao: 0000-0003-2707-5646
Qingwen Deng: 0000-0003-1443-6860
Xiang Zeng: 0000-0003-4577-749X
Bi-Qin Lai: 0000-0003-1978-3466
Yuan-Huan Ma: 0000-0001-9800-8139
Ge Li: 0000-0001-9030-884X
Yuan-Shan Zeng: 0000-0003-3804-5792
Ying Ding: 0000-0003-0862-2309

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**Supplementary Table 1. LncRNA of sequence assembly after Illumina sequencing**

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N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of GV-EA group.
GV-EA, governor vessel electroacupuncture.
Q20, the percentage of bases with a Phred value > 20; Q30, the percentage of bases with a Phred value > 30.
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### Supplementary Table 3. circRNA of sequence assembly after Illumina sequencing

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N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of GV-EA group.

GV-EA, governor vessel electroacupuncture.

Q20, the percentage of bases with a Phred value > 20; Q30, the percentage of bases with a Phred value > 30.
Supplementary Fig. 1. Schematic diagram indicates the selected 4 governor vessel (GV) acupoints.
Supplementary Fig. 2. Correlation analysis of mRNA expression. (A) Principal components analysis (PCA) analysis with 3 principal components (PC1, PC2, and PC3) was performed to demonstrate the source of variance in our data. (B) Correlation coefficient cluster analysis, the data in the color block represents the specific value of the phase relationship between 2 samples, and the color change from light to dark indicates the correlation coefficient change from low to high. N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of governor vessel electroacupuncture group.
**Supplementary Fig. 3.** Correlation analysis of lncRNA expression. (A) Principal components analysis (PCA) analysis with 3 principal components (PC1, PC2, and PC3) was performed to demonstrate the source of variance in our data. (B) Correlation coefficient cluster analysis, data in the color block represent the specific value of the phase relationship between 2 samples, and the color change from light to dark indicates the correlation coefficient change from low to high. N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of governor vessel electroacupuncture group.
Supplementary Fig. 4. Correlation analysis of miRNA expression. (A) Principal components analysis (PCA) analysis with 3 principal components (PC1, PC2, and PC3) was performed to demonstrate the source of variance in our data. (B) Correlation coefficient cluster analysis, the data in the color block represent specific values of the phase relationship between 2 samples, and the color change from light to dark indicates the correlation coefficient change from low to high. N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of governor vessel electroacupuncture group.
Supplementary Fig. 5. Correlation analysis of circRNA expression. (A) Principal components analysis (PCA) analysis with 3 principal components (PC1, PC2, and PC3) was performed to demonstrate the source of variance in our data. (B) Correlation coefficient cluster analysis, the data in the color block represent specific values of the phase relationship between 2 samples, and the color change from light to dark indicates the correlation coefficient change from low to high. N1–N3: 3 samples of sham group; C1–C5: 5 samples of control group; EA1–EA5: 5 samples of governor vessel electroacupuncture group.
Electroacupuncture for Spinal Cord Injury: A Scientific Study of Traditional Medicine

Liquan Wu
Department of Neurosurgery, Renmin Hospital of Wuhan University, Wuhan, China

Spinal cord injury is an irreversible disease with a high disability rate and leads to a heavy economic and social burden. The most common cause of spinal cord injury is trauma, but it can also be caused by tumors, infections, vascular disease, or iatrogenic injury. Spinal cord injury can lead to increased rates of depression, sleep disturbances, spasticity, bladder and gastrointestinal changes, bedsores, sexual dysfunction, involuntary movements, obesity, cardiovascular disease, and respiratory disease, etc. The treatment of spinal cord injury has always been a difficult problem in the medical field. At present, the treatment measures for spinal cord injury mainly include anti-inflammatory drugs, hyperbaric oxygen therapy, and electroacupuncture rehabilitation. The electroacupuncture stimulation treatment of spinal cord injury is a research hotspot in the field of spinal cord injury rehabilitation in recent years, and has shown good effects in both traditional medicine and modern medicine.

In 1920, Ingvars found that the electric field has an important role in the conduction of nerve fibers and could affect the growth of nerve. Marsh and Beams in 1946 first applied direct current implantation in culture medium containing chicken dorsal root ganglia and found axonal growth at the cathode. In 1988 Fehling reported that the application of direct current electric field can lead to the regeneration of spinal cord axons. Shapiro et al. first conducted experiments with electroacupuncture in in vitro and in vivo models of spinal cord injury in moray, rodent, and canine, and found that it has nutritional and positive effects on injured spinal cord axons, which can improve spinal cord functional outcomes. Then an on-body vibrating electric field stimulator (OFS) was invented and tested on 10 fully motor and sensory SCI patients and found that the OFS was safe, reliable, simple, and effective in the treatment of SCI patients. Xiao et al. observed the changes of Nogo/NgR and Rho/ROCK signaling pathway-related gene and protein expression in rats with spinal cord injury treated by electroacupuncture, and found that electroacupuncture can inhibit Nogo/NgR and Rho/ROCK signaling pathway after spinal cord injury, so that Mitigate negative effects on axonal growth.

The results of the animal experimental model of acute spinal cord injury treated by electric field show that the electric field can effectively prevent the secondary damage of the spinal cord, which is manifested in that the neurons of the spinal cord are protected and there is no liquefaction, necrosis, and cavity formation of the spinal cord. There are only a few scattered microcapsules in the white matter, and the function of the spinal cord can be largely restored. Under the electron microscope, it can be seen that there are a large number of new microvessels in the spinal cord tissue of animals with external electric field. These
microvessels play a role in improving the spinal cord microcirculation and reducing necrosis. The glial cells in the white matter repair and regenerate the myelin sheath of nerve fibers. Borgens et al. pointed out that after spinal cord injury, a strong endogenous injury current can be generated in the spinal cord injury area, which drops to a stable level at 36 hours after injury, but can last for at least 4 days or longer after injury. This injury current can increase the formation of Na+ and Ca2+ ions, which can damage the nerve meridians and promote nerve degeneration. The external electric field and the electroacupuncture electric field can generate a micro current in the spinal cord that is opposite to the direction of the endogenous injury current, thus offsetting the injury current, thus playing a role in protecting the degeneration of the spinal cord axons.

Electroacupuncture stimulation is also an effective method for treat spinal cord injury in traditional medicine. Traditional medicine believes that the injury of the Governor Vessel is the main cause of spinal cord injury. When the Governor Vessel is injured, Qi and blood cannot reach the limbs, and the muscles and fascia of the limbs lose nutrition due to the obstruction of the meridians and collaterals, leading to atrophy, and the limbs gradually lose their functions. Therefore, when using acupuncture to treat paraplegia caused by spinal cord injury, the acupoints on the Governor Vessel are the preferred treatment sites. Acupuncture on the Governor Vessel points can not only cultivate and replenish the true yang, but also can pass the meridian qi so that the upper and lower parts can be connected, and the yang qi can be connected, then the paraplegia can be cured.

Clinical studies have shown that Governor Vessel electroacupuncture has a certain curative effect in the treatment of traumatic paraplegia, but the previous Governor Vessel electroacupuncture was considered to lack scientific basis. In recent years, it has been confirmed that electroacupuncture or electroacupuncture at Governor Vessel can reduce the secondary damage after spinal cord injury and protect neurons by regulating changes in neutrotrophic factors, neurotransmitters, neuropeptides, and some signaling pathway protein molecules. And promote the regeneration of its nerve fibers and functional repair. Electroacupuncture combined with transplantation of stem cells at the spinal cord injury has become a new cell therapy strategy in recent years. Studies have shown that Governor Vessel electroacupuncture stimulates the afferent nerve fibers of the spinal meningeal branches of rats with total transected spinal cord injury or spinal cord demyelination injury to transmit information to the spinal cord, activate the synthesis and secretion of neurotrophin-3 (NT-3) by spinal cord tissue cells, mediates the survival, differentiation and migration of exogenous neural stem cells and mesenchymal stem cells expressing the NT-3 receptor TrkC in total transection spinal cord injury/transplantation or spinal cord demyelination injury/transplantation, replacing and protecting damaged host neurons, improving injured tissue microenvironment, promote nerve fiber regeneration and myelination, improve cortical motor evoked potentials and motor function of paralyzed limbs. In addition, Governor Vessel electroacupuncture mediates inflammatory regulation via NT-3 to promote the survival and functional integration of transplanted stem cell-derived neural networks within the injured spinal cord. And now this study show us a potential molecular mechanism of Governor Vessel electroacupuncture for spinal cord injury in differential expression of RNA transcripts.

In short, electroacupuncture treatment can significantly improve the internal environment of the injured spinal cord and play a very important role in alleviating the secondary injury of the spinal cord. Therefore, the combination of electroacupuncture stimulation and traditional medical concepts has great potential in the clinical treatment of spinal cord injury. Future research should further clarify the molecular biological mechanism of the combination treatment and let the world accept the scientific nature of traditional medicine, so, as to better promote the treatment of traditional medicine.

Conflict of Interest: The author has nothing to disclose.

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Minimally Invasive Posterior Facet Decortication and Fusion Using Navigated Robotic Guidance: Feasibility and Workflow Optimization

Christopher R. Good¹, Lindsay D. Orosz², Ronald A. Lehman¹, Jeffrey L. Gum⁴, Douglas Fox⁵, Isador H. Lieberman⁶

¹Virginia Spine Institute, Reston, VA, USA
²National Spine Health Foundation, Reston, VA, USA
³Columbia University Medical Center, The Och Spine Hospital at New York-Presbyterian, New York, NY, USA
⁴Norton Leatherman Spine Center, Louisville, KY, USA
⁵NeuroTexas, NeuroHealth Institute Baylor Scott and White Health, Austin, TX, USA
⁶Texas Back Institute, Plano, TX, USA

Minimally invasive spine surgery reduces tissue dissection and retraction, decreasing the morbidity associated with traditional open spine surgery by decreasing blood loss, blood transfusion, complications, and pain. One of the key challenges with a minimally invasive approach is achieving consistent posterior fusion. Although advantageous in all fusion surgeries, solid posterior fusion is particularly important in spinal deformity, revisions, and fusions without anterior column support. A minimally invasive surgical approach accomplished without sacrificing the quality of the posterior fusion has the potential to decrease both short- and long-term complications compared to the traditional open techniques. Innovations in navigated and robotic-assisted spine surgery continue to address this need. In this article, we will outline the feasibility of achieving posterior facet fusion using the Mazor X Stealth Edition Robotic Guidance System.

Keywords: Robotic guidance, MIS facet fusion, Facet trajectory planning, Mazor X Stealth Edition, Workflow

INTRODUCTION

The Mazor X Stealth Edition Robotic Guidance System (MXSE; Medtronic, Dublin, Ireland) offers the benefits of 3-dimensional (3D) segmental preoperative planning software along with bone mounted intraoperative robotic guidance and navigation confirmation. Mazor Core Technology has been shown in multiple studies to be highly efficacious for the placement of minimally invasive pedicle and cortical screw trajectories. Recent software upgrade to version 5.0 includes enhanced surgical planning capabilities and allows the use of a high-speed burr for the purposes of cannulating bone trajectories and using navigated tools independent of the robotic arm. One benefit of this evolution is the enhanced ability to drill through or make cuts in bone with a high-speed burr (75,000 RPMs) as compared to a traditional drill with a maximum speed of 250–300 RPMs. The faster speed allows for smoother, more precise bone cutting and trajectory placement. The Mazor preoperative planning software not only allows for the optimization of implant size and purchase, but also aligning screw heads to improve cadence for easier rod passage and decreasing risk of screw pull-out.

A growing body of literature demonstrates that robotic-guided spine surgery leads to decreased implant-related complica-
tions, revision surgeries, and intraoperative radiation exposure while achieving a high a degree of implant accuracy. Given the potential advantages to minimally invasive robotic-guided spine surgery combined with navigation and the latest robotic software advancements, utilization of these invaluable intraoperative tools is expected to increase. It is the authors’ opinion that future uses for these systems will include higher level bone cutting functions including facet decortications, osteotomies, and robotic-assisted spinal decompressions. The purpose of this article is to describe the technique for achieving minimally invasive surgery (MIS) posterior facet decortication and fusion using navigated robotic guidance with MXSE and to describe the authors’ early experiences with this emerging technique during minimally invasive posterior instrumented fusion. This article will demonstrate that a reproducible navigated and planned technique for achieving an MIS posterior fusion is now possible (Fig. 1A–D).

PREOPERATIVE SURGICAL PLANNING

Precise planning for minimally invasive spine surgery—including implant locations, screw head alignment, rod passage, and facet decortication—can be made with segmental planning software preoperatively using a high-resolution, 3D computed tomography (CT) scan or intraoperatively using 3D O-arm spin. It is the authors’ preferred workflow to use the preoperative CT-to-fluoro option, which affords more time for strategic planning prior to the start of the surgical procedure.

The first step in planning the surgical procedure is to plan ideal screw size, trajectory, and alignment for minimally invasive pedicle screw instrumentation. This can be done at a segmental level but also by visualizing the entire construct to optimize screw alignment and lordosis (Fig. 2A). Simultaneously, implant trajectories can be used to determine the skin incision location and can be adjusted to optimize the skin incision (Fig. 2B). In the example shown in Fig. 2B, separate stab incisions are used for the L2 and L3 percutaneous screws while paramedian incisions are used for the remaining lumbosacral pedicle screws and the contralateral S2AI screws. Using the software’s ‘planar rod function,’ the surgeon is able to identify which screws will not line up with a straight rod in the coronal plane which the software will highlight in pink. Deformity correction is then simulated if applicable to the case.

Finally, once implant trajectories are optimized, facet trajectories are planned with the goal of utilizing the same skin incision used to place the screws (Fig. 3A). The facet trajectory of any segment is best planned on the caudal segment. For instance, the decortication of the L4/5 facet should be planned on the L5 vertebral segment. This avoids any plan-to-execution mismatch, for example if an interbody device is placed that could alter the facet alignment from the preoperative CT scan to the intraoperative registration. The software allows for trajectories of different sizes to be utilized (Fig. 3B, C). In the authors’ experience, facets can be removed robotically using multiple different techniques. Facet decortication has been performed using a drill to open a 9-mm trajectory along the facet and using multiple smaller trajectories aligned along the facet. Facet trajectories can also be planned in multiple orientations

Fig. 1. Examples of facet fusions using the described technique for MIS robotic-guided facet decortication and fusion as demonstrated on computed tomography scan. (A) Coronal view of bilateral L5/S1 facet fusion. (B) Axial view of bilateral L4/5 facet fusion. (C) Sagittal view of right L5/S1 facet fusion. (D) Sagittal view of right L4/5 facet fusion.

Fig. 2. (A) Final robotic plan showing implants and rod alignment. (B) Coronal view showing skin incision locations, rod alignment, and arrow indicating the contralateral trajectory of the S2AI screw.
based on surgeon preference. A straight up and down trajectory in the axial plane allows for decortication of the facet joint without pointing the trajectory toward the canal or neural elements; however, this cannot typically be done through the same MIS skin incision used for the pedicle screw location at that level. It is the authors’ preferred technique to plan facet trajectories at an angle in-line with the facet joint angle on the axial view, which intersects with the same skin incision previously utilized for pedicle screw instrumentation. Prior to the innovation of a navigated burr combined with robotic guidance, the authors had used a single 9-mm drill trajectory. Since the release of the new upgrade, the authors typically plan multiple 3-mm trajectories to decorticate the facets using the high-speed burr. The depth is approximately 10–15 mm depending on patient anatomy, but always at least 5 mm away from the dorsal spinal canal.

**INTRAOPERATIVE TECHNIQUE**

1. Overview

The operating room setup, robotic system to bed mounting, robotic arm to patient mounting, and registration have all been described in detail in the literature. The authors prefer to attach the robotic arm to the patient using two bone mounts to the posterior superior iliac spine for additional stability. In the authors’ opinion, best practice throughout any robotic-guided minimally invasive procedure includes addressing the most mobile and distal segment from the bone mount first, then working from the least to most stable segment of the spine. It is also the preferred technique to use the robot system to cannulate all pedicles and make all robotic bone cuts prior to placing any robotic-guided instrumentation and then to place all implants sequentially as the final step of the operation. The authors choose not to place pedicle screws during the initial cannulation because a greater rotational torque is created across that spine segment which could potentially lead to a higher risk of spine shift and loss of registration. Therefore, the more delicate work is best done prior to the placement of the instrumentation.

2. Screw Cannulation

After sending the robotic arm to the most mobile segment first, the robotic-guided scalpel is used to dissect any tissue that may cause a deviation in the execution of the plan. The navigated dilator is advanced close to, but not touching, bony anatomy to prevent shift. Precise pedicle screw cannulation is achieved using a high-speed (75,000 RPMs) 3-mm end-cutting burr which greatly decreases the chance of skive or shift from the preplanned trajectory. Fluoroscopy can be used to confirm drill location.

The authors’ preferred workflow is to then send the robotic arm to the facet trajectory above that pedicle, decorticate the facet joint, and place the desired bone graft material through the same skin incision. Once drilling of the pedicles, facet decortication, and grafting are completed at all levels, the final pass is to place all pedicle screws starting with the most mobile segment.

3. Facet Decortication and Fusion Technique

To accomplish facet decortication, the robotic-guided scalpel is placed down to bone along the preplanned facet trajectory. It is the authors’ experience that there is usually a tactile sensation of cutting the facet capsule as the robotic scalpel docks to bone. It is the authors’ recommendation that the robot-assisted scalpel be advanced perpendicular to the plane of the facet joint to minimize the very small chance that the scalpel enters perfectly in-line with the facet joint and advances into the spinal canal. Next, the navigated dilator is placed and verified visually that it lines up perfectly with the planned facet trajectory. The surgeon independently verifies when the navigated dilator touches bone both visually on the screen and by the tactile sensation of bone (Fig. 4A). If at any point the visual does not line up with tactile feedback, abort the facet decortication and consider reregistration.

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**Fig. 3.** (A) Final robotic plan showing facet trajectories (cylinders). (B) Axial software planning view showing (at arrow ends) single (larger) and double (smaller) facet trajectories. (C) Coronal software planning view showing (at arrow ends) single (larger) and double (smaller) facet trajectories.
The navigated drill is turned on above the point of contact with bone, then is advanced with 2-finger light touch down to the planned depth and visualized on the navigation screen. The authors typically drill facet joints to a depth between 10–15 mm depending on patient anatomy, but always recommend stopping the facet decortication at a minimum of 5 mm away from the dorsal spinal canal (Fig. 4B). The authors recommend never planning to drill closer than 5 mm to the spinal canal, and in many cases the planned trajectories end well before this 5-mm end point, which highlights the benefit of the software advances for preplanning these precise maneuvers. The depth should always be confirmed by navigation. Fluoroscopy can also be used to confirm drill location if desired (Fig. 4C, D).

The drill is removed, and bone graft is placed into the robotic cannula and packed into the facet defect. One author creates a slurry of demineralized bone matrix and morselized bone morphogenetic protein sponges, packing 0.5–1 mL through the funnel into each decorticated facet joint, which is easily pushed through the funnel with an inverted pedicle sounder or plunger. Alternatively, a second author soaks cancellous allograft chips in previously harvested bone marrow aspirate and places the desired aliquot into each decorticated facet joint.

4. Screw Placement

Awl-tap-screws are then inserted into the screw tracks previously created, which avoids the extra time and torque associated with tapping (Fig. 5A). However, tapping followed by screw placement is an alternative method. The authors’ preferred screw placement workflow starts at the most mobile segment (often the most proximal pedicles), then screws are placed at each level bilaterally while moving towards the most stable segment with pelvic fixation being placed last.

If pelvic fixation is planned, this can be done through a small midline incision or often placed through the opposite parame-
5. Final Maneuvers

Once all screws are placed and verified, rods are measured and contoured according to the plan, then placed in a minimally invasive fashion. Additional compression, distraction, or rotation maneuvers are performed as necessary, and then set plugs are fastened. Once screws are tightened according to the manufacturer’s specifications, final x-rays are obtained to confirm the goals of surgery have been achieved (Fig. 6A, B). A comparison of the preoperative and postoperative standing x-rays for this case is shown in Fig. 6C.

This technique is commonly used in association with anterior column realignment with interbody fusion (anterior lumbar interbody fusion, lateral lumbar interbody fusion, and oblique lumbar interbody fusion) to allow for correction of coronal and sagittal deformities including flat back syndrome and spondylolisthesis. For this particular case, anterior interbody fusion was approached laterally at L2/3 and L3/4 and anteriorly at L4/5 and L5/S1.

DISCUSSION

The minimally invasive approach to both degenerative and spinal deformity surgeries has the potential to decrease short- and long-term complications compared to traditional open techniques without sacrificing the necessity of achieving solid posterior fusion.

The advantages of less tissue dissection, less blood loss, less radiation exposure, and less time under anesthesia have great potential to achieve shortened hospital stays, faster recoveries, less narcotic use, and less overall economic burden on the healthcare system. McAfee et al. retrospectively compared MIS with open spine surgery to analyze the success of the MIS approach and found that one of the clearest advantages of spinal MIS is the lower rates of infection compared to open procedures. Similarly, in a retrospective review of prospectively collected data on postoperative surgical site infections (SSI) after MIS spine surgery, O’Toole et al. concluded that minimally invasive spinal surgery techniques may reduce wound infections as much as 10-fold compared with rates of SSI after open spinal surgery published in the literature.

In the prospective comparative MIS ReFRESH study, Good et al. showed that MIS robotic-guided surgery had 5.8 times fewer surgical complications related to screw placement and 11.0 times fewer revision surgeries compared to MIS fluoroscopic-guided surgery. The study also showed a reduction of intraoperative radiation exposure by 80% with robotic guidance.

In a systematic review of minimally invasive procedures in spine surgery, Banczerowski et al. concluded that in addition to the already described lower rates of complications, further benefits of the MIS approach to spine surgery include a favorable esthetic outcome with smaller incisions and sparing of the posterior elements with effective posterior stabilization of the spine. Zhang et al. specifically compared violation of the supe-
rior-level facet joints between robot-assisted percutaneous pedicle screw placement and conventional open fluoroscopic-guided screw placement in a prospective cohort study. They concluded that MIS robot-assisted spine surgery was associated with fewer proximal facet joint violations, larger facet-to-screw distance, and higher intra-pedicle accuracy.

The pairing of real-time navigation to robotic guidance offers further benefit. Computer-assisted navigation technology allows surgeons greater visualization of bony anatomy through limited MIS incisions and has the potential to reduce radiation exposure and enhance surgical accuracy without increasing operative time.10-15

The benefits of the MIS approach to spine surgery with the use of navigation and robotic guidance are widely published in the literature; however, the need to improve upon the ability to achieve a strong posterior fusion with these MIS techniques has yet to be highlighted. Historically, facet decortication and laying down bone graft with an MIS approach was difficult and inconsistent, leaving the only way to adequately achieve a posterior fusion was with the open surgical approach. With the ongoing advancements in robotic-guided systems, preoperative planning for facet trajectories will allow for the precise intraoperative execution of facet decortication and the placement of bone graft, all achieved through the same small incision made for pedicle screw insertion.

CONCLUSION

One of the key challenges with a minimally invasive approach to spinal fusion surgery is achieving solid posterior fusion. This paper describes the feasibility and workflow for both the preoperative planning and the intraoperative execution of facet decortication and fusion in an MIS fashion. The advancement of this technique will expand the indications for using an MIS approach to spine surgery where achieving posterior fusion is a necessity.

NOTES

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ORCID

Christopher R. Good: 0000-0003-4947-5667
Lindsay D. Orosz: 0000-0002-7189-7746
Ronald A. Lehman: 0000-0002-5799-9885
Jeffrey L. Gum: 0000-0003-0471-9437
Douglas Fox: 0000-0002-8236-7898
Isador H. Lieberman: 0000-0002-6889-6136

REFERENCES


Pathological Classification of the Intramedullary Spinal Cord Tumors According to 2021 World Health Organization Classification of Central Nervous System Tumors, a Single-Institute Experience

Sung-Hye Park\textsuperscript{1,2}, Jae Kyung Won\textsuperscript{1}, Chi Heon Kim\textsuperscript{3}, Ji Hoon Phi\textsuperscript{3}, Seung-Ki Kim\textsuperscript{3}, Seung Hong Choi\textsuperscript{4}, Chun Kee Chung\textsuperscript{2}

\textsuperscript{1}Department of Pathology, Seoul National University College of Medicine, Seoul, Korea
\textsuperscript{2}Institute of Neuroscience, Seoul National University College of Medicine Neuroradiology, Seoul, Korea
\textsuperscript{3}Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea
\textsuperscript{4}Department of Neuroradiology, Seoul National University College of Medicine, Seoul, Korea

According to the new 2021 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) the classification of the primary intramedullary spinal cord tumors (IM-SCT) follows that of CNS tumors. However, since the genetics and methylation profile of ependymal tumors depend on the location of the tumor, the ‘spinal (SP)’ should be added for the ependymoma (EPN) and subependymoma (SubEPN). For an evidence-based review, the authors reviewed SCTs in the archives of the Seoul National University Hospital over the past decade. The frequent pathologies of primary IM-SCT were SP-EPN (45.1%), hemangioblastoma (20.0%), astrocytic tumors (17.4%, including pilocytic astrocytoma [4.6%] and diffuse midline glioma, H3 K27-altered [4.0%]), myxopapillary EPN (11.0%), and SP-subEPN (3.0%) in decreasing order.

IDH-mutant astrocytomas, oligodendrogliomas, glioneuronal tumors, embryonal tumors, and germ cell tumors can occur but are extremely rare in the spinal cord. Genetic studies should support for the primary IM-SCT classification. In the 2021 WHO classifications, extramedullary SCT did not change significantly but contained several new genetically defined types of mesenchymal tumors. This article focused on primary IM-SCT for tumor frequency, age, sex difference, pathological features, and genetic abnormalities, based on a single-institute experience.

Keywords: Spinal cord, Intramedullary tumor, Ependymoma, Astrocytoma, Diffuse midline glioma

INTRODUCTION

The spinal cord belongs to the central nervous system (CNS) and is a tubular structure that leads to the medulla oblongata, from which any tumor arising from the brain can develop. All intradural extramedullary spinal tumors (EM-SPT) and intramedullary spinal cord tumors (IM-SCT) are rare and account for 2%–4% of CNS tumors.\textsuperscript{1} The incidence of spinal cord tumors in Seoul National University Hospital (SNUH) is similar to that reported previously.\textsuperscript{2} Reported IM-SCT accounts for approximately about 10% of spinal cord tumors.\textsuperscript{3} For the classification of the IM-SCT according to the updated World Health Organization (WHO) classification in 2021, spinal tumors also required genetic studies with some tumors renamed by genetics and methylation profile.\textsuperscript{3} The tumor names were changed into spinal ependymoma (SP-EPN) and spinal subependymoma.
(SP-subEPN) by adding location, and grades should be written in Arabic rather than Roman characters. Here, authors have summarized the updated knowledge of pathological classification of the primary IM-SCTs.

This article describes an updated classification of IM tumors with frequency, age distribution, sex difference, pathological, and genetic hallmarks according to the 5th edition of WHO classification. Authors reviewed primary spinal cord tumors in the archives of SNUH (Table 1). For the past 10 years (2012–2021), and 329 primary IM-SCTs out of 1,765 cases of both EM- and IM-SCTs were reviewed to determine the above mentioned parameters. Intradural EM-SCT, such as schwannoma, meningioma, neurofibroma, malignant peripheral nerve sheath tumor, solitary fibrous tumor, chordoma, metastatic tumor, and vascular malformation, were excluded. Although genetic studies were not conducted in all SNUH cases, most of the genetic abnormalities screened were meaningful in making a diagnosis or predicting patient’s prognosis. Since this article is a case-based review, the authors have added genetic features to the table, but no statistical analysis has been performed. This review of electronic medical records and digital pathology images was approved by the Institutional Review Board of SNUH (IRB No: 2202-097-1301).

Among primary IM tumors at SNUH, spinal ependymomas (SP-EPN) (n = 140, 8.4% of the primary EM- and IM-SCTs and 45.1% of IM-SCT), hemangioblastoma (n = 66, 3.7% of primary spinal tumors and 20.1% of IM-SCT), myxopapillary EPN (2% of primary spinal tumors and 11.0% of IM-SCT), and astrocytic tumors (3.1% of primary spinal tumors, 8.8% of IM-SCT), including low-grade (n = 8, 14% of spinal astrocytic tumors) and high-grade (n = 34, 89.7% of spinal astrocytic tumors), were the most common. The latter high-grade astrocytic tumors included glioblastoma (GBM) IDH-wildtype CNS WHO grade 4 (n = 21, 36.8% of spinal astrocytic tumors) and diffuse midline glioma (DMG) H3 K27M-altered (n = 13, 22.8% of spinal astrocytic tumors). Spinal subEPN (0.6% of primary spinal tumors, 3.0% of the IM-SCT), ganglioglioma (0.3% of primary spinal tumors, 1.5% of IM-SCT), diffuse leptomeningeal glioneuronal tumors (DLGNT), and atypical teratoid/rhabdoid tumor (AT/RT) (0.1% of primary spinal tumors, 0.3% of IM-SCT, each) were rare (Table 1).

The main classification of EM-SPT remains unchanged in the 2021 new WHO classification, but there are newly introduced rare types of CNS mesenchymal tumors, such as intracranial mesenchymal tumor, FET family gene, composed of fused in sarcoma, the Ewing sarcoma, and the TATA-binding protein-associated factor 2N: cyclic AMP responsive element binding protein 1 (CREB) FET:CREB fusion-positive, capicua transcriptional repressor CIC-rearranged sarcoma, primary intracranial sarcoma, and DICER1-mutant, which can also occur as an EM-SPT. In order of increasing frequency, the types of EM-SPT are schwannoma, meningioma, neurofibroma, paraganglioma, chordoma, malignant peripheral nerve sheath tumors, melanocytic tumors, and metastatic tumors. These EM-SPTs are not discussed in this article.

This article summarizes the updated classification of IM-SCTs based on their pathological features and molecular genetic profiles in SNUH cases.

### SPINAL EPENDYMOMAS

SP-EPN is the most common glial tumor of the spinal cord and arises from the ependymal cells of the spinal canal. SP-EPNs were 2.6 times more common (n = 140, 42.7% of IM-SCT) than astrocytic tumors (n = 57, 17.4% of IM-SCT) at SNUH for 10 years from 2012. The incidence of SP-EPNs, myxopapillary EPN, and spinal subEPN comprised 42.7%, 11.0%, and 3.0% of IM-SCT, respectively, at SNUH. The CNS WHO grade 3 SP-EPN was rare, found in 0.5% of primary spinal tumors, 2.4% of IM-SCT, and 5.4% of SP-EPN. The common age for SP-EPN was middle-aged (median, 44 years; range, 2–73 years) with a slight female predominance (male:female ratio 1:1.1) (Table 1). Among the SNUH cases, the most common sites for SP-EPN were at the level of the cervical, lumbar, and thoracic (8:3:1).

SP-EPNs are usually well-circumscribed tumors and have typical perivascular pseudorosettes consisting of a central blood vessel and a surrounding anuclear fibrillary zone (Fig. 1) or true ependymal rosettes with lumina. Tumor cells are monotonous with uniformly round to oval nuclei and salt-and-pepper chromatin. The nucleoli are usually inconspicuous. CNS WHO grade 2 SP-EPNs have a low rate of mitosis rates and a low proliferation index, but necrosis may be present. Rarely, papillary and tanyctyic subtypes are observed in the spinal cord. Tanyctyic EPNs favor the spinal cord over the intracranium; however, they were not mentioned in the 2021 WHO classification. Tanyctyic EPN shows an astrocytoma-like fascicular appearance with indistinct perivascular pseudorosettes, but intratumoral hemorrhage is common (Fig. 2). CNS WHO grade 3 SP-EPNs exhibit high cellularity and brisk mitosis (≥ 20/10 high-power field) with microvascular proliferation, but nuclear pleomorphism is not obvious (Fig. 2). Invasion to the spinal cord parenchyma can occur in CNS WHO grade 3 EPN.
Table 1. Epidemiology of the intramedullary spinal cord tumors of SNUH cases, which are listed by their frequency in the spinal cord

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n = 329</th>
<th>% of primary spinal tumors (n = 1,765)</th>
<th>% of IM-spinal tumors (n = 329)</th>
<th>Age (yr), median (range)</th>
<th>Sex, male:female</th>
<th>Known genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ependymal tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP-EPN, CNS WHO grade 2</td>
<td>140</td>
<td>7.9</td>
<td>42.6</td>
<td>47 (6–73)</td>
<td>1:1</td>
<td>Chromosome 22 deletion (1 copy loss) NF2 mutation or deletion</td>
</tr>
<tr>
<td>SP-EPN, CNS WHO grade 3</td>
<td>7</td>
<td>0.4</td>
<td>2.1</td>
<td>44 (2–49)</td>
<td>1:2</td>
<td>+ multiple copy number aberration</td>
</tr>
<tr>
<td>SP-EPN-MYCN</td>
<td>1</td>
<td>0.1</td>
<td>0.3</td>
<td>49</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Myxopapillary EPN</td>
<td>36</td>
<td>2.0</td>
<td>11.0</td>
<td>40 (15–80)</td>
<td>1:25:1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Spinal subEPN</td>
<td>10</td>
<td>0.6</td>
<td>3.0</td>
<td>38 (21–57)</td>
<td>1:1</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Diffuse adult-type astrocytic tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma, IDH-mutant</td>
<td>0</td>
<td>IDH1/2 mutation, ATRX mutation, TP53 mutation, CDKN2A/2B homozygous deletion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendrogioma, IDH-mutant and 1p/19q-codeleted</td>
<td>0</td>
<td>IDH1/2 mutation, 1p/19q-codeletion, CIC and/or FUBP1 mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBM, IDH-wildtype, CNS WHO grade 4</td>
<td>21</td>
<td>1.2</td>
<td>6.4*</td>
<td>37 (4–59)</td>
<td>1:2</td>
<td>EGFR amplification, PTEN homozygous deletion 7p gain/10 homozygous deletion, TERT promoter mutation, TP53 mutation</td>
</tr>
<tr>
<td><strong>Diffuse pediatric-type glioma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse low-grade glioma</td>
<td>8</td>
<td>0.5</td>
<td>2.4*</td>
<td>37 (1–65)</td>
<td>1:5:1</td>
<td>Unknown</td>
</tr>
<tr>
<td>DMG, H3 K27M-altered</td>
<td>13</td>
<td>0.7</td>
<td>4.0*</td>
<td>32.5 (19–75)</td>
<td>1:1.6</td>
<td>H3F3A K27M mutation TP53 mutation, ACVR1 mutation, ATRX mutation</td>
</tr>
<tr>
<td><strong>Circumscribed astrocytic tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pilocytic astrocytoma, G1</td>
<td>15</td>
<td>0.8</td>
<td>4.6*</td>
<td>37 (1–65)</td>
<td>1:1</td>
<td>FGFR1: TACC1 fusion, BRAF V600E, KIAA1549-BRAF</td>
</tr>
<tr>
<td><strong>Glineuronal and neuronal tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>5</td>
<td>0.3</td>
<td>1.5</td>
<td>5 (2–10)</td>
<td>3:2</td>
<td>KIAA1549-BRAF fusion, NF1 mutation, BRAF V600E mutation</td>
</tr>
<tr>
<td>Diffuse leptomeningeal glioneuronal tumor</td>
<td>1</td>
<td>0.1</td>
<td>0.3</td>
<td>5 Years</td>
<td>Male</td>
<td>KIAA1549-BRAF fusion, 1p/19 codeletion or 1p deletion or 19q deletion</td>
</tr>
<tr>
<td><strong>CNS Embryonal tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical teratoid/rhabdoid tumor</td>
<td>2</td>
<td>0.1</td>
<td>0.6</td>
<td>2 Years</td>
<td>0:1</td>
<td>SMARCB1 homozygous deletion or SMCB1 mutation</td>
</tr>
<tr>
<td><strong>Germ cell tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germinoma</td>
<td>2</td>
<td>0.1</td>
<td>0.6</td>
<td>22 (the same ages)</td>
<td>0:2</td>
<td>ALK mutation, KIT mutation</td>
</tr>
<tr>
<td><strong>Mesenchymal, nonmeningothelial tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>involving spinal cord</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>66</td>
<td>3.7</td>
<td>20.0</td>
<td>43 (27–76)</td>
<td>2:1</td>
<td>VHL gene mutation</td>
</tr>
</tbody>
</table>

IM, intramedullary; SP-EPN, spinal ependymoma; CNS, central nervous system; WHO, World Health Organization; IDH, isocitrate dehydrogenase; GBM, glioblastoma; DMG, diffuse midline glioma.

*Total astrocytic tumors including adult-type and pediatric-type diffuse gliomas and pilocytic astrocytoma was 17.4%.
All types of EPNs are positive for glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA), S100 protein, and vimentin.\textsuperscript{11} GFAPs are usually more accentuated in the perivascular anucleated fibrillary zone but diffuse positivity is not uncommon. EMA positivity is represented by a dot-like or tiny ring-like appearance, which is an ultrastructural intracytoplasmic microrosette with microvilli and cilia. They are generally negative for oligodendrocyte transcription factor 2 (Olig2) and synaptophysin,\textsuperscript{11} and these markers are helpful for the differential diagnosis of astrocytic or neuronal tumors. Since SP-EPN does not show EZHIP overexpression or H3K27me3 loss in the immunohistochemical study, the presence of these 2 findings should first rule out the drop-down metastasis of posterior fossa group A-EPN. However, ZFTA-RELA fusion-positive primary SP-EPN has been reported.\textsuperscript{12}

Although SP-EPNs are morphologically similar to supratentorial and posterior fossa EPNs, the molecular genetics and methylation profiles of these SP-EPNs are different from those of intracranial EPNs.\textsuperscript{13,14} The most common genetic abnormalities of SP-EPNs are one copy loss of NF2 or NF2 mutations.\textsuperscript{11,15,16} CNS WHO grade 3 EPNs commonly have multiple chromosomal copy number aberrations, in addition to one copy loss of NF2 or NF2 mutations. According to Lee et al.,\textsuperscript{17} the frequency of NF2 mutations in spinal and intracranial EPN was 32.1 and 4.4%, respectively.

MYCN gene amplified SP-EPN (SP-EPN-MYCN) has been recognized as a rare subtype of SP-EPN characterized by multiple tumors and aggressive behavior.\textsuperscript{18} This SP-EPN-MYCN has histopathological features of high-grade ependymoma, such as high cellularity, microvascular proliferation, brisk mitosis, tumor necrosis, and high MIB-1 proliferation index. Robust nuclear MYCN expression or in situ hybridization with the MYCN locus probe may be useful for detecting MYCN amplification, as well as NGS studies (Fig. 1D).

**MYXOPAPILLARY EPENDYOMAS**

Myxopapillary EPNs, CNS WHO grade 2, are not uncommon, constituting approximately 11% of IM-SCTs in SNUH. These tumors commonly occur at the distal thoracic to lumbar region (T12 to L2, 3), including the sacrum and filum terminale, but rarely at the upper thoracic or cervical levels of the spinal cord.\textsuperscript{19} The median age of SNUH patients with myxopapillary EPNs was 40 years (range, 15–80 years). Grossly, these tumors are well-encapsulated and often dumbbell-shaped solid masses composed of hyalinized blood vessels and a myxoid or mucinous intercellular matrix. The tumor cells show a monotonous polygonal appearance but sometimes long bipolar fibrillary cytoplasmic processes. The nuclei are usually round to oval and
bland-looking, but sometimes enlarged nuclei is present due to degenerating atypia (Fig. 3). These tumors have a favorable prognosis with 10-year overall survival rates > 90%. Myxopapillary EPNs rarely metastasize to extraneural sites.

**SUBEPENDYOMA**

SubEPNs are rare primary benign IM-SCTs classified as CNS WHO grade 1 tumors. In SNUH, they account for 0.6% of SPT and 3.0% of IM-SCT and usually occurred between 20 and 60 years (median, 38 years; range, 21–57 years). They commonly occur at cervical and thoracic levels. SP-subEPNs are well-circumscribed or well-encapsulated tumors that show typical microscopic features, including alternative cellular and acellular areas with microrosette-like multiple cell aggregates (Fig. 4). Metastases are extremely rare, and neither necrosis nor spinal cord invasion are observed. Degenerative nuclear atypia is rarely found, but is not a high-grade feature. Occasionally, in otherwise typical cases, fibrillary astroglial or gemistocytic cells may appear (Fig. 4). Immunohistochemical findings are similar to those of EPN; thus, GFAP is diffusely positive and might exhibit focal dot-like positivity for EMA, but negative for synaptophysin and Olig2. Although little is known about the genetic alterations in subEPN, mutations in the TRS1 gene have been found in familial subEPNs. BRAF and H3F3A mutations are absent and H3K27me3 is retained in the tumor cells. Spinal subEPNs are also morphologically identical to intracranial subEPNs; however, the methylation profile of spinal subEPN is different from that of intracranial and posterior fossa subEPN. Even after partial resection, the prognosis is excellent, and recurrence after surgery is rare.

**DIFFUSE ASTROCYTIC TUMORS, INCLUDING ADULT-TYPE DIFFUSE GLIOMAS AND PEDIATRIC-TYPE DIFFUSE GLIOMAS**

Astrocytomas constituted 17.4% of IM-SCT, including diffuse astrocytoma (n = 29, including 8 low- and 21 high-grade astrocytomas), DMG H3K27-altered (n = 13), and pilocytic astrocytoma (n = 15). Pilocytic astrocytoma, CNS WHO grade 1 was found in 4.6% of IM-SCT; diffuse low-grade gliomas (2.4% of IM-SCT), and diffuse high-grade glioma (DHGG, 10.4% of IM-SCT). In SNUH cases, GBM IDH-wildtype (6.4% of IM-SCT) and DMG H3 K27M-altered (4.0% of IM-SCT) were the most common malignant astrocytic tumors (DHGG). According to Hamilton et al. only 13% of spinal gliomas,
including pediatric gliomas, was malignant. As the histopathology of spinal astrocytic tumors is similar to that of intracranial astrocytic tumors (Fig. 5), low-grade gliomas (LGGs) have scant mitoses, no microvascular proliferation, no necrosis and low Ki-67 labeling index (Fig. 5B). GBM usually had pleomorphic nuclei of tumor cells, microvascular proliferation, and/or necrosis (Fig. 5A, C).

The genetics of spinal LGG is not well known because they are rare, but BRAF gene alterations have been reported. Most spinal GBMs were IDH-wildtype de novo tumors with EGFR amplification and/or PTEN or CDKN2A homozygous deletion, and TERT promoter and/or TP53 mutations have been found in the SNUH series, which is similar to the cases of Nagaishi et al.

Although several cases of spinal IDH-mutant astrocytomas and spinal oligodendrogliomas have been reported, they are extremely rare. Hemispheric gliomas, such as diffuse hemispheric glioma, H3 G34-mutant, and infant-type hemispheric glioma, are also extremely rare.

DMG, H3 K27-altered in the spinal cord, is a relatively recently recognized aggressive glioma classified as CNS WHO grade 4. Since the median age of DMG H3 K27-altered was 32.5 years old (range, 19–75 years old) in SNUH cases, spinal DMG can occur at any age and is more common in adults. These tumors carry somatic mutations of H3F3A or HIST1H3B/C. Morphologically, DMG can have various grades of astrocytic tumors (Fig. 5D); therefore, it can appear as low-grade astrocytoma or typical GBM, or have a primitive neuroectodermal tumor-like appearance. The tumor cells were positive for GFAP, and the tumor cell nuclei were positive for the H3K27M-mutant specific antibody, K27M (Fig. 5D). However, spinal cord DMG H3 K27-altered has a slightly better prognosis than spinal GBM, CNS WHO grade 4, TP53, ATRX, and ACVR1 mutations commonly accompany these tumors. However, EGFR-mutant DMG, known as bithalamic glioma, and EZHIP-overexpressing spinal DMG have never been reported in the spinal cord.

CIRCUMSCRIBED ASTROCYTIC GLIOMAS

Pilocytic astrocytoma is a relatively well-circumscribed and indolent CNS WHO grade 1 astrocytoma. Although pilocytic astrocytoma commonly occurs in the posterior fossa and optic pathway in children and adolescents, spinal pilocytic astrocytoma accounted for 4.3% of all IM-spinal tumors at SNUH (Table 1). The age of onset of spinal pilocytic astrocytomas was slightly higher (median, 37 years; range, 1–65 years) than that of supratentorial tumors.

The histopathology of spinal pilocytic astrocytoma is similar to that of intracranial pilocytic astrocytoma, showing low cellularity and bland-looking elongated nuclei with bipolar cytoplasmic processes. Vascular hyalinization and rosenthal fibers are common (Fig. 6). Occasionally, degenerative nuclear atypia is observed.

Although 40% of spinal pilocytic astrocytomas have KIAA1549:BRAF fusion, BRAF V600E mutation has been found in 4% of spinal pilocytic astrocytomas. Furthermore, homozygous deletion of CDKN2A is slightly more common in spinal cord and brainstem pilocytic astrocytoma than in cerebellar ones (21.1% vs. 33.3%). FGFR1:TACC1 fusion has been reported in pilo-
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Cyto-astrocytoma occurring in the brainstem and near full-length of the cervical spinal cord of a 22-year-old female. One of our spinal pilocytic astrocytomas in a 65-year-old male had an FGFR1: TACC1 fusion.

Other circumscribed astrocytic gliomas, such as high-grade astrocytoma with piloid features, pleomorphic xanthoastrocytoma, and MN1-altered astroglioblastoma, rarely occur in the IM-spinal cord; however, subependymal giant cell astrocytoma and choroidal glioma have never been reported in the spinal cord.

GLIONEURAL AND NEURONAL TUMORS

Ganglioglioma, CNS WHO grade 1, is the most common glioma, accounting for 1.5% of primary IM-SCT in SNUH. DLGNT rarely occurred in the spinal cord (0.3% of IM-SCT).

Ganglioglioma is a relatively well-demarcated, slow-growing neoplasm of childhood. The median age of patients with ganglioglioma was 5 years old (range, 2–10 years) in SNUH. Sometimes, they involve the long segments of the spinal cord. Gangliogliomas are composed of 2 cell components, neoplastic ganglion cells and glial cells (Fig. 7). These tumors are usually caused by alterations in the MAPK signaling pathway, usually with a KIAA1549: BRAF fusion; however, BRAF V600E and NF1 (sometimes biallelic) mutations or deletions have also been observed. Very rarely, spinal gangliogliomas contain only H3K27M mutations.

DLGNT is a low-grade glioneuronal neoplasm characterized by widespread diffuse involvement of the leptomeninges and superficial brain parenchyma by monotonous oligodendroglioma-like cells with bidirectional differentiation. These tumors are commonly found in the subpial region of the basal surface of the brain, brainstem, and spinal cord. Genetically, KIAA1549: BRAF fusion was found in 72% of the studied cases while 1p and/or 19q deletion was found in other cases. 1p/19q codeletion has been identified in 18%–33%. Based on the methylation profiles, these tumors are classified into methylation classes 1 and 2 (MC1 and MC2). Although MC1 is roughly similar to CNS WHO grade 2 gliomas in clinical course, MC2 has anaplastic features, 1q gain, and/or a worse prognosis than MC1.

CNS EMBRYONAL TUMORS

Among embryonal tumors, AT/RT, CNS WHO grade 4, rarely occur in the IM-spinal cord of infants (0.6% of IM-SCT), while other embryonal tumors are extremely rare. Approximately 7.6%
If this tumor develops in the EM-spinal cord, i.e., extradural or paravertebral, or in patients aged 3 years or older, metastasis of extracranial malignant rhabdoid tumor should be ruled out first. The pathological and genetic features were identical to those of intracranial AT/RT in SNUH. The tumor presents as a monotonous small round cell tumor with an eccentric nucleus and a prominent eosinophilic rhabdoid appearance, but primitive small round cells with scanty cytoplasm can be seen (Fig. 8). Tumor cell nuclei are usually negative for INI-1, but include internal control, such as endothelial cells and some inflammatory cells are positive for INI-1 (INI-1 immunohistochemistry; scale, 50 μm). (D) The tumor cells are at least focal positive for epithelial membrane antigen (EMA; scale, 50 μm).

of AT/RT occurs in the spinal cord. If this tumor develops in the EM-spinal cord, i.e., extradural or paravertebral, or in patients aged 3 years or older, metastasis of extracranial malignant rhabdoid tumor should be ruled out first. The pathological and genetic features were identical to those of intracranial AT/RT in SNUH. The tumor presents as a monotonous small round cell tumor with an eccentric nucleus and a prominent eosinophilic rhabdoid appearance, but primitive small round cells with scanty cytoplasm can be seen (Fig. 8). Tumor cell nuclei are usually negative for INI-1 and the Ki-67 labeling index is usually very high. SMARCB1 mutations or homozygous deletions are the genetic hallmarks of this tumor.

Since poorly differentiated chordomas also have SMARCB1/INI-1 loss, pathologists should keep it in mind when making a differential diagnosis. Biologically behavior is as aggressive as intracranial AT/RT.

GERM CELL TUMORS

Mature cystic teratomas, immature teratomas, and pure germinomas can occur in the spinal cord. In the SNUH series, these germ cell tumors are extremely rare, with each tumor subtype occurring in 0.1% of SPT and 0.6% of IM-SCT. Germinoma occurred in T12–L1 and young adults, and interestingly, 2 cases of SNUH germinoma occurred in 22-year-old females. Teratomas also commonly arise in the lower spinal level from L2 to the coccyx at any age. The 2 SNUH teratomas occurred in an infant and a 56-year-old woman. The histopathology of spinal teratomas and germinomas is identical to that of extraspinal tumors. Pure germinomas consist of malignant germ cells and lymphoplasmacytic cells. Malignant germ cells are arranged in sheets of polygonal-shaped malignant germ cells, which have centrally located rounded nuclei and prominent nucleoli (Fig. 9). The cytoplasm is moderate to plump and shows a pink to clear appearance because of the large amount of glycogen and lipid vacuoles. High rates of mitosis and necrosis are also common. Characteristically, germinoma cells have a positive membranous expression of c-kit and are commonly positive for placental alkaline phosphatase. Mature teratomas have mature 3-germ-layer tissues. Immature teratomas contain primitive neuroepithelial tubules. Genetically, one germinoma of SNUH cases had an ALK gene mutation (p.Gly926fs, c.2775delAinsGG); in addition, KIT mutation and chromosome 12p gain or amplification have been reported in intracranial germ cell tumors.

HEMANGIOBLASTOMAS

Hemangioblastoma, CNS WHO grade 1, is the second most common IM-SCT after ependymomas, accounting for 3.7% of

Fig. 8. Atypical teratoid rhabdoid tumor. (A) Magnetic resonance imaging shows a 2.8-cm elongated epidural enhancing mass between C5 and T1. (B) Light microscopically the tumor shows small round cells with eccentrically located nuclei and eosinophilic cytoplasm (arrows), which is a rhabdoid feature. (C) The tumor cell nuclei are negative for INI-1, but include internal control, such as endothelial cells and some inflammatory cells are positive for INI-1 (INI-1 immunohistochemistry; scale, 50 μm). (D) The tumor cells are at least focal positive for epithelial membrane antigen (EMA; scale, 50 μm).

Fig. 9. Germinoma. (A) Magnetic resonance imaging shows T2 heterogeneous intensity mass at T12–L1 spinal cord, involving conus medullaris. (B) The tumor is composed of biphasic, malignant germ cells and lymphplasmacytic cells (H&E; scale, 20 μm). The malignant germ cells show large round nuclei and prominent nucleoli. There are frequent mitoses. (C) The tumor cell membrane is positive for c-kit (scale, 50 μm), and (D) placental alkaline phosphatase (PLAP; scale, 50 μm).
CONCLUSION

Theoretically, any type of primary CNS tumor can occur in the intramedullary spinal cord; however, the most common IM-SCT is EPN, followed by hemangioblastoma and astrocytoma. SP-EPN and SP-subEPN are morphologically identical to those of the supratentorial or posterior fossa, but their molecular genetic and methylation profiles differ from those of intracranial EPN. Therefore, these tumors should have ‘spinal’ in the tumor name. DLGNT can arise in the spinal cord and are characterized by a KIAA1549:BRAF fusion, 1p and/or 19q deletion, or 19q gain. In addition, some spinal pilocytic astrocytomas are characterized by FGFR1:TACC1 fusion, in addition to alterations in the MAPK pathway. Myxopapillary ependymomas characteristically occur in the lumbosacral area and are regarded as CNS WHO grade 2. Although spinal DMG H3 K27M-altered is a high-grade glioma, the biological behavior of spinal DMG is better than that of spinal GBM IDH-wildtype, CNS WHO grade 4. Rarely, pilocytic astrocytoma, ganglioglioma, diffuse leptomeningeal glioma, and atypical teratoid rhabdoid tumors occur in IM-SCT; they may share a KIAA1549:BRAF fusion. However, although several cases of spinal IDH-mutant astrocytomas have been reported, hemispheric gliomas (such as diffuse hemispheric glioma, H3 G34-mutant, and infant-type hemispheric glioma) or IDH-mutant gliomas (including IDH-mutant astrocytoma and oligodendroglioma) are extremely rare.

NOTES

Ethics Statement: The institutional review board of our hospital approved this study (IRB No: 2202-097-1301) and has therefore been performed under the ethical standards set out in the 1964 Declaration of Helsinki and its subsequent amendments. As this study is a retrospective review of anonymized electronic medical records, pathology, and results of NGS data utilizing a brain tumor-specific somatic gene panel, informed consent was waived from our IRB under the Korean Bioethics and Safety Act. All materials had been obtained for the electronic medical record of the patients, which were anonymized and retrospectively reviewed. No extra-human materials were obtained from the patients for this study. Under the Korean Bioethics and Safety Act, additional consent to publish was waived.

Conflict of Interest: The authors have nothing to disclose.

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**Author Contribution:** Conceptualization: SP; Data curation: JKW, CHK, JHP, SK, SC, CKC; Writing - original draft: SP; Writing - review & editing: SP

**ORCID**

Sung-Hye Park: 0000-0002-8681-1597
Jae Kyung Won: 0000-0003-1459-8093
Chi Heon Kim: 0000-0003-0497-1130
Ji Hoon Phi: 0000-0002-9603-5843
Seung-Ki Kim: 0000-0002-0039-0083
Seung-Hong Choi: 0000-0002-0412-2270
Chun Kee Chung: 0000-0003-3485-2327

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Learning Curve and Complications of Unilateral Biportal Endoscopy: Cumulative Sum and Risk-Adjusted Cumulative Sum Analysis

Jinchao Xu†*, Dong Wang‡*, Jidan Liu†, Chengyue Zhu†, Jianhang Bao†, Wenshuo Gao†, Wei Zhang‡, Hao Pan‡

†Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China
‡Department of Orthopaedics, Hangzhou Traditional Chinese Medical Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China

Objective: The purpose of this study was to investigate the learning curve and complications of unilateral biportal endoscopy (UBE) in the treatment of lumbar disc herniation (LDH) and lumbar spinal stenosis (LSS).

Methods: This was a retrospective cohort analysis of 197 consecutive patients who received UBE unilateral laminotomy bilateral decompression (UBE-ULBD) or lumbar discectomy (UBE-LD) surgery, including 107 males and 90 females with an average age of 64.83 ± 14.29 years. Cumulative sum (CUSUM) and risk-adjusted cumulative sum analysis (RA-CUSUM) were used to evaluate the learning curve, with the occurrence of complications defined as surgical failure, and variables of different phase of the learning curve were compared.

Results: The cutoff point of learning curve of UBE surgery was 54 cases according to CUSUM analysis. The learning curve of UBE-ULBD and UBE-LD were divided into 3 phases. The first cutoff points were 31 and 12 cases, and the second cutoff point were 67 and 32 cases respectively. With the progress of the learning curve, the operation time and postoperative hospital stays decreased. The visual analogue scale and Oswestry Disability Index at the last follow-up were significantly lower than that before surgery. The incidence of surgical failure was 6.11% and began to decrease after the 89th case based on RA-CUSUM analysis. The surgical failure rate decreased from 10.11% to 2.78 after the 89th case with significant different.

Conclusion: UBE surgery is effective in the treatment of LDH and LSS with low incidence of complications. But a learning curve of at least 54 cases still required for mastering UBE surgery.

Keywords: Unilateral biportal endoscopy, Lumbar disc herniation, Lumbar spinal stenosis, Learning curve

INTRODUCTION

With increasing age, the incidence of lumbar disc herniation (LDH) and lumbar spinal stenosis (LSS) gradually increases. The herniated intervertebral disc, hyperplastic facet joint, thickened ligamentum flavum (LF) and lamina lead to a reduction in spinal canal volume and compression of the central spinal canal, lateral recess or foramen, causing symptoms such as intermittent claudication, low back pain and lower limb pain. LDH and LSS are the most common indications for lumbar surgery.1,2 Although traditional open surgery has been proven to be effective, it still has some disadvantages, such as large tis-
sue injury, poor postoperative spinal stability, and many complications. Microscopy and full-endoscopy have the advantages of less trauma and quick recovery after surgery, but due to the influence of the working cannula, the range of movement of the instrument is limited, so excessive facet joint resection may be needed for sufficient decompression, which may affect the stability of the spine after operation. Recently, the unilateral biportal endoscopy (UBE) technique was used for the treatment of LDH and LSS, and several articles have reported satisfactory effect of UBE surgery. As an emerging technology, the safety and learning curve of UBE have also received widespread attention. Surgeons hope to master the skills urgently and require advices and references, but there are still few studies on the learning curve of UBE surgery so far.

The purpose of this study was to analyze the learning curve of UBE surgery through cumulative sum (CUSUM) analysis based on operation time and risk-adjusted cumulative sum (RA-CUSUM) analysis based on surgical failure rate. To the best of our knowledge, there has been no research on using CUSUM and RA-CUSUM analysis to determine the learning curve of UBE until now.

MATERIALS AND METHODS

1. Patient Selection

Consecutive patients who underwent UBE surgery in the Department of Orthopedics, Hangzhou Hospital of Traditional Chinese Medicine from December 2019 to December 2020 were analyzed retrospectively. The operation methods included unilateral laminotomy bilateral decompression (UBE-ULBD) and lumbar discectomy (UBE-LD). All operations were performed by the same surgeon who had extensive experience in percutaneous endoscopic lumbar discectomy (PELD) but had never performed arthroscopic surgery.

The institutional review committee of Hangzhou Hospital of Traditional Chinese Medicine (No. 2022KY087) approved the study. This study was not considered to require informed consent. There was no treatment other than that routinely implemented during hospitalization, as well as no additional risk for the patients involved.

Inclusion criteria: (1) Patients presented with low back pain (visual analogue scale [VAS] ≥ 6), with or without lower limb radiation pain or intermittent claudication (walking distance ≤ 100 m). (2) Magnetic resonance imaging (MRI) showed stenosis of the central spinal canal, lateral recess or nerve root canal. (3) Systematic conservative treatment for more than 3 months was unsuccessful. (4) Patients undergoing UBE-ULBD or UBE-LD surgery performed by the same surgeon.

Exclusion criteria: (1) More than 2 surgical levels. (2) Lumbar spondylolisthesis greater than grade I (Meyerding grade). (3) Lumbar scoliosis (Cobb angle > 20°). (4) Patients with a history of lumbar spinal canal decompression surgery or lumbar interbody fusion surgery at the same level. (5) Patients with spinal infection, tumor, tuberculosis.

2. Surgical Procedure

The patient was placed in a prone position under general anesthesia with the abdomen suspended. The midline, horizontal line of the intervertebral space and surface projection of pedicles were identified on the anteroposterior (AP) view of the fluoroscope. By adjusting the operating table, the horizontal line of the intervertebral space of the targeted level was ensured to be perpendicular to the ground on lateral view of the fluoroscope.

Taking the left approach as an example, the viewing portal was located on the cranial side and the working portal on the caudal side. The left-side approach was easier to perform given that most surgeons had the dominant hand on the right side. Two 1-cm incisions were made 1.5 cm above and below the horizontal line of the intervertebral space of the ipsilateral pedicular medial line (Fig. 1A). Deep fascia was incised perpendicular to the skin incision. The saline was suspended at a height of approximately 70–100 cm from the incision and connected to a 30° arthroscope.

Multifidus muscles were dissected from the spinous process (SP) and the lamina space to form a primary workspace. The
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CUSUM analysis was the best fitting model. The degree of curve fitting was judged by the coefficient $R^2$, and the closer $R^2$ was to 1, the higher the degree of curve fitting was.

2) CUSUM

The learning curve based on operation time was calculated by CUSUM analysis. The formula was defined as: $\text{CUSUM} = \Sigma_{i=1}^{n} (Xi - U)$. $Xi$ indicates the operation time of each case, $U$ represents the average operation time of all cases, and $n$ represents the consecutive case number. The scatter diagram of CUSUM analysis results was drawn by OriginPro 2021 software, and the function formula was obtained by curve fitting. A p-value of $< 0.05$ indicated that the curve fitting was successful. The degree of curve fitting was judged by the coefficient $R^2$, and the closer $R^2$ was to 1, the higher the degree of curve fitting was. The model with the highest $R^2$ was the best fitting model. The first derivation of the fitting curve was carried out, and the peak of the fitting curve was determined according to the slope value of the curve so that the learning phase was divided accordingly.

3) RA-CUSUM

In this study, surgical failure was defined as occurrence of complications, including nucleus pulposus residue, dural tear, epidural hematoma, nerve root injury, and infection. Univariate bivariate logistic regression was used to analyze potential risk factors, such as sex, age, surgical segment, EBL, BMI, hypertension and operation time. The variables with $p < 0.05$ were included in the multivariate logistic regression model to predict the probability of surgical failure in each case. The scatter diagram of RA-CUSUM was drawn according to the following formula: $\text{RA-CUSUM} = \Sigma_{i=1}^{n} (Xi - \tau) + (-1)^{Xi}Pi$. $Xi = 1$ when the operation was defined as failed, and $Xi = 0$ when the operation was successful. $\tau$ indicated the observed probability of surgical failure. $Pi$ indicated the expected surgical failure rate for each case, which was based on the result of the multivariate logistic regression. The fitting curve was made, and different learning phases were compared.

4. Statistical Analysis

Continuous variables with a normal distribution are expressed as the mean ± standard deviation. A t-test was used to compare the 2 groups of variables. One-way analysis of variance (ANOVA) and repeated measures ANOVA followed by the least significant difference test was used to compare multi-

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Fig. 2. (A) Instruments used in unilateral biportal endoscopy (UBE) surgery. (B) Schematic of UBE surgery.
ple groups of variables. Continuous variables with a skewed distribution are expressed as the median (interquartile range, IQR), and the rank sum test was used for comparisons between groups. The classified variables were expressed as percentages, and comparisons between groups were performed by the chi-square test followed by Bonferroni correction. A p-value of < 0.05 was considered statistically significant.

RESULTS

1. Characteristics of Patients

Table 1 shows the detailed baseline characteristics of all patients. A total of 197 consecutive patients who underwent single-segment UBE surgery were enrolled in this study, including 90 cases of UBE-LD and 107 cases of UBE-ULBD. The average follow-up time was 10.51 ± 2.44 months (8–20 months). There were 107 males and 90 females, including 57 patients with hypertension, with an average age of 64.83 ± 14.29 years (34–91 years) and an average BMI of 21.89 ± 2.23 kg/m². The operative segments included 16 cases of L3/4, 115 cases of L4/5 and 66 cases of L5/S1. The statistic differences of baseline characteristics between UBE-LD and UBE-ULBD groups were not noticed.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UBE-ULBD</th>
<th>UBE-LD</th>
<th>p-value</th>
<th>( \chi^2 )</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.49 ± 13.34</td>
<td>64.06 ± 15.38</td>
<td>0.483</td>
<td>-</td>
<td>0.704</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.08 ± 2.31</td>
<td>21.65 ± 2.12</td>
<td>0.179</td>
<td>-</td>
<td>1.348</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>26</td>
<td>0.990</td>
<td>0.000</td>
<td>-</td>
</tr>
<tr>
<td>Level (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L3/4</td>
<td>7</td>
<td>9</td>
<td>0.376</td>
<td>0.783</td>
<td></td>
</tr>
<tr>
<td>L4/5</td>
<td>63</td>
<td>42</td>
<td>0.087</td>
<td>2.929</td>
<td></td>
</tr>
<tr>
<td>L5/S1</td>
<td>37</td>
<td>39</td>
<td>0.209</td>
<td>1.581</td>
<td></td>
</tr>
<tr>
<td>Postoperative follow-up duration (mo)</td>
<td>10.57 ± 2.52</td>
<td>10.43 ± 2.35</td>
<td>0.696</td>
<td>-</td>
<td>0.391</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy.

2. Surgical Outcomes

The average operation time was 143.61 ± 47.25 minutes (Table 2), and the operation time of UBE-ULBD was longer than that of UBE-LD (160.38 ± 53.98 minutes vs. 123.68 ± 26.59 minutes, p < 0.05). The median EBL was 100 mL with an IQR of 50. The average postoperative hospital stays were 6.18 ± 2.47 days (2–17 days). The VAS and ODI scores at the last follow-up were significantly improved compared with those before the

Table 2. Variables related to surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>UBE-ULBD</th>
<th>UBE-LD</th>
<th>p-value</th>
<th>( \chi^2 )</th>
<th>t</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating time (min)</td>
<td>160.38 ± 53.98</td>
<td>123.68 ± 26.59</td>
<td>0.000</td>
<td>-</td>
<td>5.878</td>
<td></td>
</tr>
<tr>
<td>EBL (mL)</td>
<td>100 (50–100)</td>
<td>50 (50–100)</td>
<td>0.125</td>
<td>-</td>
<td>-</td>
<td>1.532</td>
</tr>
<tr>
<td>Postoperative hospital stays (day)</td>
<td>6.36 ± 2.04</td>
<td>5.97 ± 2.91</td>
<td>0.276</td>
<td>-</td>
<td>1.092</td>
<td>-</td>
</tr>
<tr>
<td>Approach side (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>67</td>
<td>54</td>
<td>0.707</td>
<td>0.141</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Right</td>
<td>40</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Surgical failure</td>
<td>7 (6.54)</td>
<td>5 (5.56)</td>
<td>0.773</td>
<td>0.083</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation, median (interquartile range), or number (%).

UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy; EBL, estimated blood loss.
operation (p < 0.05) (Table 3, Fig. 3).

In our study, a total of 12 cases were regarded as surgical failure because of complications (Table 4), including residual nucleus pulposus (3 cases, 1.52%), dural tear (4 cases, 2.03%), epidural hematoma (2 cases, 1.02%), and nerve root injury (3 cases, 1.52%). UBE-ULBD was considered failed in 7 cases (6.54%) and UBE-LD in 5 cases (5.56%), and the difference was not statistically significant (p = 0.773).

Residual nucleus pulposus was found in 3 patients with highly migrated LDH in early phase (3rd, 13th, 68th), all of which were reoperated by PELD surgery and satisfactory results were obtained. Four patients with dural tears were fixed with gelatin sponges during the operation, and no cerebrospinal fluid leakage, lumbar pseudomeningocele or meningitis was observed after the operation. Among them, 1 patient developed irritability, increased heart rate, hyperextension of both lower limbs and hypertonia in the recovery of general anesthesia, which relieved spontaneously after 2 hours. A case of epidural hematoma suddenly developed radiation pain in the right lower limb on the third day after the operation, and the symptoms were relieved immediately after the hematoma clearance operation (Fig. 4). The other patient did not present any clinical symptoms, and epidural hematoma was found only on MRI after the operation. Among the patients with nerve root injury, 2 presented abnormal skin sensation in the nerve control area of the lower extremities, which recovered after conservative treatment, and 1 presented a transient decrease in extensor muscle strength of

Table 3. Clinical outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>UBE-ULBD</th>
<th>UBE-LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.55 ± 1.20</td>
<td>7.33 ± 0.94</td>
</tr>
<tr>
<td>1 Month after surgery</td>
<td>3.08 ± 0.84</td>
<td>2.95 ± 0.79</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>1.43 ± 0.49</td>
<td>1.32 ± 0.47</td>
</tr>
<tr>
<td>F</td>
<td>1,362.07</td>
<td>1,402.56</td>
</tr>
<tr>
<td>p-value</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VAS back</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>7.45 ± 1.13</td>
<td>7.40 ± 1.19</td>
</tr>
<tr>
<td>1 Month after surgery</td>
<td>3.90 ± 0.81</td>
<td>3.77 ± 0.79</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>2.05 ± 0.77</td>
<td>2.02 ± 0.82</td>
</tr>
<tr>
<td>F</td>
<td>906.424</td>
<td>823.742</td>
</tr>
<tr>
<td>p-value</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ODI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>58.76 ± 16.78</td>
<td>55.53 ± 15.46</td>
</tr>
<tr>
<td>1 Month after surgery</td>
<td>29.29 ± 6.33</td>
<td>31.04 ± 6.35</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>21.39 ± 3.72</td>
<td>19.88 ± 3.03</td>
</tr>
<tr>
<td>F</td>
<td>390.176</td>
<td>294.78</td>
</tr>
<tr>
<td>p-value</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy; VAS, visual analogue scale; ODI, Oswestry Disability Index.

Table 4. Details of complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>No.</th>
<th>No. of cases occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residue</td>
<td>3</td>
<td>3rd, 13th, 68th</td>
</tr>
<tr>
<td>Dural tear</td>
<td>4</td>
<td>21st, 30th, 46th, 139th</td>
</tr>
<tr>
<td>Epidural hematoma</td>
<td>2</td>
<td>75th, 164th</td>
</tr>
<tr>
<td>Nerve root injury</td>
<td>3</td>
<td>36th, 55th, 98th</td>
</tr>
</tbody>
</table>

*Unilateral biportal endoscopy unilateral laminotomy bilateral decompression. Unilateral biportal endoscopy lumbar discectomy.

Fig. 3. The visual analogue scale (VAS) and Oswestry Disability Index (ODI) at each point in time. UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy.
the dorsalis pedis, which gradually recovered to normal during the follow-up.

3. Learning Curve of CUSUM Analysis

Curve fitting was performed for the scatter diagram drawn according to the CUSUM value (Fig. 5), and the fitting function formula was as follows: 

\[ CUSUM = 118.28991 + 4.8622 \times n + 2.12485 \times n^2 - 0.05692 \times n^3 + 5.21264e^4 \times n^4 - 9.49534e^7 \times n^5 - 1.33934e^8 \times n^6 + 8.28645e^{11} \times n^7 - 1.42398e^{13} \times n^8 \]  

\( R^2 = 0.9711 \), \( p = 0.000 \).

When the number of surgical cases accumulated to 54 of the 197 cases, the slope of the curve changed from positive to negative. Therefore, the cutoff point required to achieve technical proficiency of UBE surgery was considered as 54 cases. We further divided the learning curve of 197 cases of UBE surgery into 2 phases for data comparison: the learning phase (case 1–54) and the mastery phase (case 55–197).

CUSUM analysis of different surgical methods showed that the first cutoff points of UBE-ULBD and UBE-LD were 31 cases and 12 cases, and the second cutoff point were 67 and 32 cases respectively. Therefore, the learning curve of UBE-ULBD and UBE-LD was divided into 3 phases respectively: the learning phase, practicing phase and mastery phase (Figs. 6, 7).

The comparison of patient characteristics and perioperative data in different phases are listed in Table 5. The operation time and postoperative hospital stays decreased with the improvement of mastery (p < 0.05). The incidence of complications in the learning phase and the mastery phase were 11.1% and 4.20%.

![Fig. 4](image)

**Fig. 4.** (A, B) A case of epidural hematoma after UBE-LD surgery: a 52-year-old woman underwent UBE-LD surgery for lumbar disc herniation in the left foramen area (red arrows). (C, D) Radiation pain of the right lower limb with a visual analogue scale of 9 suddenly appeared on the third day after operation, the magnetic resonance imaging (MRI) showed the epidural hematoma (blue arrows). (E, F) The symptoms were relieved immediately after hematoma clearance operation, and MRI indicated that the epidural hematoma had been removed. UBE-LD, unilateral biportal endoscopy lumbar discectomy.

![Fig. 5](image)

**Fig. 5.** Cumulative sum (CUSUM) graph of the cohort. UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy.

CUSUM = 118.28991 + 4.8622 \times n + 2.12485 \times n^2 - 0.05692 \times n^3 + 5.21264e^4 \times n^4 - 9.49534e^7 \times n^5 - 1.33934e^8 \times n^6 + 8.28645e^{11} \times n^7 - 1.42398e^{13} \times n^8

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https://doi.org/10.14245/ns.2143116.558

Fig. 6. Cumulative sum (CUSUM) graph of unilateral biportal endoscopy unilateral laminotomy bilateral decompression.

\[ CUSUM = 163.19249 + 28.77753 \times n + 1.33211 \times n^2 - 0.07247 \times n^3 + 1.17327e^4 \times n^4 + 4.12196e^5 \times n^5 - 8.26555e^7 \times n^7 + 6.36981e^8 \times n^8 - 1.77889e^{11} \times n^{11} \]

Fig. 7. Cumulative sum (CUSUM) graph of unilateral biportal endoscopy lumbar discectomy.

\[ CUSUM = -126.94879 + 112.59308 \times n - 11.3327 \times n^2 + 0.56427 \times n^3 - 0.01506 \times n^4 + 2.17584e^4 \times n^5 - 1.60262e^6 \times n^6 + 4.71398e^8 \times n^8 \]

respectively. There was no significant difference the surgical failure rate and EBL of different phases (p > 0.05), with the exception of the learning phase and the mastery phase of UBE-LD group.

4. Learning Curve of RA-CUSUM Analysis

Univariate binary logistic regression showed that BMI, hypertension and operation time were risk factors for surgical failure (p < 0.05; odds ratio [OR], 1.921, 5.551, 1.023) (Table 6). The fitting curve generated according to the results of RA-CUSUM began to decrease after the 89th operation, which meant that the probability of surgical failure began to decrease (Fig. 8). It indicated that 89 cases were needed to overcome the learning curve of UBE surgery in RA-CUSUM analysis. Therefore, the learning curve was divided into a learning phase (case 1–89) and a mastery phase (90–197) according to the cutoff point.

As listed in Table 7, the surgical failure rate of the mastery phase (2.78%) was significantly lower than that of the learning phase (10.11%). In mastery phase, the operation time and the postoperative hospital stays were significantly lower than that in the learning phase (p < 0.05). However, there was no significant difference in EBL between the 2 phases.

DISCUSSION

To reduce the trauma and complications caused by surgery, spinal surgeons have been committed to the combination of
endoscopic technology and minimally invasive concepts. The effectiveness of lumbar discectomy and decompressive laminotomy by posterior approach using the microendoscopy or full-endoscopy have been reported.11-14 However, due to the working cannula of the microscopic or full-endoscopic system, it is sometimes difficult for the instrument to tilt to the opposite side, especially in ULBD surgery. For the purpose of complete contralateral decompression, it is necessary to tilt the operating table or even remove the contralateral facet joint needlessly in most cases.4,5,15 Excessive resection of the facet joint leads to the decrease of spinal stability after surgery. Ito et al.4 indicated that the preservation rates for facet joints of UBE-ULBD and Micro-ULBD were 78% and 86% on the ipsilateral side, while those on the contralateral side were 85% and 94%. UBE technology established portals through the skin without a cannula, so the range of movement of the instruments was large, the decompression was complete and no excessive bony removal was required. UBE has the characteristics of less trauma, less bleeding and rapid recovery, and good effectiveness in the treatment of LDH and LSS according to previous studies.15-17 In our study, UBE-ULBD and UBE-LD also showed good clinical efficacy through the decrease of VAS and ODI (Table 3, Fig. 3).

As an emerging technique, in the early proficiency phase of UBE surgery, surgeons must go through the process of learning and practicing. The learning curve reflects the rate of skills acquired within a certain period of time, which is usually determined by the number of surgical cases required for beginners’ surgical techniques to achieve relative stability.18,19 Although the
reference value of the learning curve is limited by subjective factors, it can be used to summarize objective and replicable experiences, provide technical references and reduce unnecessary learning costs. To date, there are few articles on the learning curve of UBE. Study of Choi et al.20 indicated that the operation time of UBE surgery was close to the average and remained stable after the 36th cases. Kim et al.21 considered that at least 34 cases were required to achieve sufficient mastery of lumbar interbody fusion by UBE. A surgeon with no experience with endoscopic surgery was considered to achieve adequate UBE surgical ability in the 58th cases according to the study of Park et al.22

Comparation of the learning curve of UBE and other endoscopic surgery has reference significance for surgeons who have engaged in other spinal endoscopic techniques in the past. The cutoff point of full-endoscopic surgery ranged from 10 to 43 cases, with an average of about 22 cases,23-25 and which of microscopic surgery was reported to be between 20 and 30 cases.26-29 The cutoff point of full-endoscopy and microendoscopy seems slightly earlier than for UBE surgery. In UBE surgery, the same trigonometric imaging principle as arthroscopy was applied, and excellent hand-eye coordination was required for surgeons. In the early phase of learning, the instruments may be lost under the endoscopic view, and even enter the wrong intervertebral space for the reason of the wide range of activities of endoscope and instruments. Besides, the workspace of UBE surgery was man-made, not a natural joint space like arthroscopic surgery. Therefore, lack of experience in creation of workspace will lead to the prolongation of operation time, even the blockage of saline and blurred field of vision.

CUSUM is an average-based test method that was originally mainly used to monitor the continuous change trend of the industrial sector. Because this statistical method meets the requirements of clinical technical learning and quality control, it has been used to analyze learning curves in medicine since the 1970s.30 In this study, CUSUM analysis of operation time indicated that the cutoff point required to overcome the learning curve of UBE surgery was 54 cases. The average operation time

![Risk-adjusted cumulative sum analysis (RA-CUSUM) graph of the cohort. UBE-ULBD, unilateral biportal endoscopy unilateral laminotomy bilateral decompression; UBE-LD, unilateral biportal endoscopy lumbar discectomy. RA-CUSUM = 0.12342 + 0.05918 \times n + 0.00397 \times n^2 - 1.45566 \times e^4 + 2.55111 \times e^8 + 2.61582 \times e^3 + 1.53628 \times e^{10} - 4.74322 \times e^{13} + n^5 + 5.95452 \times e^{16} \times n^7]

**Table 7.** Comparison of different phases according to the result of RA-CUSUM analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Learning phase</th>
<th>Mastery phase</th>
<th>p-value</th>
<th>$\chi^2$</th>
<th>t</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>89</td>
<td>108</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>155.56 ± 53.49</td>
<td>133.77 ± 38.99</td>
<td>0.002</td>
<td>3.205</td>
<td>1.006</td>
<td></td>
</tr>
<tr>
<td>EBL (mL), median (IQR)</td>
<td>100 (50–100)</td>
<td>50 (50–100)</td>
<td>0.315</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative hospital stays (day)</td>
<td>6.75 ± 2.71</td>
<td>5.71 ± 2.17</td>
<td>0.003</td>
<td>2.995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical failure, n (%)</td>
<td>9 (10.11)</td>
<td>3 (2.78)</td>
<td>0.032</td>
<td>4.589</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation unless otherwise indicated.

RA-CUSUM, risk-adjusted cumulative sum analysis; EBL, estimated blood loss; IQR, interquartile range.
in the mastery phase was about half an hour shorter than in the learning phase (168.37 minutes vs. 134.27 minutes). However, in the results of CUSUM analysis in this study, there was no significant difference in surgical failure rates among different phases of UBE surgery. Moreover, in previous studies using operation time as an evaluation index, there was no difference in the complication rate among different phases. Although the operation time is the key factor in determining whether the surgeon overcomes the learning curve, the evaluation of the learning curve should theoretically include the quality and safety of medical care and the substantial health benefits of patients, not just surgical proficiency. Therefore, not only the operation time but also the occurrence of complications and the failure of the operation should be considered when determining the learning curve.

Most of the evaluation indices used by CUSUM analysis were operation times, while the RA-CUSUM was used to evaluate other parameters that affect the outcome of the operation. RA-CUSUM analysis in this study used the rate of surgical failure as reference index, and indicated that at least 89 cases were required to achieve a stable success rate. The overall failure rate of UBE surgery was 6.11%. Besides, the failure rate was 10.11% in the learning phase and 2.78% in the mastery phase, with a significant decrease after the 89th case. Therefore, after reaching a sufficiently fast operation speed, surgeons still need a period of learning and experience accumulation to control the complication rate at a low level.

Research by Lin et al. indicated that the average complication rate in LDH patients who received UBE surgery (4 studies, 134 cases) was 8.3%, and 6.3% in LSS patients (6 studies, 333 patients). Kim et al. reported that the surgical failure rate of UBE surgery was 10.29%, which could drop to 5.60% after the early learning stage. In our study, the complication rate of UBE surgery was similar to that previously reported. But it is worth noting that, in our study, all 3 complications occurred in the mastery phase according to RA-CUSUM were UBE-ULBD surgery (98th, 139th, 164th), and the CUSUM analysis of the operation time also showed that the cutoff point of UBE-LD surgery was earlier. Since there was no literature showing the difference between UBE-LD and UBE-ULBD in this respect, we consider that the surgeon’s PELD experience may be the cause.

The incidence of dural tears during surgery in LSS patients (3.7%) was significantly higher than that in LDH patients (2.1%), and the risk of dural tears in ULBD surgery was higher. In our study, dural tears also mainly occurred during UBE-ULBD surgery. The space between the dural sac and lamina became narrower in LSS patients, and adhesion between the dural sac and LF appeared, resulting in a blind area during the ULBD operation that would cause dural tears. In addition, the ligament structure between the dural sac and the surrounding spinal canal wall, the meningovertebral ligaments, is tightly connected with the LF. Therefore, the LF could be torn off together with part of the dorsal dural sac and small vessels due to pulling the LF sharply. Under the combined action of meningovertebral ligaments and pressure of saline, small folds may be formed on the surface of the dural sac. It is possible to tear along with the dural sac when the lamina is removed using a Kerrison punch. In this study, one patient with dural tear presented with increased intracranial pressure during resuscitation. Saline would be infused into the subdural space from the high-pressure workspace after a dural tear, which directly leads to an increase in intracranial pressure, presenting with neck pain, headache and even seizure after surgery.

Symptoms of epidural hematoma were usually observed within 24 hours after surgery, but approximately 43% of cases did not develop symptoms until 4 days or later after operation. One patient with epidural hematoma in our study developed symptoms on the third day after the surgery. Therefore, close observation should be carried out within 1 week after the surgery. In this study, regression analysis indicated that hypertension was one of the risk factors for surgical failure (OR, 6.484), which may be related to the effect of intraoperative bleeding on the visual field of surgery. Hypertension was also one of the risk factors for epidural hematoma. In hypertensive patients with poor blood pressure management, the increase in blood pressure was more obvious after recovery from anesthesia, and unpredictable bleeding may occur.

This research was a single-center study and the surgery was performed by the same surgeon, so our experience does not apply to other surgeons. For the reason that the study of the learning curve should first be based on the subjective factor of the surgeon’s experience. Moreover, objective factors such as the volume of patients, medical insurance policies, different equipment and devices all play important roles in the learning process. Therefore, other surgeons may have cutoff point earlier or later than ours.

**SUGGESTIONS**

1. **How to Avoid Complications**
   We recommend that the deep layer of the contralateral LF be

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preserved during the operation and resected at the end. If the LF is removed first, the operation should be performed on the outside of the epidural fat as far as possible. The meningovertbral ligaments need to be explored and severed with nerve dissectors or curettes. Timely reduction of water pressure and repair by patch after the tear happened may reduce the probability of intracranial hypertension. Complete hemostasis during the surgery and blood pressure management during the perioperative period were important for the prevention of epidural hematoma. The position of the migrated LDH is changeable, and local adhesion is serious most of the time, so the conventional approach may be blocked by the bony structure and result in poor outcomes. The position of the incisions can be adjusted according to the position of the herniation, whole spinal canal exploration needs to be performed before the end of the operation, and the working portal and viewing portal can be exchanged if necessary to expand the exploration range.

2. How to Shorten the Learning Curve

In the early phase of learning, we did not avoid some difficult cases deliberately, which leads to the prolongation of the operation time and the rapid rise of the learning curve in CUSUM analysis. The resection of LF is a relatively time-consuming and tricky step in the operation. Therefore, we suggest beginners to choose simple LD surgery by the left-side approach in early phase, which may reduce the difficulty of practicing. Apply of 0° endoscope in the early phase can make beginners adapt to UBE surgery more quickly. Additionally, standardized training and practicing on models or cadavers are of great help to shorten the learning curve.

CONCLUSIONS

In this work, the learning curve of UBE surgery was evaluated by CUSUM and RA-CUSUM analysis based on operation time and incidence of complications, and satisfactory clinical outcomes were achieved with low incidence of complications. Our data indicated that the number of cases for overcoming the learning curve of UBE surgery was 54 cases, and increased to 89 cases when the incidence of complications was taken into account. The appropriate early cases selection and standardized training are helpful to shorten the learning curve.

NOTES

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ORCID

Jinchao Xu: 0000-0003-3440-4567
Dong Wang: 0000-0001-5379-2038
Jidan Liu: 0000-0001-7202-5790
Chengyue Zhu: 0000-0001-9653-7336
Jianhang Bao: 0000-0002-4629-3625
Wenshuo Gao: 0000-0003-1764-9829
Wei Zhang: 0000-0001-8949-9220
Hao Pan: 0000-0002-9140-1912

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Successful Criteria for Indirect Decompression With Lateral Lumbar Interbody Fusion

Wicharn Yingsakmongkol¹,², Khanathip Jitpakdee¹,³, Stephen Kerr⁴,⁵, Worawat Limthongkul¹,², Vit Kotheeranurak¹,², Weerasak Singhatanadgige¹,²

¹Department of Orthopaedics, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand
²Center of Excellence in Biomechanics and Innovative Spine Surgery, Chulalongkorn University, Bangkok, Thailand
³Department of Orthopedics, Queen Savang Vadhana Memorial Hospital, Thai Red Cross Society, Sriracha, Chonburi, Thailand
⁴Biostatistics Excellence Centre, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
⁵The Kirby Institute, University of New South Wales, Sydney, Australia

Objective: No consensus criteria have been established regarding ideal candidates for indirect decompression with lateral lumbar interbody fusion (LLIF), and contributing factors of indirect decompression failure were rarely reported. We aim to investigate the success rate of indirect decompression by LLIF with proposed selection criteria and identify risk factors associated with indirect decompression failure, defined as persistent pain requiring revision with direct decompression.

Methods: Data from 191 patients undergoing LLIF were retrospectively reviewed. All the following criteria must be fulfilled: (1) dynamic clinical symptoms (pain relief in supine position), (2) presence of reducible disc height (recovered disc height in supine position), (3) no profound weakness, and (4) no static stenosis. The success rate of indirect decompression with LLIF and results after at least 1 year of follow-up were collected. Preoperative, procedure-related, and postoperative factors were assessed for their relationship with failure.

Results: Of 191 patients, 13 patients (6.8%) required additional direct decompression due to persistent pain, giving a criteria success rate of 93.2%. Factors associated with indirect decompression failure included low bone mineral density (T-score < 2.1), low reducible disc height (<13%), low postoperative disc height (< 10 mm), high-grade cage subsidence, and use of plate fixation.

Conclusion: We proposed patient selection criteria for indirect decompression with LLIF which had a satisfactory success rate and identified factors associated with the need for additional direct decompression. Our proposed criteria may assist selection of patients likely to achieve good results following indirect decompression with LLIF, and optimize selection based on risk factors of failure.

Keywords: Indirect decompression, Lateral lumbar interbody fusion, Lateral lumbar interbody fusion, Oblique lumbar interbody fusion, Extreme lateral lumbar interbody fusion, Criteria

INTRODUCTION

Degenerative disease of the lumbar spine is one of the most common causes of morbidity in aging societies. Many patients with degenerative lumbar disease, who failed conservative treatment, ultimately required surgery.¹,² In cases with neural compression and segmental instability, decompression and fusion procedures are usually performed. In recent years, lateral lumbar interbody fusion (LLIF), either the prepsosas (oblique lumbar interbody fusion, OLIF) or transpsoas approach (extreme
lateral lumbar interbody fusion, XLIF), has become a popular surgical procedure. Decompression of neural elements is achieved indirectly by restoring disc and foraminal height, unbuckling of the ligamentum flavum, and correction of sagittal and coronal deformities. Many reports have shown favorable results following indirect decompression with LLIF for lumbar degenerative diseases. LLIF has many advantages, especially in elderly patients with multiple comorbidities who cannot tolerate a long operative time or significant blood loss, which can occur with traditional open direct decompressive surgery. The LLIF procedure avoids aggressive muscle dissection and preserves the posterior spinal ligament and musculature. However, in some circumstances, the indirect decompression effect is not sufficient to relieve neural compression, and thus necessitates a subsequent revision surgery for direct decompression. Most studies have defined the need for revision with direct decompression as an indirect decompression failure. To date, only a few studies with small subjects have used an algorithmic approach to select cases for this procedure. A systematic review by Kirnaz et al. estimated the pooled incidence of indirect decompression failure following LLIF as 9%, but limited studies in the review had clear patient selection criteria, and most did not investigate the causes of failure.

Despite the benefits and clinical success of indirect decompression and fusion with LLIF, no consensus criteria have been established regarding ideal candidates for this procedure, and factors that might predict candidates in whom the procedure is likely to fail. We developed a set of clinical and radiographic criteria for selecting surgical candidates. The objectives of the present study were to (1) determine the success and failure rates in patients who underwent indirect decompression by LLIF using our proposed criteria and (2) evaluate risk factors resulting in failure (persistent symptoms requiring subsequent direct decompression at the index level that occurred within 6 months following the LLIF procedure).

MATERIALS AND METHODS

1. Study Design, Patient Sample, and Selection

We conducted a retrospective analysis of consecutive patients who underwent indirect decompression with LLIF (XLIF or OLIF) at our hospital between April 2014 and June 2020. Patients with lumbar degenerative diseases undergoing 1–2 levels of indirect decompression with LLIF were eligible for inclusion if they met all of the following criteria: (1) dynamic clinical symptoms, defined as pain developing when standing or walking, but subsiding by >50% when resting in a supine position; (2) no profound weakness, defined as having motor power less than grade IV; (3) reducible disc height, defined as the presence of a recovered disc height at least 1 mm when changing from upright to supine positions; and (4) no static stenosis such as facet cysts or bony lateral recess (evaluated with magnetic resonance imaging [MRI] and computed tomography [CT], respectively). Patients who were preoperatively planned for combined direct and indirect decompression and patients with incomplete 1-year follow-up data were excluded. The participants were classified into 2 groups based on the outcome of symptom resolution postoperatively: success, and failure group which was defined by persistent pain requiring reoperation for direct decompression within 6 months after LLIF procedure. This study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital (approval #729/63) and written informed consent was obtained from all patients. The research was conducted according to the World Medical Association Declaration of Helsinki.

2. Surgical Technique

All surgeries were performed at a single institution by 1 of 3 senior spine surgeons. The LLIF procedure was performed in the right lateral decubitus or prone position. Intraoperative neurophysiological monitoring was performed in all patients with XLIF. The skin incision directed to the operated level was determined using O-arm navigation or fluoroscopy. Muscle dissection was performed layer by layer to identify the corridor for LLIF using transpoas for XLIF or the prepsoas approach for OLIF. The dilator and tubular retractor were used to access the intervertebral disc index. Annulotomy, discectomy, and cartilaginous endplate removal were performed. The trial cage for XLIF (NuVasive Inc., San Diego, CA, USA) or OLIF (Clydesdale Spinal System, Medtronic, Minneapolis, MN, USA) was inserted using an orthogonal maneuver. After the appropriate size was checked under the fluoroscope, a cage filled with bone graft or bone substitute was implanted. The instrumentation was performed in most cases using selected fixation, such as percutaneous posterior pedicular screw-rod fixation or lateral fixation with a plate or screw-rod system. Otherwise, stand-alone LLIF was selected in some cases. The implant position was confirmed using O-arm navigation or fluoroscopy before wound closure. All patients were treated according to the same pain control protocol and ambulated the day after the operation. If no complications occurred, they were discharged approximately 3 days postoperatively.
3. Data Collection and Outcome Measurement

Postoperative data were retrospectively collected from the electronic medical records and radiographs of consecutive patients treated with XLIF (NuVasive Inc.) or OLIF (Medtronic OLIF25) according to the study inclusion and exclusion criteria. Patients were scheduled for follow-up examinations at 1, 3, 6, 12, and 24 months postoperatively for clinical and radiographic assessments. Demographic clinical data retrieved included age, sex, bone mineral density (BMD), body mass index, diagnosis, number of operated levels, smoking status, history of previous lumbar surgery, comorbidities, length of follow-up period, preoperative Oswestry Disability Index (ODI), visual analogue score of leg (VASL), and back pain (VASB). The operative data collected included LLIF type, cage size, lordotic angle, cage position, type of fixation, and use of biologics. The preoperative and postoperative radiographic parameters were recorded, including reducible disc height (percentage of disc height discrepancy between supine and standing position) (Fig. 1), disc and foraminal height, lordotic angle, spinal canal diameter, and cage subsidence. Disc height was calculated as the average of the sum of the anterior and posterior disc heights. The lordotic angle was measured as the angle between the upper endplate of the upper vertebra and the lower endplate of the lower vertebrae of the fusion level. Bony fusion was evaluated with CT scan and defined as presence of continuous bony bridge connecting 2 vertebrae.\textsuperscript{12,13} Cage subsidence grading was measured by the percentage of endplate collapse as described by Marchi et al.\textsuperscript{14} which was classified as low-grade (grade 0: 0%–24% and grade I: 25%–50%) and high-grade subsidence (grade II: 51%–74% and grade III: 75%–100%).

Functional outcomes were assessed postoperatively in the form of the ODI, VAS of back and leg pain, and the satisfaction score at each follow-up. The radiographic outcome measures, including disc height, spinal canal parameters, and segmental lordosis, were evaluated. Bony fusion and postoperative complications, such as cage subsidence, migration, infection, or pseudarthrosis, were also evaluated by CT scan and MRI. Examples of success and failure cases of indirect decompression were shown in Figs. 2, 3.

4. Statistical Analysis

Demographic and disease-related characteristics were described...
in the patients overall and in the failure group. Formal comparisons between continuous parameters fixed within patients were made using the Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables. Comparisons of variables that differed by level in patients with procedures at 2 levels were assessed using generalized estimating equa-

Table 1. Preoperative demographic data, clinical and procedure-related characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 191)</th>
<th>Success (n = 178)</th>
<th>Failure (n = 13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65 (59–73)</td>
<td>65 (59–72)</td>
<td>71 (59–75)</td>
<td>0.27</td>
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<tr>
<td>Female sex</td>
<td>178 (93.2)</td>
<td>159 (89.3)</td>
<td>12 (92.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 (22.5–27.5)</td>
<td>24.7 (22.4–27.4)</td>
<td>24.8 (22.2–28.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>-1.1 (-1.8 to 0)</td>
<td>-1.04 (-1.7 to 0.1)</td>
<td>-2.7 (-2.8 to -2.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoker</td>
<td>7 (3.7)</td>
<td>6 (3.5)</td>
<td>1 (7.7)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>DDD/HNP</td>
<td>27 (14.1)</td>
<td>26 (14.6)</td>
<td>1 (7.7)</td>
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<tr>
<td>Spinal stenosis</td>
<td>20 (10.5)</td>
<td>17 (9.6)</td>
<td>3 (23.1)</td>
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</tr>
<tr>
<td>Degen. spondylolisthesis</td>
<td>62 (32.5)</td>
<td>59 (33.2)</td>
<td>3 (23.1)</td>
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<tr>
<td>Isthmic spondylolisthesis</td>
<td>8 (4.2)</td>
<td>8 (4.5)</td>
<td>0 (0)</td>
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<tr>
<td>Degenerative scoliosis</td>
<td>14 (7.3)</td>
<td>13 (7.3)</td>
<td>1 (7.7)</td>
<td></td>
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<tr>
<td>FBSS</td>
<td>9 (4.7)</td>
<td>9 (5.1)</td>
<td>0 (0)</td>
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<tr>
<td>ASD</td>
<td>51 (26.7)</td>
<td>46 (25.8)</td>
<td>5 (38.5)</td>
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<tr>
<td>ODI</td>
<td>44.4 (31.1–60)</td>
<td>45 (32–60)</td>
<td>45 (24.4–55.6)</td>
<td>0.32</td>
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<td>VASL</td>
<td>7 (5–8)</td>
<td>7 (5–8)</td>
<td>8 (0–9)</td>
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<td>VASB</td>
<td>6 (1.25–8)</td>
<td>6 (1–8)</td>
<td>6 (4–8)</td>
<td>0.22</td>
</tr>
<tr>
<td>No. of treated levels</td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>One</td>
<td>147 (77.0)</td>
<td>135 (75.8)</td>
<td>12 (92.3)</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>44 (23.0)</td>
<td>43 (24.2)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Navigated O-arm</td>
<td>74 (38.7)</td>
<td>73 (41)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Follow-up period (mo)</td>
<td>24 (12–40)</td>
<td>24 (12–39)</td>
<td>34 (24–46)</td>
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</tr>
<tr>
<td>LLIF type</td>
<td></td>
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<td>0.78</td>
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<tr>
<td>Prepsoas (OLIF)</td>
<td>82 (42.9)</td>
<td>77 (43.2)</td>
<td>5 (38.5)</td>
<td></td>
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<tr>
<td>Transpsoas (XLIF)</td>
<td>109 (57.1)</td>
<td>101 (56.7)</td>
<td>8 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Cage</td>
<td></td>
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<tr>
<td>Height</td>
<td>10 (10–10)</td>
<td>10 (10–10)</td>
<td>10 (9–11)</td>
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<tr>
<td>Width</td>
<td>18 (18–45)</td>
<td>18 (18–45)</td>
<td>18 (18–40.5)</td>
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</tr>
<tr>
<td>Length</td>
<td>55 (50–55)</td>
<td>55 (50–55)</td>
<td>50 (45–55)</td>
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<tr>
<td>Lordotic angle</td>
<td>10 (6–10)</td>
<td>10 (6–10)</td>
<td>10 (8–10)</td>
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<td>Fixation type</td>
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<td>Standalone</td>
<td>19 (8.1)</td>
<td>18 (8.1)</td>
<td>1 (7.1)</td>
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<tr>
<td>Posterior PDS</td>
<td>169 (71.9)</td>
<td>163 (73.8)</td>
<td>6 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Anterolateral plate</td>
<td>40 (17.0)</td>
<td>33 (14.9)</td>
<td>7 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Lateral screw-rod</td>
<td>7 (3.0)</td>
<td>7 (3.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%). BMI, body mass index; BMD, bone mineral density; DDD, degenerative disc disease; HNP, herniated nucleus pulposus; FBSS, failed back surgery syndrome; ASD, adjacent segment disease; ODI, Oswestry Disability Index; VASL, visual analogue scale of leg pain; VASB, visual analogue scale of back pain; LLIF, lateral lumbar interbody fusion; PDS, pedicular screw.
tions (GEE). Receiver-operating curve (ROC) analysis was used to identify thresholds for preoperative and postoperative radiographic parameters with an increased risk of failure, and cutoff values were determined using the point that maximized the sensitivity and specificity (Youden index).\textsuperscript{15} GEE with a binomial family, logit link, exchangeable correlation matrix, and robust variance estimates were used to account for the within-patient correlation when assessing associations between demographic, operative, and pre- and postoperative radiographic characteristics, and the risk of failure. Factors with \( p < 0.1 \), in univariate models, were adjusted for in a multivariable model. The probabilities predicted by this model were calculated assuming equal numbers of observations for each categorical term in the model. Decisions regarding statistical and clinical significance were made on the basis of \( p \)-values and 95% CI.\textsuperscript{16} Statistical analysis was conducted using Stata 17.0 (Statacorp, College Station, TX, USA).

**RESULTS**

Patient demographic data and clinical and procedure-related characteristics are summarized in Table 1. Of the 217 eligible patients who underwent LLIF procedures, a total of 191 (235 fusion levels) had all required clinical and radiographic data and returned for scheduled follow-up visits in the first 12 months with a median (IQR) follow-up of 24 months (12–40 months). Of the 191 patients, 147 underwent fusion at one level and 44 underwent fusion at 2 contiguous levels. Thirteen patients (6.8%) experienced unsuccessful indirect decompression at any level, giving an overall success rate of 93.2% (178 of 191). Demographic and baseline characteristics were similar between the groups. The overall median (IQR) age was 65 years (59–73 years), with a female predominance (93%, 178 of 191). The most common diagnoses were degenerative spondylolisthesis, followed by adjacent segment disease, degenerative disc disease, or herniated nucleus pulposus in 32.5%, 26.7%, and 14.1%, respectively. The most commonly operated level was L4–5 (56%). Patients in the failure group had a fixation type of anterolateral plate more than those in the success group, whereas other procedure-related characteristics did not differ between the groups, including the number of treated levels, different fusion segments, different approach directions (either OLIF or XLIF), cage profile, use of O-arm navigator, and follow-up period. In 67 patients who had a BMD available, the median (IQR) BMD was significantly lower in the failure group: -2.7 (-2.8 to -2.2) versus -1.0 (-1.7 to 0.1) respectively; \( p < 0.001 \).

All patient-reported outcomes, including ODI, VASL, and VASB score following surgery in the success group showed sta-

### Table 2. Preoperative and postoperative radiographic parameter values, by failure group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 235)</th>
<th>Success (n = 221)</th>
<th>Failure (n = 14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reducible disc height (%)</td>
<td>13.65 (8.4–21.18)</td>
<td>14.25 (8.68–22.13)</td>
<td>8.04 (5.09–11.52)</td>
<td>0.003</td>
</tr>
<tr>
<td>Disc height (mm)</td>
<td>8.07 (6.61–9.85)</td>
<td>8.08 (6.61–9.80)</td>
<td>7.47 (6.99–10.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Foraminal height (mm)</td>
<td>17 (14.98–18.69)</td>
<td>17.05 (14.95–18.8)</td>
<td>16.58 (15.9–18.46)</td>
<td>0.87</td>
</tr>
<tr>
<td>Canal diameter (mm)</td>
<td>12 (10.19–13.91)</td>
<td>11.9 (10.17–13.9)</td>
<td>12.76 (12.18–14.45)</td>
<td>0.32</td>
</tr>
<tr>
<td>Lordotic angle (°)</td>
<td>10 (5–15)</td>
<td>10 (5–15)</td>
<td>9 (7–10)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disc height (mm)</td>
<td>12.2 (10.4–13.4)</td>
<td>12.195 (10.53–13.42)</td>
<td>9.36 (8.5–11.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Foraminal height (mm)</td>
<td>19.5 (17.7–21.6)</td>
<td>19.7 (17.9–21.6)</td>
<td>18.0 (16.6–19.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Canal diameter (mm)</td>
<td>14.2 (12.5–16.1)</td>
<td>14.2 (12.4–16.1)</td>
<td>14.3 (13.1–15.5)</td>
<td>0.64</td>
</tr>
<tr>
<td>Lordotic angle (°)</td>
<td>13 (7–17)</td>
<td>13 (7–17)</td>
<td>10.5 (4–15)</td>
<td>0.22</td>
</tr>
<tr>
<td>Cage subsidence (mm)</td>
<td>2 (0.1–3.5)</td>
<td>2 (0–3.2)</td>
<td>5.1 (2.5–8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>135 (57.5)</td>
<td>133 (60.2)</td>
<td>2 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>77 (32.8)</td>
<td>73 (33.0)</td>
<td>4 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>12 (5.1)</td>
<td>11 (5.0)</td>
<td>1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>11 (4.7)</td>
<td>4 (1.8)</td>
<td>7 (50)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or number (%).
tistically significant improvements compared to the failure group at all follow-up assessments. The average ODI changes in the success group and the failure group were -29.3 ± 17.2 and 1.4 ± 9.6, respectively. The VASL changes were -4.6 ± 3.5 and -1.7 ± 2 while the VASB changes were -4.6 ± 3.5 and -1.5 ± 2.3, respectively. The median time to reoperation with additional direct decompression in the failure group was 4.5 months (range, 2.5–6.0 months).

The preoperative and postoperative radiographic factors are shown in Table 2. Reducible disc height was the only preoperative parameter that differed significantly between the success and failure groups, with a median (IQR) of 14.3% (8.7%–22.1%) and 8.0% (5.1%–11.6%), respectively (p < 0.001). Postoperative radiographic factors that differed significantly between the outcome groups were postoperative disc height and cage subsidence. Postoperative disc height was higher in the success group than the failure group at a median (IQR) of 12.2 mm (10.5–13.4 mm) and 9.4 mm (8.5–11.5 mm), respectively. Likewise, cage subsidence grading was also higher in the success group at median (IQR) of 2.0 (0–3.2) and 5.1 (2.5–8.8), respectively. Overall mean fusion rate of LLIF in this study was 93.2%, which was not significantly different between both groups. The fusion rate also did not differ by the number of fused levels.

In our ROC curve analysis, we assessed cutoff thresholds that maximized the ability of the continuous parameters to discriminate patients with failure. The cutoffs were BMD T-score < -2.1 (AROC = 0.84; 95% CI, 0.64–1.0), reducible disc height < 13% (0.71 (0.61–0.80), and postoperative disc height ≤ 10 mm 0.69 (95% CI, 0.56–0.83). The sensitivity, specificity, and AROC of these parameters at their cutoff points are shown in Table 3. Five factors showed an association with failure in the univariate analysis (Table 4). Of these, BMD assessments were only conducted in 35% of the study participants, therefore we were unable to adjust for this variable in our multivariable model. In the model that adjusted for the remaining factors, 3 factors were independently associated with a significantly increased risk of failure. These were high-grade subsidence (OR, 13.9; 95% CI, 3.4–56.0; p < 0.001), reducible disc height < 13% (OR, 18.9; 95% CI, 3.8–93.9; p < 0.001), and postoperative disc height ≤ 10 mm (OR, 3.6; 95% CI, 0.98–12.9; p = 0.054). In those with none of these risk factors, the predicted failure probability (95% CI) was 0.3 (0%–0.8%). The combination of high-grade subsidence, postoperative disc height ≤ 10 mm, and reducible disc height < 13% resulted in a predicted failure probability of 71.7% (44.9%–98.5%).

DISCUSSION

In this study, we reported the rate of indirect decompression failure after applying our selection criteria to be as low as 6.8% which was relatively lower than those reported in previous studies.8,9,17-19 All criteria were made of patient characteristics which

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**Table 3.** Table showing sensitivity and specificity at dichotomized cutoffs for continuous parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AROC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducible disc height &lt; 13%</td>
<td>85.7</td>
<td>56.0</td>
<td>0.71 (0.61–0.80)</td>
</tr>
<tr>
<td>Postop disc height &lt; 10 mm</td>
<td>57.1</td>
<td>82.4</td>
<td>0.69 (0.56–0.83)</td>
</tr>
<tr>
<td>BMD T-score &lt; -2.1</td>
<td>80.0</td>
<td>88.9</td>
<td>0.84 (0.64–1.0)</td>
</tr>
</tbody>
</table>

AROC, area under the receiver-operating characteristic curve; CI, confidence interval; Postop, postoperative; BMD, bone mineral density.

**Table 4.** Univariable and multivariable of factors associated with failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>BMD T-score &lt; -2.1</td>
<td>32.6 (3.0–351.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>O-arm navigated vs. nonnavigated</td>
<td>0.2 (0.02–1.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Reducible disc height &lt; 13%</td>
<td>6.7 (1.8–25.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Postoperative disc height &lt; 10 mm</td>
<td>5.1 (2.0–12.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fixation</td>
<td>0.02</td>
<td>0.21</td>
</tr>
<tr>
<td>Lateral screw-rod or posterior PDS</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Anterolateral plate</td>
<td>5.6 (1.7–18.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Standalone</td>
<td>1.5 (0.2–13.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>High-grade subsidence</td>
<td>15.6 (4.8–50.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

OR, odds ratio; aOR, adjusted OR; PDS, pedicular screw; BMD, bone mineral density.

*Since BMD was available in only 35% of patients, we were unable to include this variable in the multivariate model.
all of them were nonmodifiable patient factors, so we believed that these factors would comprise a practical prerequisite for the procedure. While the analyzed risk factors leading to failure were modifiable factors either preoperatively or intraoperatively. These factors should be adjusted to optimize the outcomes. The identified risk factors leading to indirect decompression failure in this study included low BMD, low preoperative reducible disc height, low postoperative disc height, fixation with anterolateral plate and high-grade subsidence. The reported rate of failure in a study by Oliveira et al.\textsuperscript{19} showed that 9.5% of patients had insufficient relief of nerve compression symptoms and required additional direct posterior decompression. The causes of failure were identified to be cage subsidence, loss of sagittal alignment correction, and persistent central and foraminal stenosis. Rentenberger et al.\textsuperscript{20} reported an 18.8% surgical revision rate due to neurological symptoms, pain, or radiculopathy, while other studies have reported significantly higher failure rates. The rate of additional posterior decompression after XLIF was 60% in a study reported by Kim et al.\textsuperscript{21} and Park et al.\textsuperscript{2} reported that the need for direct decompression and instrumentation in a second operation was as high as 72.1% in patients with leg pain that improved ≤ 50% after the index procedure.

Although many published studies have reported indirect decompression failure following LLIF, only a few have provided clear guidance for selecting appropriate candidates to undergo indirect decompression with LLIF. Lim et al.\textsuperscript{23} proposed the prerequisite of preoperative postural pain status to guide patient selection for indirect decompression with XLIF. The ability to achieve a pain-free position, such as sitting or lying, was a clinical predictor of successful XLIF for patients with lumbar spinal stenosis. An algorithmic approach to predict success of indirect decompression with LLIF was suggested by Gabel et al.\textsuperscript{24} in a case series of 28 patients. Patients who achieved pain relief at rest and lacked facet fusion, free disc fragments, facet cysts, osteoporosis, and severe spinal stenosis were unlikely to require revision surgery for direct decompression.

In this study, we proposed criteria for selecting surgical candidates for indirect decompression with LLIF. Each criterion had a significant impact on the results of the procedure; therefore, all criteria must be met for patients to be eligible for the surgery. First, we defined dynamic clinical symptoms as the ability to achieve pain relief of more than 50% when resting in a supine position compared with standing or walking. This definition was referenced in the study by Gabel et al.\textsuperscript{25} who also proposed the same criterion. As mentioned earlier, the reduction of preoperative pain when resting in a supine position is one of the clinical predictors of successful LLIF without direct decompression in patients with lumbar spinal stenosis.\textsuperscript{10} Significant pain relief could imply that the dynamic disc distraction and ligamentotaxis effects from LLIF resulted in an increased interlaminar space and that unbucketing of the ligamentum flavum was effective and adequate. Conversely, persistent pain despite resting in a supine position suggests the presence of severe spinal canal stenosis with significant static nerve compression that would only be sufficiently relieved with a direct decompression.\textsuperscript{10} Moreover, even the direct decompressive laminectomy was also reported to result in a significantly better pain relief in patients with dynamic clinical symptoms versus those with constant pain not improved with posture.\textsuperscript{22} Second, patients must have no significant weakness, which is defined as having motor strength less than grade IV; the greater severity of weakness correlates with a higher degree of neural compression that may not be sufficiently relieved by indirect decompression alone. The third criterion was the presence of a disc height discrepancy ≥ 1 mm between supine and upright positions. The ability to restore the disc height when lying in a supine position indicates the flexibility of the affected segment. Thus, we hypothesized that patients with intervertebral disc structures with less stiffness are more likely to obtain more disc height from the LLIF interbody cage, leading to an increased indirect decompression effect. Similarly, Choi et al.\textsuperscript{26} described the discrepancy of the disc height on postural change. This phenomenon may suggest the advanced desiccation and vertical instability of the segment, which results in poor outcomes following surgical decompression alone. This sign was also described as an effective screening method for discogenic back pain in patients with lumbar disc degeneration.\textsuperscript{24} The last criterion was that spinal canal stenosis must not be caused by facet cyst or bony lateral recess, evaluated with MRI and CT,\textsuperscript{2,25} as these static lesions significantly decrease the indirect decompression effect from the ligamentotaxis mechanism and have been proven to contribute to failure of indirect decompression alone.\textsuperscript{2,18,25}

With all the criteria applied, the success rate of indirect decompression with LLIF was 93.2%. To the best of our knowledge, when compared with previous literature, this study included more subjects and also demonstrated a relatively high success rate with significant improvement of clinical and radiographic outcomes (Table 5). Our proposed criteria were developed because of their theoretical advantages that would contribute to satisfactory results, and each was supported by evidence from previous studies. The suggested criteria consisted of a combination of clinical and radiographic considerations. More-

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over, each criterion had a clear and strict definition that was simple to apply in clinical practice.

All of the patients in the failure group had revision surgery with posterior direct decompression. Intraoperative findings revealed significant remaining neural compression especially from the buckling ligamentum flavum, that were correlated with the postoperative MRI. Following the direct decompression, the pain was significantly relieved in all patients. Thus, we concluded that poor outcomes among these patients may contribute from the failed indirect decompression. To avoid revision surgery, many studies have identified factors contributing to the failure of indirect decompression with LLIF. Wang et al. studied the preoperative radiographic factors of failed indirect decompression via XLIF and concluded that bony lateral recess stenosis is a significant factor resulting in failure to achieve adequate decompression via XLIF. Oliveira et al. reported multiple factors including the presence of congenital stenosis or short pedicles, uncontained disc fragments, locked facets with calcified discs, the presence of posterior endplate osteophytes compromising the lateral recess, and synovial cysts and radiculopathy unimproved with flexion posture.

We also analyzed risk factors of indirect decompression failure, leading to reoperation for direct decompression. A low postoperative disc height, especially less than 10 mm, was found to be associated with failure. This finding is in accordance with the study by Park et al. which found that the subjects who needed direct decompression following LLIF had mean postoperative disc height of 9.4 mm. The degree of postoperative disc height had positive effects on the increased foraminal height and ligamentotaxis that indirectly decompressed the neural elements.

Although OLIF and XLIF had different approach directions that made the cage position slightly different, our study did not find any significant effect on postoperative clinical outcomes following both approaches. The number of operated levels, different fusion segments, and cage characteristics were also not the contributing factors to failure. These findings were consistent with previous literature.

The degree of reducible disc height, defined as the preoperative disc height discrepancy between the standing and supine positions, also affected the surgical outcome. A higher disc height obtained in the supine position was associated with successful results. This could be explained by the lower segmental stiffness, resulting in a greater postoperative disc height and more indirect decompression effect. Moreover, if the segment is too rigid to be restored, the risk of subsidence increases. Our results showed that when the restored disc height in the supine position was less than 13%, the risk of failure increased significantly.

Although not an independent predictor of failure, our study found an increased risk of failure when supplementary fixation was achieved using anterolateral plates after adjusting for other covariates. Previous biomechanical studies also showed that this type of fixation may not be strong enough, thus leading to an increased risk of subsidence as a consequence of high cage and endplate stress. The standalone LLIF construct has also been

<table>
<thead>
<tr>
<th>Study</th>
<th>Need additional direct decompression</th>
<th>Criteria applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oliviera et al.,19 (2010)</td>
<td>9.5% (2/21)</td>
<td>Not specific</td>
</tr>
<tr>
<td>Malham et al.,7 (2015)</td>
<td>9% (11/122)</td>
<td>Not specific</td>
</tr>
<tr>
<td>Gabel et al.,11 (2015)</td>
<td>3.5% (1/28)</td>
<td>1. Lack of facet fusion on computed tomography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. No free disc fragment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. No compressive facet cyst on magnetic resonance imaging (MRI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. No frank osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. No congenital and/or severe spinal stenosis on MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Significant reduction (&gt; 50%) in leg and back pain at rest</td>
</tr>
<tr>
<td>Wang et al.,18 (2017)</td>
<td>29% (13/45)</td>
<td>Not specific</td>
</tr>
<tr>
<td>Lim et al.,10 (2019)</td>
<td>2% (1/50)</td>
<td>Dynamic clinical symptoms (able to achieve a pain-free position preoperatively)</td>
</tr>
<tr>
<td>Rentenberger et al.,16 (2020)</td>
<td>19% (25/133)</td>
<td>Not specific</td>
</tr>
<tr>
<td>Park et al.,8 (2020)</td>
<td>72% (62/86)</td>
<td>Not specific</td>
</tr>
<tr>
<td>This study (2021)</td>
<td>6.8% (13/191)</td>
<td>1. Dynamic clinical symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Presence of reducible disc height</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. No profound weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. No static stenosis</td>
</tr>
</tbody>
</table>
reported to be at a higher risk of subsidence and failure; however, the number of patients with this type of construct in our study was low. Therefore, the failure rate of this construct may be underrecognized.\cite{12, 27-29} According to our results and previously published data, we note that both standalone LLIF and anterolateral plate fixation are at high risk of failure and recommend their use with caution, especially in patients with osteoporosis or significant instability.

Our study's overall fusion rate of LLIF was as high as 93.2%, regardless of the number of fused levels, and did not significantly differ between both groups. Despite using bone substitutes, the fusion rate of LLIF in our study was comparable to those reported in previous studies and also not different from posterior fusion using autologous bone graft.\cite{12, 30, 31} The benefits of LLIF in terms of bony fusion included the larger cage containing more bone grafts, and the ability to be placed to cover dense apophyseal rings bilaterally for structural support.\cite{30}

Cage subsidence is generally known as a major cause of indirect decompression failure as it directly lessens the decompression effect after LLIF, resulting in revision surgery.\cite{32-34} This is supported by our results that high-grade subsidence (grades II–III) was associated with failure. Therefore, intraoperative endplate injury should be avoided, especially in patients with other known risk factors of subsidence, such as advanced age, osteoporosis, and specific endplate morphology.\cite{34, 35}

There are some limitations to our study. The retrospective design was subject to selection bias as well as incomplete data; however, we attempted to minimize these factors by enrolling all eligible patients and using electronic medical records. The BMD as an important risk factor for failure was only available in approximately one-third of patients, so assessing how other factors might be influenced after adjustment for BMD was not possible. Additionally, because of the small number of revision surgeries, the power to ascertain a potential association of factors that might be associated with a small to moderate increased risk of failure was reduced. As etiologies of indirect decompression failure were multifactorial, there were other factors that potentially contributed to failure in LLIF. For example, the preoperative shape of spinal canal stenosis could potentially affect postoperative clinical and radiological results following indirect decompression with LLIF. However, previous studies failed to reach conclusion on the correlation between shape of spinal canal and outcomes after decompression.\cite{36, 37} Moreover, the shape of the spinal canal was difficult to determined and classified into groups to be analyzed. Thus, a further study focusing on types of spinal canal morphology and indirect decompression effect was required. The strengths of our study include the large number of patients, all operated on at a single center, and identical standard operating procedures and similar standards of care to all patients. Nevertheless, further studies with larger sample sizes are necessary to confirm our findings and identify additional significant risk factors for failure. Moreover, applying our proposed criteria for patient selection in posterior fusion with direct decompression surgery would be an interesting further study.

**CONCLUSION**

Our study presents the patient selection criteria for indirect decompression with LLIF; which resulted in a satisfactory success rate. Risk factors for reoperation with direct decompression included low BMD, low preoperative disc height discrepancy between standing and supine position, use of supplemental fixation with anterolateral plate, low postoperative disc height, and high-grade cage subsidence. Our proposed criteria and reported risk factors may provide guidance for spine surgeons to select appropriate patients who could achieve good results following indirect decompression with LLIF and optimize patient selection based on modifiable risk factors resulting in failure.

**NOTES**

**Conflict of Interest:** WL and WS have received speaker and consultant honoraria from Medtronic company. Other authors declare they have no financial interests. The other authors have nothing to disclose.

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**ORCID**

Wicharn Yingsakmongkol: 0000-0002-8784-7604
Khanathip Jitpakdee: 0000-0002-5955-0037
Worawat Limthongkul: 0000-0002-0116-8791
Weerasak Singhatanadgige: 0000-0001-7166-1381
Vit Kotheeranurak: 0000-0002-9593-429X

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Objective: The specific association between morphometric characteristics of the syrinx and the prognosis of Chiari malformation type I (CM-I) with syringomyelia following surgical procedure seems to have not been fully elaborated. This study focused on the preoperative clinical and radiologic parameters in CM-I patients with syringomyelia to find out the relationship between the patients’ clinical status and the phenotypes of the syrinx with surgical outcome.

Methods: A continuous series of pediatric and adult patients with CM-I and syringomyelia from a prospectively maintained database in a single center were included, and we explored the related factors affecting the prognosis following decompression surgery through retrospective analysis of clinical presentations, imaging characteristics, and the morphological features of syringomyelia, to provide a clinical reference for the treatment of syringomyelia.

Results: There were 28 pediatric patients (13.8%), and 174 adults (86.2%) included in our study. The average Chicago Chiari Outcome Scale score was 14.56 ± 1.78. The overall prognosis after surgery was good in our series, among them 152 cases (75.25%) with a favorable prognosis, and syrinx was resolved effectively in 172 cases (85.15%). According to the univariate and multivariate analyses, the preoperative symptom duration, observation time, and with/without moniliform type were independent factors affecting the prognosis in adults. The most obvious difference between moniliform type and nonmoniliform type lies in the preoperative symptom duration, ventral subarachnoid space at the foramen magnum, and with/without straightened cervical physio-curve.

Conclusion: Timely decompression surgery could achieve a better outcome in CM-I patients with syringomyelia. Moniliform syringomyelia may suggest a relatively better prognosis.

Keywords: Syringomyelia, Chiari malformation type 1, Posterior fossa decompression, Morphometric feature, Prognosis
INTRODUCTION

Syringomyelia is a fluid-filled cavity that originates in the tissue or central canal of the spinal cord.\(^1,2\) That may occur secondary to various etiologies, including Chiari malformation type I (CM-I), trauma, tumor, tethered cord syndrome, or spinal arachnoiditis.\(^3,4\) Among these, CM-I is a condition characterized by caudal displacement of the cerebellar tonsils through the foramen magnum (FM).\(^5\) Many hypotheses have been brought forward to explain the pathophysiological basis for the development of the syringomyelia associated with CM-I, which usually points to a gradual neurological deterioration caused by subarachnoid space (SAS) obstruction that extends over many years.\(^6-8\) At present, the conclusions on the pathogenic mechanisms of the disease and related predicting factors remain inconsistent.

In recent years, with the widespread use of magnetic resonance imaging (MRI), there was an increasing number of patients screened with syringomyelia. Surgical management initially focused on treating the etiology of the syringomyelia,\(^9\) primarily by re-establishing the physiologic pathways of cerebrospinal fluid (CSF) in the SAS.\(^10\) Mostly, the surgical goal is to reconstruct the craniovertebral junction (CVJ) with duraplasty.\(^11\) Previous studies have suggested that early diagnosis and surgical intervention such as posterior fossa decompression (PFD) have made it possible to reduce the size of the syrinx.\(^12\) No evidence was seen for surgical treatment of incidental asymptomatic syringomyelia, but it is recommended to treat without delay for stepwise evolutive syringomyelia, which means a severe disease with a bad impact on quality of life.\(^13\) There have been numerous case series of pediatric and adult patients describing clinical presentation and prognosis following surgical procedure, with widely varying surgical outcomes.\(^14-17\) Neither the extent of tonsillar herniation nor the size of the posterior cranial fossa would necessarily predict the presence or resolution of syringomyelia and surgical outcome.\(^17,18-21\) Therefore, there may be other factors playing a role in the pathogenesis and prognosis of syringomyelia. The morphometric characteristics of the syrinx in CM-I patients may contain different parameters, such as the size, length, configuration, and deviation of the syrinx, while the specific association between morphometric characteristics of syrinx with the prognosis seems to have not been elaborated.

In the present study, a continuous series of CM-I patients with syringomyelia from a single center were included. We explored the related factors affecting the prognosis of neurological function through retrospective analysis of clinical presentations, imaging characteristics, and the morphological features of syringomyelia, to provide a clinical reference for improving the prognosis.

MATERIALS AND METHODS

1. Patient Selection

From January 2017 to December 2020, a consecutive series of CM-I patients with syringomyelia were retrospectively reviewed in a single institution. Clinical records and radiologic data in this study were retrospectively analyzed from a prospectively maintained syringomyelia database. According to screening, a total of 202 pediatric and adult CM-I patients with syringomyelia who underwent PFD finally met the inclusion criteria of our study.

Inclusion criteria: (1) CM-I with syringomyelia, with MRI showing cerebellar tonsils more than 5 mm below the FM; (2) patients underwent PFD with duraplasty in our center.

Exclusion criteria: (1) patients with atlantoaxial dislocation, basilar invagination, congenital vertebral anomalies, degenerative cervical spondylosis, tumor, trauma, myelomeningocele, or tethered cord; (2) secondary CM-I due to hydrocephalus or intracranial space-occupying lesions; (3) a history of CVJ surgery with cervical or occipital fusion and instrumentation; (4) incomplete clinical data or lost follow-up after surgery.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Xuanwu Hospital, Capital Medical University (No. 2018027). We obtained consent from all patients participating in this study.

2. Clinical Evaluation

Clinical symptoms were divided into general symptoms, spinal cord-related symptoms such as suspended sensory disorder, atrophy and weakness of limbs, and other symptoms such as cerebellar syndrome and cranial nerve dysfunction. Some patients had multiple clinical symptoms at the same time. The Chiari Severity Index (CSI), a preoperative grading system proposed by Greenberg et al.\(^22\) was used to assess the preoperative status of each patient. The specific data were summarized in Table 1.

3. Radiographic Evaluation

Preoperative x-rays were measured using the CAD Canvas X (ver. 20.0; Canvas GFX, Boston, MA, USA), a computer-aided drafting software. All relative radiologic measurements were
repeated at least 3 times, independently by one surgeon and another radiologist. We could determine whether there was obvious scoliosis (Cobb angle of main curve ≥ 10° in the coronal x-ray). The value of cervical Cobb angle in the sagittal plane at the range of -5° to 5° was defined as the straight cervical spine, and the positive value larger than this range was defined as the lordosis; the negative value lower as the kyphosis.

RadiAnt DICOM Viewer software (ver. 4.6.9, Medixant, Poznan, Poland) was used to view and measure MRI images. A routine MRI examination was taken within 1 week before surgery. Postoperative MRI was conducted regularly on a 1 month, 3 months (± 1 month), 6 months (± 3 month), 1 year, 1.5 years basis, and later every year after decompression surgery until evidence for effective syrinx resolution was found. The following indicators were measured at the T2-weighted median sagittal and transverse positions of MRI: (1) maximal syrinx/cord (S/C) ratio: the ratio of syrinx diameter to the spinal cord diameter at the same level. (2) syrinx length: the number of vertebral segments spanned by the syrinx. (3) A radiographic improvement rate in the maximal S/C ratio or syrinx length was calculated using the following formula: (preoperative value–postoperative value)/preoperative value. Furthermore, we assessed the following angles that related to the CVJ region and posterior cranial fossa: basal angle, the angle of the tentorium cerebelli to the Twinning line, clivo-axial angle, clivus gradient, and ventral and dorsal SAS at FM on median sagittal MRI (Supplementary Fig. 1)

### 4. Operation Strategy

Operation reports were reviewed including 202 patients who underwent PFD with duraplasty and C1 laminectomy. The pos-

| Table 1. Preoperative clinical data of the patients included in this study |
|-------------------------------------------------|----------------|----------------|-----------------|----------------|
| Variable                          | Overall (n = 202) | Pediatric group (n = 28) | Adult group (n = 174) | t/p²/H score | p-value |
| Sex | 141 | 16 | 125 | 2.471 | 0.116 |
| Female | | | | |
| Male | 61 | 12 | 49 | |
| CSI grade | 1 | 69 | 9 | 80 | 1.561 | 0.118 |
| 2 | 119 | 17 | 83 | |
| 3 | 14 | 3 | 11 | |
| Preoperative symptom duration (mo), mean ± SD | 35.4 ± 66.5 | 12.3 ± 18.8 | 34.1 ± 70.68 | 1.996 | 0.047 |
| Chief complaint | Headache and/or neck pain | 54 | 8 | 46 | 0.056 | 0.815 |
| Spinal cord symptom | | | | |
| Weakness of limbs | 38 | 1 | 37 | 4.943 | 0.026 |
| Muscle atrophy | 12 | 1 | 11 | 0.020 | 0.888 |
| Paresthesia of limbs | 113 | 4 | 109 | 22.884 | < 0.001 |
| Suspended sensory disorder | 27 | 1 | 26 | 1.801 | 0.180 |
| Other symptoms | 44 | 4 | 40 | 1.072 | 0.300 |
| Finding scoliosis | 22 | 16 | 6 | 66.225 | < 0.001 |
| Syringomyelia resolution | Resolved effectively (≥ 20%) | 172 | 17 | 155 | 0.613 | 0.434 |
| Resolved not effectively (< 20%) | 30 | 5 | 25 | |
| Chicago Chiari Outcome Scale | Favorable prognosis | 152 | 23 | 129 | 0.659 | 0.510 |
| No obvious improvement | 42 | 3 | 39 | |
| Worse prognosis | 6 | 2 | 4 | |

CSI, Chiari Severity Index; SD, standard deviation.
†Other syndromes include cranial nerve dysfunction or cerebellar symptoms: ataxia, dysarthria, diplopia, and dysphagia.
terior arch of the C1 (1.5 cm on each side) and the FM (1.5 cm on each side, about 3 cm upwards) were resected until the dura mater transition at the cerebellar hemisphere was seen. After incision of the dura mater, the arachnoid was opened for further exploration of the fourth ventricle outlet.

5. Prognostic Evaluation

Immediate postoperative outcomes were evaluated at discharge. Long-term follow-up was defined as the last available follow-up that was more than 6 months after surgery.

The Chicago Chiari Outcome Scale (CCOS) was used to evaluate the surgical efficacy from 4 aspects: pain symptoms, non-pain symptoms, functionality, and complications, with a score from 1 to 4 for each item.23 The better the prognosis, the higher the score, with the CCOS score groupings (4–8, 9–12, 13–16) presenting the prognosis as favorable between 13 and 16, no obvious improvement between 9 and 12, and worse between 4 and 8. The latter 2 groups (4–12) were defined as having no improvement.

6. Variable Definition

The preoperative symptom duration was defined as the time from the onset of symptoms to the initial diagnosis of syringomyelia at admission to our institution. Observation time represented the time from the indication for surgery determined (with syringomyelia confirmed by MRI, but the patient refused surgery) to decompression surgery. The postoperative syrinx was reported to be either reduced (syrinx decreased in size ≥ 20%) or unchanged (syrinx decreased in size less than 20% or remained the same size). The event of significant improvement of syrinx was defined as a more than 20% decrease in maximal S/C ratio on follow-up MRI.

As previously proposed by Ono et al.,24 the configuration of syrinx can be divided into 4 types: A, distended type; B, moniliform type; C, slender type; D, circumscribed type (Fig. 1). Syrinx with continuous septations (≥ 3) was referred to as moniliform type. The preoperative degree of cerebellar tonsillar descent was divided into 3 stages: grade 1, the cerebellar tonsil descends beyond the FM but does not reach the C1 arch; grade 2, reaches the C1 arch; grade 3, descends beyond the C1 arch.

7. Statistical Analysis

IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. For continuous variables, the mean values are presented with standard deviations, and the differences between the 2 groups were analyzed using the Student t-test. A chi-square or Fisher exact test was used to assess associations between dichotomous categorical variables. The Kruskal-Wallis H test was used for multiple categorical variables. A p-value of < 0.05 was considered statistically significant. Intraclass correlation coefficient (ICC) was used to evaluate the intrarеpeatability of different observers (interobserver reliability). One independent researcher blinded to the group allocation completed the evaluations.

RESULTS

1. Patient Characteristics

A total of 202 CM-I patients with syringomyelia were admitted to a single center between January 2017 and December 2020. There were 28 cases (13.8%) younger than 18 years old, including 16 females (57.1%) and 12 males (42.9%) with a mean age of 7.8 ± 4.1 years (range, 1.0–17.0 years) in the pediatric group. There were 71.8% females and 28.2% males with a mean age of 47.4 ± 10.4 years (range, 23.0–73.0 years) in the adult group. Compared with the adult group, the pediatric group showed a much lower incidence of paresthesia of limbs and a proportion of patients who suffered weakness of limbs. There was quite a high incidence of scoliosis in children than in adults. A longer clinical presentation was seen in the adult group (Table 1).

At admission, the mean maximal S/C of the syrinx was 0.61 ± 0.18 (ICC = 0.911) and the mean syrinx length (vertebral segments) was 8.55 ± 3.62 (ICC = 0.924). The difference was not seen in syrinx location, syrinx deviation, and cervical physio-curve. There was no significant difference in CSI and degree of cerebellar tonsillar descent between the 2 groups. Moniliform type was more common in children than adults (Table 2).

2. Surgical Outcome

The average CCOS score was 14.56 ± 1.78 points. The overall postoperative prognosis was good, among all the patients, 152 cases (75.25%) with a favorable prognosis, and 50 cases (24.75%) were without improvement. There was no significant difference in the prognosis evaluated by CCOS and effective resolution of syrinx between the 2 groups. Syrinx was resolved effectively in 172 cases (85.15%), and 30 cases (14.85%) stayed unchanged or worsened in terms of syrinx resolution.

No serious neurologic complications occurred in the 2 groups of patients. There were 7 cases (3.5%) with postoperative transient headache, 9 cases (4.5%) with short-term CSF leakage, and 4 cases (1.5%) with incisional infection.
3. Factors Predicting the Surgical Outcome in the Adult Group

The preoperative clinical parameters and radiologic measurements from the 174 adult patients were assessed using univariate and multivariate analyses to identify factors for predicting clinical improvement (composite CCOS) following surgery (Table 3).

The primary univariate test showed that longer preoperative syndrome duration ($p < 0.001$) and longer observation time ($p < 0.001$) were associated with a statistically significant increase in the likelihood of no improvement. In addition, moniliform type ($p = 0.008$) and syrinx length ($p = 0.002$) were also significant predictors of clinical improvement (composite CCOS). However, CSI, degree of cerebellar tonsillar descent, CVJ parameters including basal angle, clivo-axial angle, and clivus gradient, or any other factors were not associated with prognosis.

Through further multivariate analysis, it was found that preoperative syndrome duration, observation time, and with/without moniliform type were independent factors affecting the prognosis. The receiver operating characteristic (ROC) curve suggested that the preoperative syndrome duration predicted the clinical improvement (composite CCOS) with high accuracy (area under the curve = 87.1%, $p < 0.001$) (Fig. 2).

A Kaplan-Meier analysis demonstrated the cumulative incidence rate of effective syrinx resolution. The effectiveness of syrinx resolution in patients with moniliform type was significantly higher than that with the nonmoniliform type ($p < 0.001$ by log-rank test) in the adult group. It was seen that pediatric patients with moniliform type could also achieve better syrinx resolution ($p = 0.042$ by log-rank test) (Fig. 2).
4. Differences Between Moniliform Type and Nonmoniliform Type

The most obvious difference between moniliform type and nonmoniliform type lies in the preoperative symptom duration \((p = 0.029)\), ventral SAS at the FM \((p < 0.001)\), and the patients with straightened cervical physio-curve or not \((p < 0.001)\) (Table 4).

**DISCUSSION**

Due to CM-I often associated with other CVJ malformations, there are inevitably some confounding factors that make the evaluation criteria of CM-I inconsistent.\(^{25}\) Moreover, children and adults share different clinical courses, not only for the natural history but also the postoperative prognosis. Our study focused on the preoperative clinical and radiologic parameters in simple CM-I patients with syringomyelia to find out the relationship between the clinical status of the patients and the morphometrical characteristics of the syrinx with surgical outcome.

1. Differences Between Pediatric and Adult Patients With CM-I and Syringomyelia

It is considered that children are still in the stage of growth and development. In a subset of pediatric patients with Chiari malformation without surgical treatment, the syringomyelia could even resolve spontaneously at follow-up.\(^{26}\) According to comparisons of the preoperative clinical and radiologic characteristics in our continuous series of patients between adults and children, it was illustrated that the main difference lies in the duration of preoperative symptoms. What's more, children often found CM-I with syringomyelia on further workup due to scoliosis. In adults, syringomyelia is mostly diagnosed when

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**Table 2. Radiologic measurements of the patients included in this study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall ((n = 202))</th>
<th>Pediatric group ((n = 28))</th>
<th>Adult group ((n = 174))</th>
<th>(t/\chi^2/H) score</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar tonsillar descent (mm), mean ± SD</td>
<td>0.91 ± 0.38</td>
<td>0.82 ± 0.39</td>
<td>0.92 ± 0.37</td>
<td>1.362</td>
<td>0.175</td>
</tr>
<tr>
<td>Degree of cerebellar tonsillar descent</td>
<td></td>
<td></td>
<td></td>
<td>1.838</td>
<td>0.175</td>
</tr>
<tr>
<td>Grade 1</td>
<td>102</td>
<td>18</td>
<td>84</td>
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<td></td>
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<tr>
<td>Grade 2</td>
<td>89</td>
<td>8</td>
<td>81</td>
<td></td>
<td></td>
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<tr>
<td>Grade 3</td>
<td>11</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syrinx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal syrinx/cord (%), mean ± SD</td>
<td>61.01 ± 18.25</td>
<td>59.03 ± 14.64</td>
<td>61.33 ± 18.78</td>
<td>0.738</td>
<td>0.464</td>
</tr>
<tr>
<td>Syrinx length (segment), mean ± SD</td>
<td>8.55 ± 3.62</td>
<td>9.07 ± 4.14</td>
<td>8.47 ± 3.36</td>
<td>0.822</td>
<td>0.412</td>
</tr>
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<td>Syrinx location</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>34</td>
<td>4</td>
<td>30</td>
<td>1.013</td>
<td>0.314</td>
</tr>
<tr>
<td>Cervicothoracic</td>
<td>152</td>
<td>20</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holocord</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syrinx configuration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distended type</td>
<td>41</td>
<td>6</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moniliform type</td>
<td>43</td>
<td>13</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slender type</td>
<td>55</td>
<td>4</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumscribed type</td>
<td>63</td>
<td>5</td>
<td>58</td>
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<td></td>
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<tr>
<td>Syrinx deviation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>99</td>
<td>12</td>
<td>87</td>
<td></td>
<td></td>
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<tr>
<td>Enlarged</td>
<td>78</td>
<td>14</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deviated</td>
<td>25</td>
<td>2</td>
<td>23</td>
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<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>49</td>
<td>17</td>
<td>32</td>
<td>23.514</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Straightened cervical curve</td>
<td>54</td>
<td>9</td>
<td>45</td>
<td>0.486</td>
<td>0.486</td>
</tr>
</tbody>
</table>

SD, standard deviation.
weakness or paresthesia of limbs occurs. All patients in the 2 groups completed the operation successfully, and there was no perioperative death or serious fatal complications.

Improvements in syringomyelia-related symptoms, however, do not always correspond to reductions in the size of the syrinx, so we analyzed both syrinx resolution and CCOS score respectively to comprehensively assess the surgical outcomes. The prognosis of both groups was generally favorable, no significant differences existed in the syrinx resolution and clinical outcomes between the 2 groups. Through further comparisons of radiologic parameters, it was found that syrinx in moniliform type was more common in children, which may be related to the relatively shorter natural history of CM-I in the pediatric group. There were no statistically significant differences in other baseline factors. It is unknown whether the more frequent occurrence of the moniliform syrinx in children is due to the high compensation of syringomyelia in pediatric CM-I. If so, it is necessary to further include phenotypic factors of syringomyelia in adults to analyze its association with prognosis through multivariate analysis.

2. Univariate and Multivariate Logistic Regression Models in Adult Patients

By reviewing the natural history of CM-I in children and adults, combined with the comparison between the 2 groups of cases in this series (children vs. adults), it is suggested to further explore the relevant factors affecting the prognosis in adult patients, and whether it is related to the specificity of typical moniliform type.

Firstly, through univariate analysis in adults, we concluded that preoperative syndrome duration (p < 0.001), observation time (p < 0.001), the length of the syrinx (p = 0.002), and with/
without moniliform type (p = 0.008) were related factors affecting the prognosis. Next, the multivariate analysis illustrated that the duration of preoperative symptoms, observation time before surgery, and with/without moniliform type were independent prognostic factors. Moreover, the effectiveness of syrinx resolution in patients with moniliform type was significantly higher than that with nonmoniliform type.

Appropriate time of intervention for syringomyelia was important. The shorter the preoperative symptom duration and the shorter the observation time for decompression surgery, the better the prognosis. Timely decompression surgery could achieve a better outcome, which was reflected in a higher CCOS score and syrinx resolution rate. The ROC curve also illustrated the duration of preoperative symptoms to guide prognosis with high accuracy. Therefore, surgical decompression should be taken as soon as possible once the indication for surgery is determined, which is beneficial to improving the prognosis. According to the natural history of the occurrence and development of syringomyelia, timely surgical intervention for the moniliform syringomyelia may allow patients to obtain better surgical efficacy, which would be discussed further in the following text.

There was a paucity of detailed studies on the relationship between prognosis after decompression surgery and syringomyelia morphology, which contained syrinx length, width, configuration, and deviation. Syrinx configuration has rarely been regarded as predicting factors in previous studies. Our results confirmed that most factors above were not involved in predicting surgical outcomes. The syrinx length was only a related factor, rather than an independent factor affecting the prognosis. However, we interestingly found that the CCOS score improvement in syrinx with moniliform type was relatively better than that with nonmoniliform type.

3. The Particularity of Syringomyelia With Moniliform Type

Why does syrinx with moniliform type show better prognostic improvement? Does the formation of moniliform syrinx indicate some kind of protective mechanism, or bring about some inspiration in the clinical diagnosis and treatment of the syringomyelia-related disease? The clinical prognosis of syringomyelia in moniliform type is relatively better, simultaneously with higher effectiveness of syrinx resolution shown by the survival curve in both pediatric and adult groups (Fig. 2). On the one hand, this may be related to the relatively short duration of its natural history, on the other hand, such syrinx may have strong compensatory effects for decompression surgery. During the postoperative follow-up, we found that the moniliform syringomyelia tended to move towards a smaller S/C, but the intrinsic separation of the syringomyelia appeared to persist in the short period after surgery (Figs. 3, 4). In terms of imaging characteristics, its continuous separation located inside the syrinx may be the source of the highly compensatory pathophysiological mechanism of such syringomyelia.

From the point of the association among cerebellar tonsillar herniation, CSF circulation obstruction, and syringomyelia, we agreed that syringomyelia generally underwent a dynamic process: presyringomyelia stage, progressive stage, and stable stage. We further analyzed the differences of various factors at baseline between moniliform type and nonmoniliform type syringomyelia and tried to trace the particularity from the origin and development of the moniliform syringomyelia. Such configuration tends to have a shorter duration of preoperative symptoms, and ventral SAS ≥ 2 mm is more concentrated in this type, suggesting that a moniliform type may represent the morphological feature

Fig. 3. A 10-year-old girl with Chiari I malformation and moniliform syringomyelia. (A, C) Preoperative magnetic resonance images showed a syrinx with a maximal syrinx/cord (S/C) ratio of 0.844 and a length of 14 vertebral segments. (B, D) The 3-month postoperative magnetic resonance imaging showed that the S/C ratio had decreased to 0.637, and the length of the syrinx had decreased to 7 vertebral segments.
in the early course of the disease. Because the cerebellar tonsillar herniation obstructs the circulation of CSF at the FM (especially in dorsal SAS), ventral SAS ≥ 2 mm was more common in the moniliform type group, which could be derived from some “buffer space” in the ventral SAS in the early stage.

Moreover, straightened cervical physio-curve appears to be more common in patients with moniliform syrinx than non-moniliform syrinx. Some scholars have previously reported that compared with normal people, patients with syringomyelia will have a certain loss in cervical lordosis, but they have not mentioned the intrinsic relationship between the specific syringomyelia type and the corresponding changes in cervical sagittal alignment. We speculated that the compensatory decrease in cervical lordosis during syringomyelia formation may act as a compensatory physiological response to get better CSF circulation in the SAS. This mechanism may be more pronounced in the moniliform syrinx. With the syrinx resolution after surgery, the lordosis may have a certain tendency to recover (Fig. 4), but that still needs to be confirmed by more randomized controlled trials.

4. Clinical Significance of This Study

The results in this study did not show that other factors such as CSI, degree of cerebellar tonsillar descent, CVJ measurements, the presence or absence of scoliosis, and cervical physio-curve were directly related to clinical prognosis, nor did it show a difference in these factors between the moniliform and non-moniliform syringomyelia. Although they may be relevant factors that need to be comprehensively considered before surgery, they had no obvious predictive significance for guiding prognosis. However, CM-I often accompanies other CVJ malformations, and it is difficult to identify the prognosis through only one single index. It must be analyzed on a case-by-case basis combined with other comprehensive factors.

This paper proposes a special morphological feature of syringomyelia, the moniliform type syringomyelia, associated with the surgical outcome from the perspective of clinical symptoms, imaging features (phenotypes of syringomyelia and biomechanical structures of the CVJ and cervical spine), and multivariate prognostic analysis. Based on the previous studies, we give a new definition for this type of syringomyelia, that is moniliform syrinx with continuous obvious separation on MRI, which presents as a wide ventral SAS at FM, and tends to have a relatively shorter natural history and more common straightened cervical curve, and most importantly it may suggest a better prognosis. In the future, more clinical research is needed to dynamically observe the change of syringomyelia from the perspective of the pathophysiological mechanism of the occurrence and development of syringomyelia, finally to make clear the structure and function of syringomyelia separation and the biological characteristics of moniliform syringomyelia.

5. Strengths and Limitations

Moniliform type was elicited based on clinical and radiographic comparisons between different age groups. It was confirmed that such type may have an impact on the prognosis in adults, which was assessed using both syrinx resolution and CCOS. Finally, the particularity of moniliform syringomyelia was analyzed.

However, it was undeniable that there were some shortcomings in our study. The survival curve was analyzed based on the...
### Table 3. Factors predicting composite CCOS improvement using univariate and multivariate logistic regression models in adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improvement</th>
<th>No improvement</th>
<th>$t/\chi^2$ score</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>93</td>
<td>32</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
<td>0.900</td>
</tr>
<tr>
<td>Preoperative symptom duration (mo)</td>
<td>16.17 ± 16.97</td>
<td>105.02 ± 113.22</td>
<td>5.244</td>
<td>2.562</td>
<td>0.999</td>
<td>0.934–0.999</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Observation time (mo)</td>
<td>0.92 ± 2.65</td>
<td>62.62 ± 103.61</td>
<td>3.994</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syrinx width at maximal S/C (%)</td>
<td>60.97 ± 17.79</td>
<td>61.16 ± 19.77</td>
<td>0.065</td>
<td></td>
<td></td>
<td></td>
<td>0.948</td>
</tr>
<tr>
<td>Syrinx length (segment)</td>
<td>7.94 ± 3.32</td>
<td>9.95 ± 3.72</td>
<td>3.204</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Syrinx deviation</td>
<td>19</td>
<td>4</td>
<td>0.992</td>
<td></td>
<td></td>
<td></td>
<td>0.319</td>
</tr>
<tr>
<td>Moniliform type</td>
<td>28</td>
<td>2</td>
<td>6.966</td>
<td></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Tonsillar hernia (mm)</td>
<td>0.89 ± 0.38</td>
<td>0.97 ± 0.36</td>
<td>1.267</td>
<td></td>
<td></td>
<td></td>
<td>0.209</td>
</tr>
<tr>
<td><strong>CVJ and PCF measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal angle (°)</td>
<td>117.75 ± 7.44</td>
<td>116.07 ± 7.35</td>
<td>0.620</td>
<td></td>
<td></td>
<td></td>
<td>0.540</td>
</tr>
<tr>
<td>Angle of the TC to TL (°)</td>
<td>42.31 ± 3.38</td>
<td>41.86 ± 3.39</td>
<td>0.367</td>
<td></td>
<td></td>
<td></td>
<td>0.716</td>
</tr>
<tr>
<td>Clivo-axial angle (°)</td>
<td>154.06 ± 10.07</td>
<td>148.14 ± 12.52</td>
<td>1.435</td>
<td></td>
<td></td>
<td></td>
<td>0.162</td>
</tr>
<tr>
<td>Clivus gradient (°)</td>
<td>53.25 ± 5.76</td>
<td>54.64 ± 6.03</td>
<td>0.647</td>
<td></td>
<td></td>
<td></td>
<td>0.523</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>22</td>
<td>10</td>
<td>0.527</td>
<td></td>
<td></td>
<td></td>
<td>0.468</td>
</tr>
<tr>
<td>Straightened cervical curve</td>
<td>34</td>
<td>11</td>
<td>0.356</td>
<td></td>
<td></td>
<td></td>
<td>0.551</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative symptom duration</td>
<td>0.072</td>
<td>0.758</td>
<td>0.658–0.874</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observation time</td>
<td>0.015</td>
<td>0.964</td>
<td>0.935–0.993</td>
<td>0.016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moniliform type</td>
<td>1.757</td>
<td>0.021</td>
<td>0.001–0.667</td>
<td>0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± standard deviation unless otherwise indicated.

†Only variables in the effective equation of multivariate analysis are displayed.

CCOS, Chicago Chiari Outcome Scale; SE, standard error; OR, odds ratio; CI, confidence interval; S/C, syrinx/cord; CVJ, craniovertebral junction; PCF, posterior cranial fossa; TC, tentorium cerebelli; TL, Twining’s line.

### Table 4. Comparison of parameters between moniliform type and nonmoniliform type in 174 adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moniliform type</th>
<th>Nonmoniliform type</th>
<th>$\chi^2/t$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>25</td>
<td>101</td>
<td>2.164</td>
<td>0.141</td>
</tr>
<tr>
<td>Preoperative symptom duration (mo)</td>
<td>13.62 ± 16.96</td>
<td>44.47 ± 72.91</td>
<td>2.199</td>
<td>0.029</td>
</tr>
<tr>
<td>Tonsillar hernia (mm)</td>
<td>0.92 ± 0.38</td>
<td>0.91 ± 0.37</td>
<td>0.071</td>
<td>0.943</td>
</tr>
<tr>
<td><strong>CVJ and PCF measurements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal angle (°)</td>
<td>116.25 ± 8.18</td>
<td>118.4 ± 5.30</td>
<td>0.752</td>
<td>0.458</td>
</tr>
<tr>
<td>The angle of the TC to TL (°)</td>
<td>42.5 ± 3.14</td>
<td>41.7 ± 1.57</td>
<td>0.756</td>
<td>0.456</td>
</tr>
<tr>
<td>Clivus gradient (°)</td>
<td>54.40 ± 5.65</td>
<td>52.90 ± 6.35</td>
<td>0.658</td>
<td>0.516</td>
</tr>
<tr>
<td>Clivo-axial angle (°)</td>
<td>152.20 ± 10.98</td>
<td>149.50 ± 12.83</td>
<td>0.601</td>
<td>0.553</td>
</tr>
<tr>
<td>Subarachnoid space at FM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral subarachnoid space ≥ 2 mm</td>
<td>12</td>
<td>2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dorsal subarachnoid space ≥ 2 mm</td>
<td>1</td>
<td>1</td>
<td>0.316</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>2</td>
<td>30</td>
<td>3.220</td>
<td>0.068</td>
</tr>
<tr>
<td>Straightened cervical curve</td>
<td>16</td>
<td>29</td>
<td>17.135</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± standard deviation.

CVJ, craniovertebral junction; PCF, posterior cranial fossa; TC, tentorium cerebelli; TL, Twining’s line; FM, foramen magnum.
event of the effective resolution of the syrinx by postoperative MRI, so a short time interval was selected as much as possible, but there was still interval error, for example, the occurrence of the event happened to fall within the empty period between the checkpoints. Besides, there was a lack of longer follow-up after the effective resolution of the syringomyelia, so more research and evaluations are needed in the future to achieve the maximal ablation effect of the syringomyelia.

CONCLUSION

Timely decompression surgery could achieve a better outcome in CM-I patients with syringomyelia. The moniliform syringomyelia with representative syrinx separations may suggest a relatively better prognosis. That provides more insight into the pathophysiological mechanism during the dynamic progression of syringomyelia to find the intrinsic protection strategy from the clinical experience.

NOTES

Supplementary Material: Supplementary Fig. 1 can be found via https://doi.org/10.14245/ns.2244332.166.

Conflict of Interest: The authors have nothing to disclose.

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ORCID

Chunli Lu: 0000-0003-2825-5833
Lei Cheng: 0000-0001-6328-7852
Xinyu Wang: 0000-0002-6248-9601
Wanru Duan: 0000-0003-4751-3666
Zan Chen: 0000-0002-0104-115X
Hao Wu: 0000-0002-8118-9989
Fengzeng Jian: 0000-0001-7860-278X

REFERENCES

**Supplementary Fig. 1.** Measurements of craniovertebral junction (CVJ) and posterior cranial fossa (PCF): basal angle (BA), the angle of the tentorium cerebelli to the Twining line (TTA), clivo-axial angle (CAA), clivus gradient (Cl-Gr), Ventral subarachnoid space (VSAS) and dorsal subarachnoid space (DSAS) at foramen magnum (FM), and tonsillar herniation (TH) on median sagittal magnetic resonance imaging. (A) Schematic diagram of the mechanism demonstration in our speculation about the relationship among the syrinx, cerebrospinal fluid (CSF) circulation, imaging factors of CVJ, PCF, and cervical spine. (B) The wider subarachnoid space at FM and the loss of cervical lordosis may both help to ensure the CSF circulation.
Biomechanical Effects of Proximal Polyetheretherketone Rod Extension on the Upper Instrumented and Adjacent Levels in a Human Long-Segment Construct: A Cadaveric Model

Bernardo de Andrada Pereira¹, Jennifer N. Lehrman¹, Anna G.U. Sawa¹, Piyanat Wangsawatwong¹, Jakub Godzik², David S. Xu², Jay D. Turner², Brian P. Kelly¹, Juan S. Uribe²

¹Spinal Biomechanics Laboratory, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, AZ, USA
²Department of Neurosurgery, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, AZ, USA

Objective: The high mechanical stress zone at the sudden transition from a rigid to flexible region is involved in proximal junctional kyphosis (PJK) physiopathology. We evaluated the biomechanical performance of polyetheretherketone (PEEK) rods used as a nontraditional long semirigid transition phase from a long-segment metallic rod construct to the nonfused thoracic spine.

Methods: Pure moment range of motion (ROM) tests (7.5 Nm) were performed on 7 cadaveric spine segments followed by compression (200 N). Specimens were tested in the following conditions: (1) intact; (2) T10-pelvis pedicle screws and rods (PSRs); and (3) extending the proximal construct to T6 using PEEK rods (PSR+PEEK). T10–11 rod strain, T9 anterolateral bone strain, and T10 screw bending moments were analyzed.

Results: At the upper instrumented vertebra (UIV)+1, PSR+PEEK versus PSR significantly decreased ROM in flexion (115%, p = 0.02), extension (104%, p = 0.003), left lateral bending (46%, p = 0.02), and right lateral bending (63%, p = 0.008). Also, at UIV+1, PSR+PEEK versus intact significantly decreased ROM in flexion (111%, p = 0.01) and extension (105%, p = 0.003). The UIV+1 anterior column bone strain was significantly reduced with PSR+PEEK versus PSR during right lateral bending (p = 0.02). Rod strain polarities reversed with PEEK rods in all loading directions except compression.

Conclusion: Extending a long-segment construct using PEEK rods caused a decrease in adjacent-level hypermobility as a consequence of long-segment immobilization and also redistributed the strain on the UIV and adjacent levels, which might contribute to PJK physiopathology. Further studies are necessary to observe the clinical outcomes of this technique.

Keywords: Biomechanical phenomena, Bone malalignment, Kyphosis, Polyetheretherketone, Mechanical stress

INTRODUCTION

Biomechanical understanding of long-segment fusion for adult spinal deformity has progressed in recent years; nevertheless, proximal junctional kyphosis (PJK) remains an unresolved complication of this procedure. The term PJK is used broadly to define clinical observations ranging from loss of alignment to compression fracture and junctional mechanical failure above an upper instrumented vertebra (UIV).¹ PJK is a potential cause of fixation failure (i.e., top screw loosening and pullout)
and consequently an important factor contributing to high rates of revision surgery. Increasing the durability of multilevel constructs and preventing PJK remains challenging and has been the focus of extensive research efforts.

The elasticity modulus of metallic spinal rods (i.e., titanium or cobalt-chrome) commonly used for fusion procedures is much greater than that of tissue, including bone, and this difference in elasticity may significantly alter the distribution of load along the anterior and posterior vertebral columns at the instrumented and adjacent levels during physiologic loading. The high mechanical stress zone created directly above the UIV by the sudden transition from an instrumented rigid to a native flexible region has been hypothesized to be one of the most important factors in the physiopathology of PJK. The occurrence of PJK is notable in the lower thoracic spine, which acts as a fulcrum subjected to high physiological forces created by the passage of lumbar lordotic to thoracic kyphotic curvature—a region under constant gravitational influence of upper body weight. Most strategies described to attenuate this blunt transition consist of creating an intermediate semirigid bridge connecting the 2 very distinct mechanical regions. Previously reported techniques include hooks, posterior bands or ligament augmentation, or cement augmentation, with variable results.

Polyetheretherketone (PEEK) rods have been used as a biomaterial in various configurations for semirigid and dynamic stabilization spinal procedures. PEEK is a thermoplastic, biocompatible, radiolucent polymer that resists chemical and radiation damage and that has less rigidity than metallic rods; thus, it has an elasticity modulus that is closer to cancellous bone.

Traditionally, titanium and cobalt-chrome alloys have been used as materials for pedicle screw and rod (PSR) instrumentation. Several laboratory studies have compared PEEK and metallic rod mobility for index-level stabilization, but they have not looked to adjacent-level behavior. The biomechanical performance of PEEK rods used as a semirigid transition from a long-segment metallic rod construct spanning from the lumbar region to the nonfused thoracic spine has not been studied in vitro, to our knowledge. Theoretically, flexible PEEK rods connected immediately above the UIV have the potential to create a more evenly distributed load across columns and thus provide a softer transition that may protect the adjacent spinal level from high mechanical stress. This cadaveric study observed the UIV and adjacent-level range of motion (ROM) and strain distribution (posterior rod and anterior column bone) to investigate how this strategy might help to mitigate PJK occurrence.

**MATERIALS AND METHODS**

Seven fresh-frozen human T2-pelvis cadaveric specimens with intact rib cages were selected for this study; 2 were female and 5 were male, with a mean (standard deviation [SD]) age of 60.7 (4.9) years. Medical records and plain film radiographs were reviewed, and direct manual inspection was performed to ensure no obvious pathology was present that might affect the study results. Dual-energy x-ray absorptiometry scans were performed on L4 of each specimen to assess bone mineral density, and the mean (SD) was 0.91 (0.16) g/cm². Informed consent for this study was not required, and institutional review board approval was not sought because of the cadaveric nature of the investigation.

Specimens were stored at -20°C until test day and then thawed in normal saline at 21°C. Muscles and soft tissues were removed while keeping intact all ligaments, joint capsules, and intervertebral discs. The main rib cage structure was entirely preserved below the second rib; specifically, the intercostal musculature, costovertebral joints, costal cartilage, body of sternum, and xiphoid process were preserved. The first rib and manubrium were removed. The ischium was bilaterally reinforced with household wood screws, placed in a rectangular metallic mold, and embedded using fast-curing resin (Smooth-Cast, Smooth-On, Inc., Easton, PA, USA) to permit attachment to the base of the testing apparatus. The top vertebra (T2) was also reinforced with household screws and embedded in the same resin in a cylindrical-shaped pot for test frame attachment and loading.

1. **Instrumentation**

All specimens were initially tested intact before undergoing PSR fixation. The PSR condition comprised insertion of polyaxial pedicle screws (6.5 × 45 mm, CD Horizon, Medtronic, Dublin, Ireland) from T10 to S1 and S2 alar-iliac screws (8.5 × 80 mm, CD Horizon) placed under fluoroscopy guidance (Fig. 1A). Two 5.5-mm diameter cobalt-chrome rods (NuVasive, San Diego, CA, USA) were contoured bilaterally to fit screw heads from T10 to S2 to minimize the need for reduction. After specimens were tested in the PSR condition, the PSR+PEEK condition was tested. The PSR+PEEK condition comprised additional pedicle screws (6.5 × 45 mm, CD Horizon) that were inserted bilaterally at T6, and the upper instrumented level of the construct (T10) was extended to this level using PEEK rods (6.35 × 120 mm, CD Horizon) connected to the primary construct using inline axial connectors (Fig. 1B).

PJK revision for constructs with T10 UIV often involves con-

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struct extension to T6, while current posterior tension band techniques similarly aimed at offsetting PJK often extend fixation 2 levels above the UIV. Thus, the rationale for investigating a non-traditional extension to T6 was that PEEK rods and screws (T6) could be placed percutaneously, maintain the posterior tension band, and thereby move ahead of T10 PJK by providing a well-distributed “soft landing” above the UIV.

2. Biomechanical Tests

Test specimens were fixed caudally to the testing frame table to permit unconstrained relative medial-lateral translation between ilia, and they were fixed cranially to the end effector of a 6-degree-of-freedom robotically controlled test frame16 (Fig. 1C). For each condition tested (Fig. 2), specimens underwent dynamic nondestructive pure moment flexibility tests of 7.5 Nm at a mean global rotation rate of approximately 1.5° per second for the following motions: flexion, extension, right and left lateral bending, and right and left axial rotation, followed by a vertical compression of 200 N. ROM stability, anterior column bone strain, rod strain, and screw bending moments were assessed for all conditions.

3. Angular Motion Tracking

Angular ROM was obtained from 3-dimensional motion measurement with the Optotrak 3020 camera apparatus (Northern
Digital, Waterloo, Ontario, Canada). This system measured stereophotogrammetrically the 3-dimensional motion of infrared-emitting markers attached in a noncollinear arrangement to each vertebra. Custom software was used to convert the marker coordinates to angles about each of the anatomical axes.¹⁷

4. Anterior Column Bone Strain

Each specimen was instrumented with a stacked rosette strain gauge (C2A-06-G1350-120, Micro-Measurements, Raleigh, NC, USA) placed on the left anterolateral surface of the anterior column of the T9 vertebral body (Fig. 3). Principal T9 bone strains during loading in each direction were calculated from strains recorded at 10 Hz using a StrainSmart data acquisition system (Vishay, Micro-Measurements, Raleigh, NC, USA).

5. Screw Bending Moment and Rod Strain Monitoring

Before being inserted into bone, the T10 screws on the right side of the specimen were instrumented with 4 circumferentially placed uniaxial strain gauges (C2A-06-015LW-120, Micro-Measurements). A loading calibration procedure was performed on each screw before insertion to establish a strain versus screw bending moment relationship.¹⁸ The right-side rod was instrumented posteriorly with a stacked rosette strain gauge (C2A-06-G1350-120, Micro-Measurements) midway between T10 and T11. The rod gauge was attached after rod contouring, and the instrumented rod was not calibrated before use. Rod and screw strain gauge placements are illustrated schematically in Fig. 2. Rod and screw strains were recorded simultaneously with the bone strains using the same data acquisition system.

6. Statistical Analysis

Statistical comparisons of ROM among conditions (intact, PSR, and PSR+PEEK) were assessed using a one-way repeated-measures analysis of variance followed by Holm-Šidák post hoc comparisons as needed, using an alpha level of p = 0.05 (SigmaStat, Systat Software, San Jose, CA, USA). Screw bending moments and bone and rod strains (PSR vs. PSR+PEEK) were analyzed using paired t-tests (Excel, Microsoft, Redmond, WA, USA).

RESULTS

Overall results showed no obvious evidence of screw or instrumentation loosening, pull out, or failure.

1. Range of Motion

ROM values are summarized in Table 1, and all p-values comparing ROM for PSR and PSR+PEEK conditions are summarized in Table 2.

1) Upper instrumented level (T10–11) ROM

Compared to the intact condition, PSR instrumentation decreased ROM at the uppermost instrumented level (T10–11) in all loading directions (mean 80%); however, the decrease was only statistically significant during flexion (70%, p = 0.003). When extending the PSR construct with PEEK rods, no significant difference was noted between PSR and PSR+PEEK (p ≥ 0.06). Compared to the intact condition, the PSR+PEEK condition showed a decrease in ROM in all directions of pure moment loads with a mean decrease of 89% and statistical significance in flexion (91%, p = 0.001), extension (96%, p = 0.047), and right lateral bending (101%, p = 0.035).

2) Upper level adjacent to PSR construct (T9–10) ROM

Compared to the intact condition, ROM after PSR instrumentation was slightly higher at the upper level adjacent to the PSR construct (T9–10) for all load directions except flexion (mean decrease of 28%); however, no statistically significant difference
was observed (p ≥ 0.27). After extending the construct with PEEK rods, compared to PSR, ROM decreased in all directions with statistically significant differences in flexion (115%, p = 0.02), extension (104%, p = 0.003), left lateral bending (46%, p = 0.02), and right lateral bending (63%, p = 0.008), compared to PSR. Compared to the intact condition, PSR+PEEK showed a significant decrease in flexion (111%, p = 0.01) and extension (105%, p = 0.003).

3) New upper level adjacent to PEEK rod (T5–6) ROM

At the upper level adjacent to the PEEK construct (T5–6), when compared to the intact condition, PSR decreased ROM for flexion, extension, and right lateral bending (mean decrease 21%), and increased ROM for left lateral bending and left and right axial rotation (mean increase 10%), but these differences were not statistically significant (p ≥ 0.15). For the PSR+PEEK versus PSR only, ROM decreased in all directions (mean 27%) but only significantly during right axial rotation (40%, p = 0.04). Compared to the intact condition, PSR+PEEK significantly decreased ROM during flexion (41%, p = 0.048) and right axial rotation (45%, p = 0.044).
Fig. 4. Comparison of mean strain for PSR versus PSR+PEEK test conditions. (A) T9 anterior column bone primary principal strains (left anterolateral side). Note the reduced mean primary principal strains with PSR+PEEK versus PSR only, with the greatest reductions during right lateral bending (p = 0.02) (Fig. 4A). (Note that no pedicle screws were inserted at this level.)

2) T10 right pedicle screw bending moments

Compared to the PSR condition, the addition of the PEEK rods caused a slight increase in mean T10 screw bending moment during bending in flexion (21%), extension (43%), right lateral bending (25%), left lateral bending (36%), and compression (24%), but these differences were not statistically significant (p ≥ 0.07). During axial rotation, added PEEK rods significantly reduced the mean right-side T10 screw bending moment by 37% during left axial rotation (contralateral side, p = 0.03); during right axial rotation, the bending moment decreased by 14%, which was not significant (ipsilateral side, p = 0.53) (Fig. 4B).

3) T10-11 right-side posterior surface rod strains

Compared to PSR alone, the addition of PEEK rods significantly decreased rod strain at T10–11 by 67% (188.8 µE, p = 0.002) in right lateral bending and by 27% (24.5 µE, p = 0.001) in compression, and it significantly increased strain by 83% (26.2 µE, p = 0.02) in left rotation and by 134% (70.3 µE, p = 0.001) in right axial rotation. Rod strain from the posterior side of the right rod between T10 and T11 shows that the direction of bending was reversed with PSR+PEEK versus PSR during all directions of loading (Fig. 4C). That is, local rod bending between T10 and T11 screws switched polarity from flexural rod strain to an extension strain or vice versa with PSR+PEEK rods, except during compression when a flexural strain was maintained (Fig. 4C).

DISCUSSION

The incidence of PJK after spinal fusion ranges from 17% to 62%. PJK was defined by Glattes et al. as a proximal junctional sagittal Cobb angle between the lower endplate of the UIV and the upper endplate of the 2 supra-adjacent vertebrae conditions are summarized in Table 2, and comparisons of mean (SD) for PSR versus PSR+PEEK conditions are shown in Fig. 4.

1) T9 anterior column bone strains

Despite a large variability among specimens in terms of T9 anterior column bony surface strain, extending the PSR instrumentation above T9 with PEEK rods reduced the mean primary principal strain in most directions of motion in comparison to the PSR condition, with a statistically significant reduction during right lateral bending (p = 0.02) (Fig. 4A). (Note that no pedicle screws were inserted at this level.)

2) T10 right pedicle screw bending moments

Compared to the PSR condition, the addition of the PEEK rods caused a slight increase in mean T10 screw bending moment during bending in flexion (21%), extension (43%), right lateral bending (25%), left lateral bending (36%), and compression (24%), but these differences were not statistically significant (p ≥ 0.07). During axial rotation, added PEEK rods significantly reduced the mean right-side T10 screw bending moment by 37% during left axial rotation (contralateral side, p = 0.03); during right axial rotation, the bending moment decreased by 14%, which was not significant (ipsilateral side, p = 0.53) (Fig. 4B).

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DISCUSSION

The incidence of PJK after spinal fusion ranges from 17% to 62%. PJK was defined by Glattes et al. as a proximal junctional sagittal Cobb angle between the lower endplate of the UIV and the upper endplate of the 2 supra-adjacent vertebrae.
of $\geq 10^\circ$ or at least 10$^\circ$ greater than the preoperative measurement; other authors have suggested 20$^\circ$ as the cutoff.$^{22,23}$ Currently, the term PJK has much broader connotations and includes different degrees of severity; however, an angulation of at least 10$^\circ$ greater than the preoperative angle is the most accepted definition of PJK.$^{24,25}$ Fracture at the UIV and screw loosening are the most common consequences. Risk factors include violation of posterior soft elements$^{26}$ (i.e., facet joint capsules, posterior tension band), large intraoperative curvature correction (>30$^\circ$), stiffness of the constructs, extension of the fusion, choice of the UIV, preexisting osteoporosis, older age (>55 years), and high body mass index.$^1$ Because the stiffness of the construct is implicated in the development of PJK,$^{27,28}$ several prophylactic strategies have been discussed.$^{5,11}$ The biomechanical concept of using a semirigid bridge as a transition from a rigid to a flexible nonfused zone was addressed in this study, using PEEK rods attached to the proximal end of the PSR construct with inline connectors.

Using finite element analysis of long-segment spinal fusion, Yagi et al.$^{29}$ observed compressive stresses concentrated on the anterior column at both the UIV and adjacent level compared to intact spine. The strain measured on the anterolateral bone surface at UIV+1 (T9) in our study indicated a decrease in strain after extending the construct upward with PEEK rods. This finding potentially supports the hypothesis that the described technique can protect the anterior column from damaging shifts in mechanical stress involved with PJK genesis.

The choice for the cadaveric specimens and construct designs in the current study was made based on the attempt to approximate the physiological scenario but maximize the sensibility given the risk factors. We believe that our study is the first to demonstrate this result in cadavers and, more specifically, with long-segment constructs to the pelvis in specimens with the entire rib cage structure preserved. To the best of our knowledge, this study is the first T10-pelvis construct reproduced using cadavers with intact ribs in a biomechanical laboratory. Bridwell et al.$^{32}$ hypothesized that a stiffer construct may increase the risk of PJK. The choice of UIV at T10 in our study is supported by Bridwell et al.$^{32}$ who reported that a UIV lower than T8 could increase the incidence of PJK. Previous clinical studies have shown that fusion to the sacrum and/or the ilium is also a significant risk factor.$^{30,31}$ A study by Kim et al.$^{34}$ supports the theory that distal spinal stability may be related to proximal stress via a relationship between iliac screw loosening and PJK. Preservation of the rib cage in the current study sought to mimic the physiological scenario because the rib cage has a stabilizing effect.$^{35,36}$

In the present study, upper adjacent-level (T9–10) motion slightly increased after PSR, but not significantly. Extending the construct up to T6 with PEEK rods significantly decreased motion at this level in all directions compared to PSR. The effects of this decreased motion were noted in terms of decreased strain (i.e., stress) across the anterior column at T9 as well, with PEEK rods significantly decreasing left-side anterior column strain compared to PSR alone during right lateral bending ($p = 0.02$). The motion of the upper instrumented level (T10–11) decreased after PSR, with further increased rigidity achieved by the addition of PEEK rods. Ponnappan et al.$^{14}$ demonstrated in vitro that PEEK rods offer stability comparable to titanium rods (both 5.5-mm diameter) for lumbar fusion at the index level (not adjacent); however, the angular displacement achieved without failure was also in excess of that expected for normal nonfused physiologic lumbar motion.$^{37}$ Following PEEK rod extension in our specimens, the motion of the new adjacent level (T5–6) was significantly reduced in right axial rotation compared to PSR, unlike the “old adjacent level” (T9–10). This last finding may be important as it corroborates the hypothesis that the strategy studied has the potential to mitigate PJK because the motion is reduced and not increased at the new, more cranial adjacent level.

The addition of PEEK rods caused small to moderate increases in T10 screw bending moments in the sagittal plane, lateral bending, and in compression but did not reach statistical significance. Overall, and despite a statistically significant decrease in screw bending moments with PEEK compared to PSR during left axial rotation, no substantial differences in magnitudes were noticed. Changes with screw strains may be explained by the cantilever effect of bending loads applied to PEEK rods and transferred via the inline connector attached to the top of the titanium rod directly above the T10 screw. This connector receives and shares loads from spinal levels above (T6 to T9) spanning the PEEK rod stabilization. It may be hypothesized that if the extended UIV level were caudal to T6, this effect might be attenuated, especially given that there was no anchorage point between T10 and T6 in the PEEK condition.

Similar to T10 screw bending moments, PEEK rod extensions did not produce significant changes in T10–11 rod strain magnitudes in flexion and extension. PEEK rod extensions, however, significantly reduced rod strain in right lateral bending compared to PSR (the highest PSR rod strain magnitudes were noted in this direction) and significantly increased the smallest rod strains observed in the PSR condition in axial rotation. Rod strain
the notable observation in the current study of reversed T10–11 rod strain polarity with PEEK rod extension was also evident in changes in T9–10 flexion-extension ROM for the same condition. The rationale for this is unclear; however, several factors, including presence of the rib cage, the extended length of the instrumented specimens, and a transitional region between thoracic and lumbar curvature, may have played a role. Notably the caudal PEEK rod attachment was located at or near the inflection point of these 2 curvatures. The concave and kyphotic curvature of the extension may have thus acted to influence directionality of cranially applied loads. The clinical significance of reversed strain polarity remains unclear.

The disruption of facet joint capsules and paraspinal musculature during open surgery approaches have been discussed as a potential risk factor for the development of PJK via the weakening of the soft tissue posterior tension band.\textsuperscript{38} The strategy investigated in this study of extending the construct using PEEK rods can be performed through a minimally invasive approach and thus also has the potential to preserve these elements. This potential advantage was not addressed in the current study, and therefore further clinical studies are necessary.

The cadaveric biomechanics testing paradigm is a limitation of this study in that it only evaluates immediate stability. Further limitations include the absence of paraspinal and trunk muscles that play a role in stabilizing the spine and the absence of a targeted disease mechanism that represents an indication for the surgery. Our analysis of rod strain was localized and may not be reflective of overall strain distributions. Different types of distal ends in long-segment constructs commonly used in a clinical scenario might have affected the proximal junction differently (i.e., use of anterior column support at the base with interbody devices on L5–S1, use of multirod configurations, as well as stopping the construct at the sacrum and not extending to sacropelvic fixation). Strain gauge application near the head of the T6 screw required the screw head and neck region to extend substantially outside the pedicle. When combined with the fixed curvature of the PEEK rods, which cannot be bent to accommodate individual specimens, this construct was not practically viable in the cadaver anatomy and hence strain gauged T6 screws were not used. Following testing of the selected construct, other PEEK rod lengths were also practically difficult to implement in the same set of cadavers due to facet joint violation effects. The lack of other similar techniques for comparison is also acknowledged as a limitation of the present study. PJK is a multifactorial complication. Other loading scenarios not tested in the current study, as well as changing internal mechanical stresses that are not currently measurable, may be present.\textsuperscript{39} Factors related to sagittal malalignment, misalignment or overcorrection are also part of the PJK pathogenesis.\textsuperscript{40} Cyclic loading was not included in the current study design as we believe that nondestructive load magnitudes used in standard biomechanical tests, coupled with tissue degeneration outside of the body, preclude any meaningful measure or simulation of prolonged \textit{in vivo} service.

\section*{CONCLUSION}

Extending a long-segment construct using PEEK rods with connectors redistributed the strain on the upper instrumented and adjacent levels and caused a decrease in adjacent-level hypermobility that might be a contributing factor to the physiopathology of PJK. Additionally, this technique decreased the strain measured at the upper adjacent-level anterior column with, however, the trade-off of mildly increased proximal screw bending moment. Further studies are necessary to understand the biomechanical clinical outcomes of this technique.

\section*{NOTES}

\textbf{Conflict of Interest}: Juan S. Uribe receives consulting fees and royalties from NuVasive Medical, Inc., and is a consultant for Masonix, Inc., and SI-BONE, Inc. Jay D. Turner is a consultant for NuVasive, SeaSpine, and AlphaTec. No other potential conflict of interest relevant to this article was reported.

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ORCID
Bernardo de Andrada Pereira: 0000-0002-3990-9057
Jennifer N. Lehrman: 0000-0002-4364-8072
Anna G. U. Sawa: 0000-0003-3932-6668
Piyanat Wangsawatwong: 0000-0001-5797-7179
Jakub Godzik: 0000-0003-0645-6212
David S. Xu: 0000-0001-8987-4545
Jay D. Turner: 0000-0001-6867-3568
Brian P. Kelly: 0000-0002-5551-2834
Juan S. Uribe: 0000-0002-8910-6578

REFERENCES
Safety and Efficacy of Recombinant Human Bone Morphogenetic Protein-2 in Multilevel Posterolateral Lumbar Fusion in a Prospective, Randomized, Controlled Trial

Ho Yong Choi¹, Seung-Jae Hyun², Chang Hyun Lee², Ji Hyun Youn³, Mi Young Ryu⁴, Ki-Jeong Kim⁴

¹Department of Neurosurgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea
²Department of Neurosurgery, Spine Center, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
³CG Bio Co., Ltd., Seoul, Korea

Objective: This study is an investigator-initiated, prospective, randomized, controlled study to evaluate the efficacy and safety of the combined use of recombinant human BMP-2 (rh-BMP-2) and a hydroxyapatite (HA) carrier in multilevel fusion in patients with adult spinal deformity (ASD).

Methods: Thirty patients underwent posterolateral fusion for lumbar spinal deformities at 3 to 5 segments between L1 and S1. The patients received rhBMP-2+HA or HA on the left or right side of the transverse processes. They were followed up regularly at 1, 3, 6, and 12 months postoperatively. Fusion was defined according to the bone bridging on computed tomography scans. The fusion rate per segment was subanalyzed. Function and quality of life as well as pain in the lower back and lower extremities were evaluated.

Results: The union rate for the rhBMP-2+HA group was 100% at 6 and 12 months. The union rate for the HA group was 77.8% (21 of 27) at 6 months and 88.0% (22 of 25) at 12 months (p = 0.014 at 6 months; not significant at 12 months). All segments were fused at 6 and 12 months in the rhBMP-2+HA group (p < 0.001). In the HA group, 108 of 115 segments (93.5%) were fused at 6 months and 105 of 109 segments (96.3%) at 12 months. Other clinical parameters (visual analogue scale, 36-item Short Form Health Survey, and Scoliosis Research Society-22 scores) improved compared to baseline.

Conclusion: Combining rhBMP-2 and an HA carrier is a safe and effective method to achieve multilevel fusion in patients with ASD.

Keywords: Adult spinal deformity, Bone graft, Bone morphogenetic protein-2, Hydroxyapatite, Posterolateral fusion, Lumbar fusion

INTRODUCTION

Posterolateral lumbar fusion (PLF) is performed to correct adult spinal deformity (ASD).¹ Autologous bone grafts for PLF are usually harvested from the iliac crest, requiring additional surgery; moreover, it may not yield sufficient bone. It can also be associated with donor site complications (hematoma, fracture, wound healing problems, persistent pain, pelvic deformity, and neurovascular injuries).²⁻³ Many ASD cases require multilevel fusion, requiring more bone grafts than typical single-level fusion. Thus, multilevel fusion decreases the union rate and increases surgical blood loss, operative time, length of hospital...
Various materials have been explored as autogenous bone substitutes. However, noncalcium phosphate-based bone substitutes demonstrate poor mechanical properties, low biocompatibility, and poor tissue adhesion. Therefore, calcium phosphate-based ceramics, such as hydroxyapatite (HA), have been developed to address these issues. HA is a naturally-occurring form of calcium phosphate and the most abundant inorganic constituent of human bones. Unlike allografts, HA shows no risk of virus transmission. Moreover, it is nonallergenic with excellent osseointegration. Therefore, HA is preferred as a bone graft or extender in orthopedics.

Bone morphogenetic proteins (BMPs) have been considered for bone graft enhancement. Among the various BMPs, factors with osteogenic activity are limited. Recombinant human BMP-2 (rhBMP-2) is commercially available and approved by the U.S. Food and Drug Administration for anterior lumbar interbody fusion (ALIF). Treatment with rhBMP-2 results in a higher union rate than autologous bone and significantly improves several clinical parameters in a single-level fusion through ALIF and PLF. Melconrey et al. demonstrated rhBMP-2 efficacy in multilevel fusion in 98 patients with ASD. Application of rhBMP-2 at an average of 2.6 levels per patient resulted in a 95% union rate. However, these studies have not identified any interpatient factors with statistically significant effects on the bone union. Therefore, this investigator-initiated exploratory study on multilevel fusion compared the outcomes of the combined use of rhBMP-2 and HA alone in the same patients to exclude interpatient factors.

**MATERIALS AND METHODS**

1. **Study Design**

   This study was a investigator-initiated, prospective, single-center, randomized, controlled, exploratory clinical trial. Patients were enrolled with institutional review board approval between October 2016 and December 2019. This study was registered with the Clinical Research Information Service (CRIS No. KCT-0006545) and conducted according to the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice.

   Patients who visited to the clinic and met the following inclusion criteria were consecutively enrolled: (1) age, 19–80 years, (2) pain associated with ASD at 3–5 segments between L1 and S1 necessitating intertransverse process lateral fusion, (3) voluntary participation in this clinical trial with written consent. The exclusion criteria were as follows: (1) participation in another clinical trial within 1 month before enrollment, (2) history of fusion surgery on the same site, (3) osteoporosis; average T-score ≤ -3.0 at lumbar, (4) immunosuppression or autoimmune disease, (5) rhBMP-2 hypersensitivity, (6) history of malignant tumors, (7) fractures, acute infections, hemorrhagic diseases, active systemic infections, osteodystrophy, or infections at the surgical site, (8) serious diseases that could affect surgery, (9) use of contraindicated concomitant drugs, (10) alcohol or drug addiction, or mental illness, (11) pregnancy, lactation. Detailed criteria for ASD are scoliosis Cobb angle of 20° or more, sagittal vertical axis of 5 cm or more, pelvic tilt of 25° or more, and/or pelvic incidence–lumbar lordosis of 10° or more. All patients enrolled in this study received the same posterior column osteotomy, and none underwent 3-column osteotomy that would have been a confounder to the study. Since this is an investigator-initiated exploratory trial, the sample size was not statistically calculated. In addition, the clinically significant effect sizes, limits, and standard deviations required to calculate the number of subjects could not be obtained due to the absence of adequate previous studies. The number of subjects was determined based on clinical experience (the number of patients visiting the hospital, the enrollment rate, etc.) and the dropout rate of 20%. Eligible subjects were assigned numbers according to pregenerated randomization of the order of participation. A block randomization was conducted through a web-based simple randomization service (https://www.sealedenvelope.com/simple-randomiser/v1/lists) provided by Sealed Envelope. Control (HA) or test sites (rhBMP-2+HA) were randomly assigned to the left or right side of one patient’s transverse processes in a 1:1 ratio. The surgeon was blinded until the day of surgery and was unable to preidentify the randomization code for the patient. Patients received follow-ups at 1, 3, 6, and 12 months after surgery with physical examination and static radiography at every follow-up visit, dynamic radiography at 3, 6, and 12 months after surgery, and computed tomography (CT) scans at 6 and 12 months following surgery. For clinical outcomes, we evaluated visual analogue scale (VAS) and Oswestry Disability Index (ODI) scores for back and leg pain at baseline and at 6 and 12 months after surgery. 36-item Short Form Health Survey (SF-36) and Scoliosis Research Society-22 (SRS-22) questionnaires were administered at baseline and 12 months after surgery. Samples for rhBMP-2 antibody testing were collected and analyzed at baseline and at 3 and 12 months after surgery.

2. **Intervention**

   After general anesthesia, we used a midline skin incision and
a posterior approach\textsuperscript{18,19} to expose the origin of the transverse processes on both sides, with bilateral retraction. The affected nerve root was decompressed by laminectomy. Pedicle screws were inserted into the vertebral body with an appropriate medical angulation. The anterior cortical bone of the vertebra was fixed to sufficient depth without damage using a rod. The lateral surface of the vertebral joint, the recess at the origin of the transverse process, and the bone surface of the transverse process were removed and irrigated with saline. Bone grafts were placed on the assigned side according to randomization results. Instrumentation was performed at all fused segments. The test site (rhBMP-2+HA) received 3.0 g of a porous HA carrier (Bon-gros-HA, CG Bio Co., Ltd., Seoul, Korea) adsorbed with 3.0 mg of \textit{E. coli}-derived rhBMP-2 (Novosis, CG Bio Co., Ltd., Seoul, Korea) per level for posterolateral bone fusion. The average amount of rhBMP-2 applied per patient was 12.78 ± 2.71 mg (9–15 mg rhBMP-2 for 3–5 level fusion). The dose setting of 3.0 mg of rhBMP-2 per level was based on previous studies.\textsuperscript{16} For the control site (HA), 3.0 g of HA carrier, loaded with saline, was mixed with 2.5 g of HA carrier only and transplanted.

3. Evaluation
The primary efficacy endpoint was the CT-based union rate at 12 months, and the secondary efficacy endpoint was the CT-based union rate at 6 months. The union was judged as grade I–IV according to the bone bridging pattern on the CT scan as follows\textsuperscript{20}: grade I, complete fusion; grade II, partial fusion; grade III, unipolar pseudarthrosis; grade IV, bipolar pseudarthrosis. Grades I and II were considered “bone union.” Two spinal neurosurgeons who did not participate in this study evaluated the results as independent evaluators. Where there were conflicting opinions between the 2 evaluators, the result was nonunion. In this study, “union” was judged only when all segments were fused and “nonunion” when even one segment was not fused. The evaluation was subject and operator-blinded, and the sites for assessment (test and control site) were also blinded to minimize bias. Changes in VAS, ODI, SF-36, and SRS-22 scores from baseline were analyzed using the paired t-test or Wilcoxon signed-rank test. Two-sample t-test or Mann-Whitney U-test was used to compare demographic factors in union and non-union cases. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The threshold for statistical significance was set at p < 0.05.

4. rhBMP-2 Antibody Analysis
We modified the study plan for analyzing increased rhBMP-2 antibodies during the clinical trial. An enzyme-linked immuno-
subjects for analysis at 6 months and 25 subjects at 12 months. The number of subjects enrolled, assigned, lost at follow-up, and analyzed are summarized in the flow diagram (Fig. 1). Data on patient baseline characteristics and operated segments are presented in Table 1.

2. Union Rate

We evaluated the union rates separately for control and test sites (Table 2). At 6 months, the union rate was 100% (27 of 27) at the test site and 77.8% (21 of 27) at the control site, indicating a statistically significantly higher union rate at the test site (p = 0.014). At 12 months, the union rate was 100% (25 of 25) at the test site and 88.0% (22 of 25) at the control site (p = 0.083). Based on Cohen kappa (0.86), interobserver reliability between evaluators (98.1%) for fusion evaluation indicated almost perfect agreement. The union rate per segment was subanalyzed (Table 3). In the subanalysis, a total of 115 segments (in 27 patients) were included at 6 months and 109 segments (in 25 patients) at 12 months. The union rate at the control site was 93.9% (108 of 115) at 6 months and 96.3% (105 of 109) at 12 months. At 6 months, 6 of 7 nonunion segments were L5–S1, and one was L3–4. At 12 months, 3 of 4 nonunion segments were L5–S1 and one L3–4. In the test group, the union rates at 6 and 12 months were both 100%, and the differences between the groups were significant at both time points (p < 0.001). Fusion characteristics on CT scans were slightly different between the 2 groups. Although both sites showed fusion mass, continuity of the fused mass was more prominent and uniformly observed at the test site than at the control site (Fig. 2).

3. Clinical Outcomes

ODI and VAS scores for back and leg pain significantly decreased compared to baseline at all time points (all p < 0.01) (Table 4). The Physical Component Summary and Mental Component Summary scores in the SF-36 questionnaire (to evaluate the quality of daily life) had significantly improved 12 months after surgery compared to baseline (p < 0.001) (Table 5). The SRS-22 score significantly improved compared to baseline values (p < 0.001) (Table 5).

4. Safety

We analyzed safety in 30 enrolled subjects. Eleven subjects had TEAEs (36.67%, 23 cases). Among TEAEs, fluid collection

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### Table 1. Patient demographics (n = 27)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.07 ± 5.78</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153.61 ± 9.13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.01 ± 11.31</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>0.08 ± 1.65</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Drinking</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>No. of fused levels</td>
<td></td>
</tr>
<tr>
<td>3 Levels</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>4 Levels</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>5 Levels</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Fusion levels</td>
<td></td>
</tr>
<tr>
<td>L1–4</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>L2–5</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>L3–S1</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>L1–5</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>L2–S1</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>L1–S1</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Fused levels per patient (level)</td>
<td>4.26</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%), unless otherwise indicated. BMD, bone mineral densitometry.

---

### Table 2. Fusion rate on computed tomography scan

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>Test site (rhBMP-2+HA)</th>
<th>Control site (HA)</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months (n = 27)</td>
<td>27 (100)</td>
<td>21 (77.8)</td>
<td>0.014*</td>
</tr>
<tr>
<td>12 Months (n = 25)</td>
<td>25 (100)</td>
<td>22 (88.0)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

Values are presented as number (%). rhBMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; HA, hydroxyapatite. *p < 0.05, statistically significant differences. †McNemar test was used to compare the fusion rates between the test and control sites.

---

### Table 3. Subanalysis of fusion rate according to the segment on computed tomography

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>Test site (rhBMP-2+HA)</th>
<th>Control site (HA)</th>
<th>p-value&lt;sup&gt;†&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months (n = 115)</td>
<td>115 (100)</td>
<td>108 (93.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>12 Months (n = 109)</td>
<td>109 (100)</td>
<td>105 (96.3)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are presented as number (%). rhBMP-2, *Escherichia coli*-derived recombinant human bone morphogenetic protein-2; HA, hydroxyapatite. *p < 0.05, statistically significant differences. †McNemar test was used to compare the fusion rates between the test and control sites.
Table 4. Changes from baseline to 6 and 12 months in the Oswestry Disability Index (ODI) and visual analogue scale (VAS) scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n = 27)</th>
<th>6 Months (n = 27)</th>
<th>p-value*</th>
<th>12 Months (n = 27)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODI</td>
<td>25.59 ± 8.51</td>
<td>19.11 ± 5.90</td>
<td>0.004*</td>
<td>18.85 ± 8.37</td>
<td>0.004*</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>6.70 ± 2.15</td>
<td>2.89 ± 1.95</td>
<td>&lt; 0.001*</td>
<td>2.62 ± 2.06</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Left leg</td>
<td>5.78 ± 3.04</td>
<td>2.78 ± 2.39</td>
<td>&lt; 0.001*</td>
<td>3.04 ± 2.78</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Right leg</td>
<td>5.22 ± 3.85</td>
<td>2.48 ± 2.83</td>
<td>0.001*</td>
<td>2.41 ± 2.85</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
*p < 0.05, statistically significant differences. tPaired t-test was used.

at the surgical site developed in 2 patients, but symptoms (buttock pain) improved after percutaneous catheter drainage, and bacterial cultures were negative.

Three patients (10.0%) had 4 serious TEAEs, 1 mild (adjacent disc herniation at T8–9 at 9–12 months), and 3 moderate (acute kidney injury between baseline and 1 month, thoracic vertebral compression fracture at T11 at 1–3 months, gait disturbance after 12 months). Most serious TEAEs (3 patients) resolved with conservative drug treatment and rehabilitation. However, one patient with a fracture recovered after 8 weeks of fusion extension surgery. No subject developed ADEs or serious ADEs. Laboratory and electrocardiogram tests revealed no abnormal findings.

We analyzed the antibody response according to the high-dose rhBMP-2. One patient was temporarily positive at 3 months but negative at 12 months. This patient achieved radiographic union at both control and test sites at all time points, with no rhBMP-2-related complications.

DISCUSSION

This study had a split-body trial design with a control or test site assigned to the left/right side of the transverse process of one subject. An average of 4.26 segments were fused. The union rate at the test site was 100% at 6 and 12 months. Despite using multilevel fusion, our results were similar to previously reported union rates achieved with rhBMP-2 with single-level fusion. Cho et al. applied 3.0 mg of rhBMP-2 along with an HA carrier to a single level PLF. The union rate achieved in the rhBMP-2+HA group at 3 and 6 months was 100%, superior to that of the ICBG group (3 months, 90.2%; 6 months, 94.1%). Therefore, the present study demonstrated that 3.0 mg of rhBMP-2 per level was sufficient to achieve bone fusion, even at multiple fusion levels (3–5 levels).

In the HA group, we applied a high-purity synthetic HA ce-
Choi HY, et al.

Spine Deformity Surgery Using rhBMP-2

HA is a low-biodegradable osteoconductive material that can serve as a long-term carrier due to high rhBMP-2 affinity. Because HA effectively adsorbs rhBMP-2 to the surface due to its high affinity and porosity, it can slowly and continuously release rhBMP-2 through adjacent bodily fluid streams. This study showed a 77.8% union rate for the HA group at 6 months and 88.0% at 12 months, higher than the union rates achieved in previous PLF studies on a single level. Nam and Yi applied HA or demineralized bone matrix (DBM) as a bone graft extender for PLF, but the union rate at 12 months in the HA group was 58%, not significantly different from the 73% achieved in the DBM group. Our study used only the HA carrier at the control site for multilevel fusion. The high union rate achieved at the control site could be due to earlier fusion at the contralateral test site that received rhBMP-2 with HA. Early union of the test site would have a positive effect on the union rate by providing stability to the control site.

Table 6. Analysis of the demographic factors of nonunion cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonunion (n = 6)</th>
<th>Union (n = 21)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69.83 ± 2.23</td>
<td>71.43 ± 6.45</td>
<td>0.562</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (33.3)</td>
<td>8 (23.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>4 (66.7)</td>
<td>16 (76.2)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.93 ± 16.31</td>
<td>152.95 ± 6.31</td>
<td>0.492</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.38 ± 11.28</td>
<td>58.90 ± 11.60</td>
<td>0.929</td>
</tr>
<tr>
<td>BMD (T-score)</td>
<td>0.27 ± 2.20</td>
<td>0.02 ± 1.53</td>
<td>0.758</td>
</tr>
<tr>
<td>Smoking</td>
<td>5 (83.3)</td>
<td>2 (9.5)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Drinking</td>
<td>3 (50.0)</td>
<td>2 (9.5)</td>
<td>0.056</td>
</tr>
<tr>
<td>No. of fused levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Levels</td>
<td>0 (0)</td>
<td>8 (38.1)</td>
<td>0.171</td>
</tr>
<tr>
<td>4 Levels</td>
<td>1 (16.7)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>5 Levels</td>
<td>5 (83.3)</td>
<td>10 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Fusion levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1–4</td>
<td>0 (0)</td>
<td>2 (9.5)</td>
<td>0.757</td>
</tr>
<tr>
<td>L2–5</td>
<td>0 (0)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>L3–S1</td>
<td>0 (0)</td>
<td>4 (19.1)</td>
<td></td>
</tr>
<tr>
<td>L1–5</td>
<td>0 (0)</td>
<td>1 (4.8)</td>
<td></td>
</tr>
<tr>
<td>L2–S1</td>
<td>1 (16.7)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>L1–S1</td>
<td>5 (83.3)</td>
<td>10 (47.6)</td>
<td></td>
</tr>
</tbody>
</table>
| Fused levels per patient (level) | 4.83 | 4.10 | -

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.

BMD, bone mineral densitometry.

*p < 0.05, statistically significant differences. †Two-sample t-test or Mann-Whitney U-test was used.

Table 5. Changes from baseline to 12 months in 36-item Short Form Health Survey (SF-36) and Scoliosis Research Society-22 (SRS-22) scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n = 25)</th>
<th>12 Months (n = 25)</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>14.80 ± 15.38</td>
<td>35.80 ± 24.82</td>
<td>0.001*</td>
</tr>
<tr>
<td>Role-physical</td>
<td>24.90 ± 21.41</td>
<td>48.63 ± 18.95</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>21.78 ± 15.89</td>
<td>53.64 ± 23.15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>General health</td>
<td>33.40 ± 20.55</td>
<td>45.60 ± 15.16</td>
<td>0.006*</td>
</tr>
<tr>
<td>Vitality</td>
<td>35.14 ± 19.96</td>
<td>48.06 ± 19.45</td>
<td>0.023*</td>
</tr>
<tr>
<td>Social functioning</td>
<td>33.44 ± 22.42</td>
<td>51.30 ± 19.78</td>
<td>0.004*</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>20.60 ± 15.67</td>
<td>58.80 ± 21.69</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mental health</td>
<td>44.20 ± 21.92</td>
<td>61.00 ± 18.98</td>
<td>0.008*</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>23.64 ± 13.08</td>
<td>45.71 ± 17.66</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>33.22 ± 15.08</td>
<td>54.53 ± 16.80</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>SRS-22</td>
<td>2.22 ± 0.60</td>
<td>3.20 ± 0.65</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.

*p < 0.05, statistically significant differences. †Paired t-test was used.
smokers, the union rate at 6 months was 79.2% (19 of 24), and the union rate at 12 months was 87.0% (20 of 23). The union rate per segment at 6 months was 94.2% (98 of 104), and the union rate per segment at 12 months was 96.0% (97 of 101).

The segment with the highest nonunion rate was L5–S1 (at 6 months; 85.7%; 12 months, 75.0%). The L5–S1 region exhibits a high nonunion rate due to poor sacral bone quality, complex sacral anatomy, and high biomechanical forces exerted on the lumbosacral junction. Nevertheless, the rhBMP-2+HA group showed union at all segments and time points. Therefore, the application of rhBMP-2 with HA can increase the union rate in long-segment fusion, including the lumbosacral junction (L5–S1), where nonunions are frequent.

The rhBMP-2 is a growth factor with osteoinductive ability. Consequently, there have been concerns about side effects with high doses. This study used 3.0 mg per segment and 9–15 mg rhBMP-2 per patient. Assuming that the average weight of patients was 60 kg, the dose per patient was 0.15–0.25 mg/kg, which was lower than the dose at which no adverse effects of rhBMP-2 were observed in rats (0.5 mg/kg) and markedly lower than the lethal dose in rats (7.0 mg/kg).

Some side effects associated with rhBMP-2 in the lumbar region are postoperative radiculitis, postoperative nerve root injury, ectopic bone formation, vertebral osteolysis/edema, and retrograde ejaculation. However, no severe AEs due to rhBMP-2 occurred in this study. Furthermore, this clinical trial evaluated the antibody response according to rhBMP-2 application in some subjects at 3 and 12 months. Only one subject temporarily tested positive at 3 months but negative at 12 months, a finding consistent with the results of a prospective, longitudinal cohort study. Burkus et al. analyzed antibody production and clinical symptoms in patients receiving rhBMP-2 in the lumbar region. Antibody formation against rhBMP-2 peaked at 3 months and decreased to baseline at 12 months. The overall antibody elevation rate was 0.8%–6.4%, but all were non-neutralizing antibodies. These nonneutralizing antibodies generated due to an immune response to the therapeutic protein can bind to the protein without affecting its activity. Therefore, even if an antibody is present, it is important to determine whether it is a neutralizing antibody and exhibits actual clinical effects.

In this study, one subject with antibody formation showed bone union at both control and test sites, with no other clinical AEs.

This study had several limitations. The number of patients was too small to sufficiently detect differences in effects between groups. The follow-up period was short (1 year). Therefore, it is necessary to verify long-term clinical results with a larger cohort in the future. We applied 2 interventions simultaneously in each subject that could have mutually influenced the outcomes of each treatment group. The split-body trial has an advantage that the confounding factors between groups can be removed because the subjects of the test group are the same. However, since half of the human body is not completely independent, the difference in effects between groups may be underestimated, and systemic side effects may be masked. Therefore, this study was able to directly compare the difference in effects according to BMP-2 without confounding factors between individuals, but the degree of difference may have been underestimated. In addition, safety could not be evaluated separately between groups.

In conclusion, this study demonstrated the clinical efficacy and safety of combined rhBMP-2 and HA in multilevel PLF fusion for ASD correction. Complete fusion was achieved at 6 months with 3 mg of rhBMP-2 per level for multilevel fusion (3–5 levels) without causing antibody production that resulted in clinical symptoms.

CONCLUSION

This prospective, randomized, controlled trial investigated the efficacy and safety of the combined use of rhBMP-2 and a HA carrier in multilevel fusion in patients with ASD. The union rate for the rhBMP-2+HA group was 100% at 6 and 12 months. The union rate for the HA group was 77.8% (21 of 27) at 6 months and 88.0% (22 of 25) at 12 months. (p = 0.014 at 6 months; not significant at 12 months). In subgroup analysis per segment, 108 (93.9%) of a total of 115 segments at the control site and all segments at the test site were fused at 6 months (p < 0.001). At 12 months, 105 (96.3%) of a total of 109 segments at the control site and all segments at the test site were fused (p < 0.001). Clinical- and functional parameters (VAS, SF-36, and SRS-22 scores) improved significantly compared to baseline.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Methodology: HYC; Project administration: SH; Writing - original draft: SH; Writing - review & editing: SH, CHL, JHY, KK.

ORCID
Ho Yong Choi: 0000-0002-5545-4283
Seung-Jae Hyun: 0000-0003-2937-5300
Chang Hyun Lee: 0000-0003-0134-2101
Ji Hyun Youn: 0000-0003-2939-8457
Mi Young Ryu: 0000-0002-9671-0095
Ki-Jeong Kim: 0000-0001-8547-8545

REFERENCES
To the editor,

I read with interest the article by Okamoto et al.,¹ as it directly relates to our clinical interests. The article is focused on observations of facet joint degeneration and its relationship with degenerative cervical myelopathy. Unfortunately, the authors did not include our several publications on the subject in their reference list.²-⁸ I wish to update this subject, particularly as regards the clinical implications of facet joint degeneration. The observations of the authors regarding facet joint degeneration reinforce our hypotheses on the subject.²-⁸ Although we agree with the authors that the evaluation of facets is less debated and that are only a few relevant reports, we contest their statement that the relationship between facet joint degeneration and degenerative spinal disease is unknown.²-¹¹

Mobility and stability are essential elements of life. Human beings are additionally burdened by their unique natural gift of a posture standing on 2 legs. The major bulk of human muscles is located on the extensor compartment of the body, or on its “back,” and cater to movements that facilitate sitting, standing, and running. However, relatively few strands of muscles are located in the flexor or anterior compartment of the body, flexion movement being essentially of a passive nature. The activity of all major extensor muscles is focused on the facetal articulation, which forms the point of fulcrum of all movements. In essence, the activity of no major muscle group is focused on the disc or the odontoid process, or in other words, the disc or the odontoid process does not form a fulcrum point of movement. Our articles have discussed the role of the disc and the odontoid process in human movements. We philosophized that both the disc and odontoid process are like opera conductors who regulate all music without holding any instrument in their hands.¹² While muscles are the brawn, the disc (and odontoid process) is the brain of all movements.

We hypothesized that the weakness of muscles related to their disuse, abuse, or injury forms the basis of all spinal instability and deformities.²-¹¹ As the facets are the focal point of activity of spinal muscles and their movements, muscle incompetence has its initial impact on the facets and their articulation. We identified for the first time in the literature that such muscle weakness leads to telescoping or listhesis of the facets of spinal segments and labeled it as “vertical” spinal instability.⁹ We hypothesized that vertical facetal instability is the primary issue in spinal degeneration and reduction in the disc space, bulging of the disc into spinal canal, buckling of intervertebral ligaments (including the posterior longitudinal ligament and ligamentum flavum), osteophyte formation, facetal and vertebral body fusion, and all the other known so-called “pathological” entities that lead to reduction in the spinal and neural canal dimensions are secondary natural responses.⁷-¹¹ Essentially, we observed that it is not disc fluid reduction or disc degeneration that is the primary point of inertia of...
spinal degeneration, but instead vertical spinal instability. In their study that focused on the pathology of facets, while evaluating the listhesis of vertebral bodies, the authors could have evaluated the listhesis of the facets even if it was of a subtle nature. Acute muscle weakness-related spinal instability can lead to disc herniation and listhesis of the spinal segment and acute clinical symptoms, usually in the form of radiculopathy. The authors referred to this group of patients as the "rapid progression group." In contrast, chronic and longstanding instability leads to chronic secondary alterations and multisegmental cervical and lumbar canal stenosis and subtle and relentlessly progressive symptoms. The authors referred to this group of patients as the "slow progression group."

The authors correctly mentioned that the lateral location of the facet articulation, which is away from spinal neural structures, makes the identification of instability difficult or impossible. The authors used high-definition imaging to identify the various types of facet degeneration, which include joint space narrowing, articular surface irregularity, facet joint opening, cyst formation, and ankylosing changes. As we speculated earlier, the authors identified facet articulation changes in all patients with degenerative spinal disease. It can be added to the authors' observations that all these facet changes are secondary to vertical spinal instability, which originates from muscle weakness.

The authors mentioned their observations of facet alterations in asymptomatic patients and in the adjoining segments, even when this was not corroborated with parallel clinical symptoms and radiological changes. In our articles on the subject, we have discussed this issue and identified spinal instability by clinical and radiological guides and by direct confirmation by the manual manipulation of bones. We have resorted to spinal fixation even when there was no radiological evidence of degeneration. Understanding the fact that chronic muscle weakness is usually not segmental, but is often multisegmental, and segments adjacent to those evident radiological guides can be unstable can avoid the commonly encountered issue of "adjacent segment disease."

We observed that the atlantoaxial facet joint, which is the most mobile joint of the body, is most susceptible to instability. The subject of craniovertebral junction "degeneration" has been seldom discussed in the literature. Our experience suggests that atlantoaxial instability can be present either discretely or can frequently be associated with multisegmental cervical spinal degeneration, more often in patients who present with symptoms related to severe myelopathy. Atlantoaxial instability is usually of the central or axial variety and is chronic in nature. As discussed in our articles, atlantoaxial instability can be difficult or impossible to diagnose on radiological assessment of dynamic imaging and has to be diagnosed on the basis of tell-tale evidence. All the facet changes discussed by the authors can be starkly observed in the craniovertebral junction facets in the scenario of degeneration. In addition, we discussed the presence of retro-odontoid pseudotumors in terms of their relationship with atlantoaxial instability. We are convinced that ignoring atlantoaxial instability in such cases can lead to surgical failure. It is unfortunate that the authors have ignored the evaluation of atlantoaxial facets in their study.

In 2011, we identified facet distraction and fixation-arthrod elis (both cervical and lumbar) by deploying the specially designed "Goel facet spacer" as treatment for single-segmental and multisegmental spinal degeneration-related radiculopathy and/or myelopathy. The treatment resulted in secondary spinal decompression. Our article was the first in the literature to mention that "decompression" by the removal of parts of bones, soft tissues, and osteophytes can be avoided in cases of spinal degeneration.

As we mature further, we realize that instability is the cause and stabilization is the treatment for spinal degeneration. Our multiple articles on the subject discuss this issue. We have observed that ossification of the posterior longitudinal ligament (OPLL) is also a consequence of spinal instability, and only stabilization and not decompression is the treatment. Although the authors evaluated the facet articulation in cases of OPLL, they did not clearly delineate their specific pathological features.

We resort to the Camille technique of transarticular fixation and find it strong, simple, and safe; more importantly, it focuses on the fulcrum point of movements. Using the strongest part of the spinal segment provides a base for strong screw purchase, firm stabilization, and a reliable opportunity for arthrodesis.

Essentially, muscle weakness-related facet degeneration leads to instability, and spinal stabilization is the treatment. All secondary alterations, such as osteophyte formation and ligamentum flavum buckling, are secondary, protective, and potentially reversible. Compression of neural structures is always secondary to instability and decompression by removal of bone/soft tissues in an unstable spinal situation can be counter-effective.

Conflict of Interest: The author has nothing to disclose.
REFERENCES


Reply Letter to “Cervical Facet Joint Degeneration”

Yasuhiro Takeshima, Ai Okamoto, Shohei Yokoyama, Fumihiko Nishimura, Ichiro Nakagawa, Young-Soo Park, Hiroyuki Nakase

Department of Neurosurgery, Nara Medical University School of Medicine, Nara, Japan

To the editor,

We thank Dr. Goel for his insightful comments on our recent article. The comments are very helpful to readers when considering the value of diagnosing facet joint degeneration. He stated that all facet degenerations are secondary to vertical spinal instability that originates from the weakness of back extensor muscles. Our study showed that facet degeneration is not related to cervical spondylolisthesis in patients with rapid progression of myelopathy, which supports the arguments he mentioned, but there are a few disagreements and misunderstandings, which we discuss below.

He emphasized that cervical stabilization is essential treatment for facet degeneration related to muscle weakness. Although his treatment strategy of stabilization first is reasonable, in our daily clinical practice we feel that it is also good to provide a surgical approach without spinal stabilization. Actually, 65.7% of patients in the recent article subsequently underwent cervical posterior decompression surgery. In Japan, a super-aging society, the number of healthy elderly people is increasing. With the recent development of general anesthesia, there are increasing opportunities to perform surgery not only on patients in their 80s but also in their 90s. Indeed, the oldest patient in our case series was aged 93 years. Spinal fusion could remove dynamic pathological factors, and the short-term clinical outcomes are great. But very long-term effects cannot be predicted. Aging generally causes restricted range of motion of the spinal column. In the spine, which is composed of multiple mobile joints, restricted range of motion means reduced ability to adjust. Therefore, if a history of previous fixation were added to the situation, it can easily lead to spinal malalignment due to further loss of adjustment reserve. This is a real issue that cannot be overlooked, especially in a super-aged society. On the other hand, because our study is only an investigation of the prevalence of cervical facet degeneration, the results cannot suggest any treatment approach or strategy. Further follow-up studies over a very long term on this controversial issue are warranted.

He also noted that it is unfortunate that our study ignored the evaluation of atlantoaxial facets, which have the highest potential for degeneration. The facet joints of the atlantoaxial and subaxial levels differ greatly in the orientation of joint surfaces and direction of loading, and it is necessary to consider them to be different in pathophysiology. Thus, the atlantoaxial facet joints were intentionally excluded from this evaluation. This joint is also a site of degenerative change; we consider it a subject for future study.

In addition, we would like to correct his understanding of the rapid progression group in...
our study as there seems to be some misunderstanding. He describes rapid progression as being caused by spinal instability associated with acute muscle weakness that occurs in radiculopathy. In our study, we excluded patients that clearly had radiculopathy in order to elucidate the pathophysiology of cervical myelopathy. Therefore, we emphasize that this group did not have radiculopathy; instead, they had rapidly progressive myelopathy.

We also included patients with ossification of posterior longitudinal ligament (OPLL) in our study. Indeed, OPLL is a unique pathological condition. However, since we expected stability and bony fusion in the adjacent intervertebral space to affect facet joint degeneration, we considered it unnecessary to exclude OPLL in our evaluation of facet joints. Since more detailed differences need to be investigated, this is also an issue for future study.

Overall, his hypothesis is highly compatible with our results. Since we are far from a complete understanding of the pathological significance and clinical implications of facet joint degeneration, it is indisputable that this is an area that warrants further study and discussion.

**Conflict of Interest:** The authors have nothing to disclose.

**REFERENCES**

I. General Information

*Neurospine* provides spine clinicians and researchers with peer-reviewed articles on basic and clinical investigation of spine and spinal cord to enhance patient management, education, clinical or experimental research, and professionalism. The journal will consider submissions in areas on craniocervical to lumbosacral spine including the followings; neuroscience and pain research, bone mineral research, disc and joint research, bio and industrial technology, pathophysiology, risk factors, symptomatology, imaging, treatment, rehabilitation of spine, and spinal cord/ peripheral nerve diseases. Specifically, basic and technology researches include the most influential research papers from all fields of science and technology, revolutionizing what physicians and researchers practicing the art of spinal neurosurgery worldwide know. Thus, we welcome valuable basic and translational technology research articles to introduce cutting-edge research of fundamental sciences and technology in clinical spinal neurosurgery. Clinical or Basic Research Articles, Review Articles, and Letters to the Editor written in English will be accepted.

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The introduction should address the purpose of the article concisely, and include background reports mainly relevant to the purpose of the paper. Detailed review of the literature should be addressed in the discussion section.

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1) The authors should logically describe their results of observations and analyses performed using methodology given in the previous section and provide actual data.
2) For biometric measurements in which considerable amount of stochastic variation exists, a statistical evaluation is mandatory. The results must be solely from the findings of the current study and not refer to any previous reports.
3) While an effort should be made to avoid overlapping descriptions by Tables and by main text, important trends and points in the Table should be described in the text.

7. Discussion
Discussions about the findings of the research and interpretations in relation to other studies are made. It is necessary to emphasize the new and critical findings of the study, not to repeat the results of the study presented in the previous sections. The meaning and limita-
tion of observed facts should be described, and the conclusion should be related to the objective of the study only when it is supported by the results of the research.

8. Conclusion
The conclusion section should include a concise statement of the major findings of the study in accordance with the study purpose.

9. References
The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. End-Note users can access a direct download of the updated Neurospine Publications style at https://www.e-neurospine.org. References should be numbered consecutively in the order in which they are first mentioned in the text. All references cited in the text must be both listed and cited by the reference number (footnotes are not accepted). Use superscript numerals outside periods and commas, inside colons and semicolons. When more than 2 references are cited at a given place in the manuscript, use hyphens to join the first and last numbers of a closed series; use commas without space to separate other parts of a multiple citation (e.g., As reported previously,1,3-8,19 ...The derived data were as follows3,4,12:) Do not link the references to the text. Cite unpublished data, such as papers submitted but not yet accepted for publication or personal communications, in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at https://www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html. Sample references are given below:

• Journal article

• Book chapter

• Entire book

• Software

• Online journals

• Database

• World Wide Web

10. Tables
1) Tables should be created using the table formatting and editing feature of Microsoft Word. The title of the table must be noted. Tables cannot be submitted in a picture format.
2) Tables should be prepared in detail, in order to understand the contents of the manuscript without further reference.
3) Tables should be submitted separately from manuscript. Do not include vertical lines in table, and refer to the table formats in Neurospine.

11. Figures and Illustrations
1) Figures should have resolution of 300 dpi or above and should be submitted individually (Namely, if Figure 1 is divided into A, B, C, and D, do not combine them into one, but submit each of them separately). Allowable file format for figures are JPG or TIF (TIFF) only.
2) Figures should be named according to figure name (example: Fig-1A.tif). If the quality of the photographs is considered as inappropriate for printing, resubmission of them can be requested by the journal.
3) Authors should submit figures in black and white if they want them to be printed in black and white. Authors are responsible for any additional costs of producing color figures (Additional cost for color printing is determined by the editorial board).
4) Line art should have resolution of 1,200 dpi or more in JPG or TIF format.

12. Author Check List
1) Before submitting the manuscript, authors should double-check all requirements noted in the agreement form regarding the registration and copyrights of their manuscript. A manuscript that does not fit the author instructions of the journal regarding format and references will be returned to the authors for further correction.
Instructions for Authors

IV. Peer Review Process

All manuscripts are considered confidential. They are peer-reviewed by at least 2 anonymous reviewers selected by the Editor. The corresponding author is notified as soon as possible of the Editor’s decision to accept, reject, or ask for revisions. The average time interval for an initial review process that involves both editorial and peer reviews is approximately 1 month; occasionally, there are unavoidable delays, usually because a manuscript needs multiple reviews or several revisions. When manuscripts are returned for revision, a cover letter from the Editor provides directions that should be followed carefully. When submitting the revised manuscript, authors should include a Response Letter, which describes how the manuscript has been revised. A point-by-point response to the Editor should be included with the revised manuscript. Authors who plan to resubmit but cannot meet this deadline should contact the Editorial Office. Manuscripts held for revision will be retained for a maximum of 90 days. The revised manuscript and the author's comments will be reviewed again. If a manuscript is completely acceptable, according to the criteria set forth in these instructions, it is scheduled for publication in the next available issue.

We neither guarantee the acceptance without review nor very short peer review times for unsolicited manuscripts. Commissioned manuscripts also are reviewed before publication.

We adopt double-blind peer review in which case, not only authors but also reviewers do not know each other.

V. Publication and Charges

1) Once a manuscript is accepted for publication by the journal, it will be sent to the press, and page proofs will be sent to authors. Authors must respond to the page proofs as soon as possible after making necessary corrections of misspellings, and the location of the photographs, figures or tables. Authors can make corrections for only typing errors, and are not allowed to make any author alteration or substantive changes of the text. Proofs must be returned to the press within 48 hours of receipt. No response from the authors within this time frame will lead the publication of the proof read without corrections, and the editorial board will not be responsible for any mistakes or errors occurring in this process.

2) There is no article processing charge (APC), also known as a publication fee including submission fee, for accepted articles.

VI. Ethical Guidelines

1. Research Ethics

1) All of the manuscripts should be prepared in strict observation of research and publication ethics guidelines recommended by the Council of Science Editors (CSE), International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), and the Korean Association of Medical Journal Editors (KAMJE).

2) Any study including human subjects or human data must be reviewed and approved by a responsible institutional review board (IRB). Please refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials.

3) Animal experiments also should be reviewed by an appropriate committee (Institutional Animal Care and Use Committee, IACUC) for the care and use of animals. Also studies with pathogens requiring a high degree of biosafety should pass review of a relevant committee (Institutional Biosafety Committee, IBC). The editor of Neurospine always request submission of copies of informed consents from human subjects in clinical studies or IRB approval documents.

2. Conflict of Interest

1) The corresponding author of an article is asked to inform the Editor of the authors’ potential conflicts of interest possibly influencing their interpretation of data. A potential conflict of interest should be disclosed in the cover letter even when the authors are confident that their judgments have not been influenced in preparing the manuscript. Such conflicts may be financial support or private connections to pharmaceutical companies, political pressure from interest groups, or academic problems. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (http://www.icmje.org/coi_disclosure.pdf).

2) The Editor will decide whether the information on the conflict should be included in the published paper. Before publishing such information, the Editor will consult with the corresponding author. In particular, all sources of funding for a study should be explicitly stated. The Neurospine asks referees to let its Editor know of any conflict of interest before reviewing a particular manuscript.
3. Journal Policies on Authorship and Contributorship

1) Authors are required to make clear of their contribution to their manuscript in cover letter. To be listed as an author one should have contributed substantially to all three categories established by the International Committee of Medical Journal Editors (ICMJE): (1) conception and design, or acquisition, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

2) When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. Authors are responsible for replying to all questions asked by reviewers or editors that relate to the accuracy or integrity of any part of the work. All persons who have made a substantial contribution, but who are not eligible as authors, should be named in the acknowledgments. Authors are expected to consider carefully the way authors should be listed and ordered before submitting their manuscripts, and to provide a definitive list of authors with their original submission. Any addition, deletion, or rearrangement of author names in the authorship list should be made before the manuscript has been accepted—and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the corresponding author: (a) the reason for requesting a change in the list of authors; and (b) written confirmation (by e-mail or letter) from all authors to say that they agree with the addition, removal, or rearrangement.

4. Redundant Publication and Plagiarism

1) Redundant publication is defined as “reporting (publishing or attempting to publish) substantially the same work more than once, without attribution of the original source(s)”. Characteristics of reports that are substantially similar include the following: (a) “at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication),” (b) “the subject or study populations are often the same or similar,” (c) “the methodology is typically identical or nearly so,” and (d) “the results and their interpretation generally vary little, if at all.”

2) When submitting a manuscript, authors should include a letter informing the editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to Neurospine differs substantially from this other material. If all or part of your patient population was previously reported, this should be mentioned in the Materials and Methods, with citation of the appropriate reference(s).

3) The editorial committee checks the similarity by using the iThenticate (http://www.ithenticate.com/) program for all submitted articles to prevent plagiarism. The editorial committee rejects the article suspected of plagiarism and asks the author to check whether it is plagiarized and make a resubmission.

5. Readership

It is primarily for clinicians and researchers who care patients with spine and spinal cord diseases. They are able to obtain tailored information to adopt for their research and practice. Its readership can be expanded to other positions: • Researchers can get the recent topics of clinical research in spine and spinal cord field and detailed research methods; • Clinicians in the field can get the new information and recent development for care of patients; • Medical teacher can access methods; • Clinicians in the field can get the new information and adopt a variety of data in medical educations; • Allied health professionals including nurses are able to get the recent information for care of patients with spine and spinal cord diseases; • Medical health students can understand the recent trends of the field and interesting cases for their work; • Policy makers are able to reflect the results of the articles to the nation-wide health care policies for patients with spine and spinal cord diseases; • The public, especially family of patients with spine and spinal cord diseases are able to read the advancement in their family’s diseases so that they have a better knowledge on the diseases and a confidence in the clinicians’ devotion to their family.

6. Obligation to Register Clinical Trial

1) Clinical trial defined as “any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome” should be registered to the primary registry to be prior publication.

7. Process for Identification of and Dealing With Allegations of Research Misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

Neurospine adheres to the research and publication ethics policies outlined in International Standards for Editors and Authors (http://publicationethics.org) and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://icmje.org). Any studies involving human subject must comply with the principles of the World Medical Association Declaration of Helsinki. Clinical research should be approved by the Institutional Review Board, as well through patient consent. A patient's personal information cannot be published in any form. However, if it is absolutely necessary to use a patient's personal information, the consent of the patient or his/her guardian will be needed before publishing. Animal studies should be performed in compliance with all relevant guidelines, observing the standards described in the NIH Guide for the Care and Use of Laboratory Animals.

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts available from: http://publicationethics.org/resources/flowcharts. If correction is needed, it will follow the ICMJE Recommendation for Corrections, Retractions, Replications and Version Control available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html as follows:

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Minimum standards are as follows: First, it shall publish a correction notice as soon as possible, detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing; Second, it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; Third, it shall archive all prior versions of the article. This archive can be either directly accessible to readers; and Fourth, previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

8. Handling Complaints and Appeals

The policy of the journal is primarily aimed at protecting the authors, reviewers, editors, and the publisher of the journal. If not described below, the process of handling complaints and appeals follows the guidelines of the Committee of Publication Ethics available from: https://publicationethics.org/appeals

Who complains or makes an appeal?

Submitters, authors, reviewers, and readers may register complaints and appeals in a variety of cases as follows: falsification, fabrication, plagiarism, duplicate publication, authorship dispute, conflict of interest, ethical treatment of animals, informed consent, bias or unfair/appropriate competitive acts, copyright, stolen data, defamation, and legal problem. If any individuals or institutions want to inform the cases, they can send a letter to editor through https://www.e-neurospine.org/about/contact.php. For the complaints or appeals, concrete data with answers to all factual questions (who, when, where, what, how, why) should be provided.

Who is responsible to resolve and handle complaints and appeals?

The Editor, Editorial Board, or Editorial Office is responsible for them.

What may be the consequence of remedy?

It depends on the type or degree of misconduct. The consequence of resolution will follow the guidelines of the Committee of Publication Ethics (COPE).

9. Postpublication Discussions and Corrections

The postpublication discussion is available through letter to the editor. If any readers have a concern on any articles published, they can submit letter to the editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

10. Policies on data sharing and reproducibility

Until 2020, authors will be encouraged to share their data openly, but starting in 2021, they will be mandated to do so. The related regulation follows the open data sharing policy outlined below.

1) Open data sharing policy

For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository, for example, Harvard Dataverse (https://dataverse.harvard.edu/) after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data, authors should contact the editorial office.

2) Clinical data sharing policy

This journal follows the data sharing policy described in “Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors” (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018 manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing state-
Table. Examples of Data Sharing Statements That Fulfill These ICMJE Requirements*

<table>
<thead>
<tr>
<th>Example</th>
<th>Will individual participant data be available (including data dictionaries)?</th>
<th>What data in particular will be shared?</th>
<th>What other documents will be available?</th>
<th>When will data be available (start and end dates)?</th>
<th>With whom?</th>
<th>For what types of analyses?</th>
<th>By what mechanism will data be made available?</th>
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<tr>
<td>1</td>
<td>Yes</td>
<td>All of the individual participant data collected during the trial, after deidentification.</td>
<td>Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code</td>
<td>Immediately following publication. No end date.</td>
<td>Anyone who wishes to access the data.</td>
<td>Any purpose.</td>
<td>Data are available indefinitely at (Link to be included).</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).</td>
<td>Study Protocol, Statistical Analysis Plan, Analytic Code</td>
<td>Beginning 3 months and ending 5 years following article publication.</td>
<td>Researchers who provide a methodologically sound proposal.</td>
<td>To achieve aims in the approved proposal.</td>
<td>Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (Link to be included).</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).</td>
<td>Study Protocol</td>
<td>Beginning 9 months and ending 36 months following article publication.</td>
<td>Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.</td>
<td>Not applicable</td>
<td>Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University’s data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (Link to be provided).</td>
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<td>4</td>
<td>No</td>
<td>Not available</td>
<td>Not available</td>
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* These examples are meant to illustrate a range of, but not all, data sharing options.

ment as described below. Clinical trials that begin enrolling participants on or after January 1, 2019 must include a data sharing plan in the trial’s registration. The ICMJE’s policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record. All of the authors of research articles that deal with interventional clinical trials must submit data sharing plan of example 1 to 4 in Table 1. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

For the policies on the research and publication ethics not stated in this instructions, International standards for editors and authors (https://publicationethics.org/resources/resources-and-further-reading/international-standards-editors-and-authors) can be applied.

All correspondences, business communications and manuscripts should be mailed to:

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   The author(s) certify that the contents of the manuscript have not been published and are not being considered for publication elsewhere.

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   If there are conflicts of interest, authors should state their content on the title page of the manuscript.

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1) Abstract should have no longer than 250 words for original articles and review articles. ☐ Yes / ☐ No
2) Abstract includes Objective, Methods, Results, and Conclusion in clinical or laboratory research. ☐ Yes / ☐ No
3) The selection of Key Words is based on medical subject headings (MeSH) terms. ☐ Yes / ☐ No

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1) Text is written in 11-point fonts with double line spacing. ☐ Yes / ☐ No
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1) References should be numbered consecutively in Arabic numeric order in which they are first men- tioned in the text. ☐ Yes / ☐ No
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4) If there are more than 3 authors in end-reference list, name only the first 3 authors and then use et al. ☐ Yes / ☐ No
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1) Tables and figures are prepared in separate files. ☐ Yes / ☐ No
2) Figures are submitted individually not incorporated into one file. ☐ Yes / ☐ No
3) Figures and illustrations are saved in JPG or TIF file format and have a resolution of 300 DPI or more. (Line art should have resolution of 1,200 dpi or more) ☐ Yes / ☐ No
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☐ Yes / ☐ No

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For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Materials and Methods section.

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