

Summer 2019

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# JHN JOURNAL

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**Joshua E. Heller, MD, MBA**

## Dear Colleague,

It is my pleasure to welcome you to the latest issue of the JHN Journal.

Spine surgery is continuously evolving with improvements in techniques, and advancements in technology. As always, the Spine Surgeons at Jefferson Health are at the forefront of this change.

Whether it's the adoption of image guidance and robotics, implementation of new minimally invasive techniques, advancements in neuromodulation, or collaboration in novel therapies for spinal cord injury, Jefferson continues to lead the way.

This very special issue of the JHN journal will highlight some of the important work that the Neurological Spine Surgeons at Thomas Jefferson University Hospital, and Jefferson Abington Hospital are doing to improve patient outcomes through advancements in technology.

I am very proud of the work that we do, and I am certain that the articles contained within this issue will prove to be enlightening.

Sincerely,

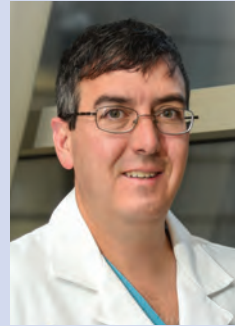
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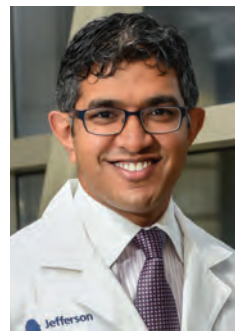
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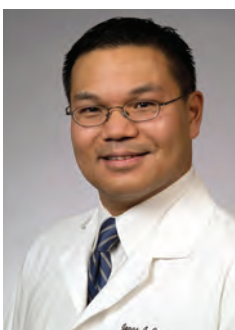
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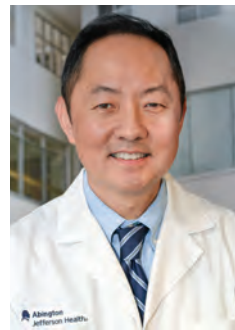
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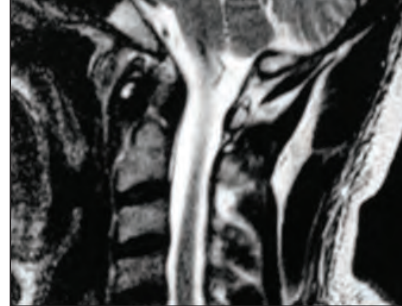
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## Table of Contents



### Sacroiliac Joint Fusion — Impact of a New Image-Guidance Protocol on Safety and Complications

Christian Hoelscher, MD; Daniel Franco, MD; Joshua Heller, MD, MBA ..... 2

### Spinal Cord Injury: Current and Novel Treatment Strategies

Anthony Stefanelli, MD; Umma Fatema; Alexandra Emes; James Harrop, MD, FACS ..... 9

### Multiple Contiguous-Level Cervical Disc Arthroplasties: Unique Considerations

Alejandro J. Lopez, DO; Jonas Gopez, MD ..... 12

### Minimal Access Expandable Mesh Device for Transforaminal Lumbar Interbody Fusion: A Case Series

Ryan Moncman, DO; Michael Yoon, MD..... 16

### Spinal Cord Stimulation in the 21st Century — Reviewing Innovation in Neuromodulation

Victor Sabourin, MD; Justin Turpin, BA; Jeffrey Head, BA; Chengyuan Wu, MD; Ashwini Sharan, MD; Christian Hoelscher, MD..... 20

Recent Noteworthy Publications ..... 25



# Sacroiliac Joint Fusion – Impact of a New Image-Guidance Protocol on Safety and Complications

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## INTRODUCTION

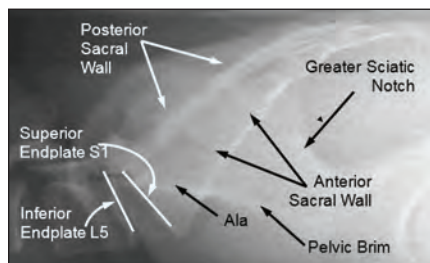
Low back pain is a common affliction impacting patients worldwide. The burden of low back pain on modern society in terms of direct costs associated with diagnosis and treatment, as well as indirect costs such as time missed from work for both patients and caregivers, is estimated to be as high as \$100 billion annually in the United States alone.<sup>1,2</sup> Up to 2-3% of physician visits are thought to be related to chronic low back pain.<sup>1,3</sup> While the traditional focus of healthcare providers has been on lumbosacral pathology, sacroiliac joint dysfunction is an underappreciated and underdiagnosed cause of low back pain. Previous studies<sup>3-8</sup> have suggested that 15-30% of chronic low back pain is due to pathology located in the sacroiliac joint. Historically, recognition of this pathology was difficult, limited by lack of standardized diagnostic criteria and disease-specific outcome measures. Traditional treatment focused on conservative therapy, such as physical therapy with focus on core and pelvic stability, orthoses, pain and anti-inflammatory medication, weight loss, intra- or peri-articular injections, and radiofrequency ablation.<sup>4,5,9-12</sup> Early surgical intervention came in the form of morbid open approaches often utilizing iliac crest autografting. More recently, minimally invasive techniques for sacroiliac fusion have been developed that allow for significant sparing of muscle dissection, shorter operating room times and blood loss, reduced length of stay, and fewer complications.<sup>13-17</sup> Such techniques are often performed with fluoroscopic guidance. However, three-dimensional sacral anatomy can be challenging to conceptualize on fluoroscopic imaging and several centers are now beginning to perform the procedure utilizing image-guidance with intraoperative CT data. This is particularly helpful in patients with transitional lumbosacral anatomy or those undergoing revision procedures. Complications such as pseudarthrosis and neural injuries, while rare, are often associated with need for revision surgery and poorer outcome.<sup>18,19</sup> The transition to CT-based image-guidance aims to reduce such complications. The purpose of this study is to review our series of minimally invasive sacroiliac fusion with a focus on safety and complications, and to review differences in these parameters between patients undergoing fluoroscopic technique versus CT-based image-guidance.

## METHODS

We performed a PubMed literature search utilizing the following terms: sacroiliac joint fusion, SI joint fusion, minimally invasive, complications, image guidance. Only English language articles were reviewed. All studies documenting large case series and prospective trials regarding minimally invasive sacroiliac joint fusion were included. The data extraction was performed by two reviewers (CH, DF), and reviewed by the senior author (JH). The selected studies were analyzed, and relevant results were reviewed. In addition, a retrospective review of minimally invasive sacroiliac joint fusion procedures performed at our institution was performed spanning 2013-present. Patient demographics, type of imaging used (traditional fluoroscopy versus CT and Stealth image guidance) follow-up, and complications were recorded. Complications of particular interest were neurologic complications, pseudarthrosis, and need for revision surgery, among others. Comparisons were made between patients undergoing fluoroscopy and CT/Stealth guidance.

## Technique – Fluoroscopy

After administration of general endotracheal anesthesia and placement of neuromonitoring leads, the patient is positioned prone on a Jackson table with careful attention to adequately padding pressure points and ensuring the abdomen hangs free. Fluoroscopy is used to mark the skin on the ipsilateral side the location of the sacral ala as well as the posterior aspect of the sacral canal. This serves as a marking point for the incision and helps with orientation of the implants (Figures 1-2). The skin is then prepped and draped in standard fashion. The incision is created with a #10 blade and the subcutaneous tissue is dissected with monopolar electrocautery. A hemostat is used to open the fascia. A Steinmann pin is placed at the level of the ilium with lateral fluoroscopic guidance at a location below the sacral ala. Pelvic inlet and outlet views are obtained to demonstrate adequate positioning of the pin relative to the ilium, SI joint, and neural foramina (Figure 3). The first pin is then tamped through the ilium, across the SI joint, and into the sacrum. The soft tissue dilator is then placed over the pin, followed by a soft tissue protector. A drill is then advanced over the pin and advanced across the SI joint. The broach is then advanced across the SI joint with fluoroscopic guidance on lateral, pelvic inlet, and pelvic outlet views. The broach is then removed. The first implant is then advanced over the pin and tamped into position using fluoroscopic guidance (Figure 4). A parallel pin guide is then used to assist with placement of the next Steinmann pin inferior to the first implant, and the procedure is repeated for a second implant. The parallel pin guide is then used to place a Steinmann pin in the ideal location of the third implant relative to the first two. The authors preference is to place the third implant in a position anterior and inferior to the first. The same procedure is repeated for placement of the final



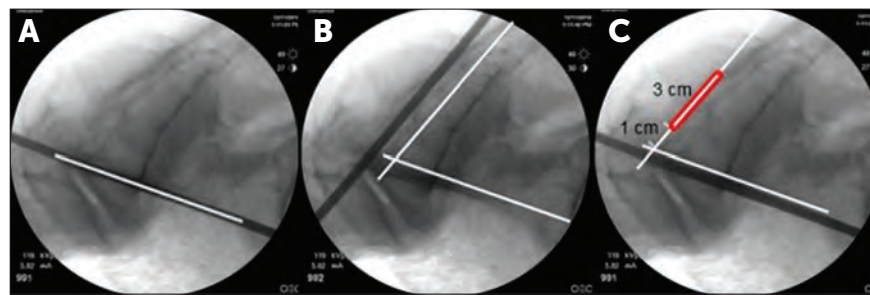
**Figure 1. Anatomic Landmarks**

Relevant anatomic landmarks as seen on a lateral fluoroscopic view

implant. Neuromonitoring signals are checked after placement of each implant. Final fluoroscopic images are obtained confirming trajectory and final position across the SI joint into the sacrum without breach of the neuroforamina. The wound is then copiously irrigated with antibiotic solution. The soft tissue is anesthetized with Marcaine solution. The deep dermal layer is closed with 2-0 vicryl suture in an inverted fashion and the skin is closed with a 4-0 monocryl subcuticular suture, followed by skin glue and a sterile dressing.

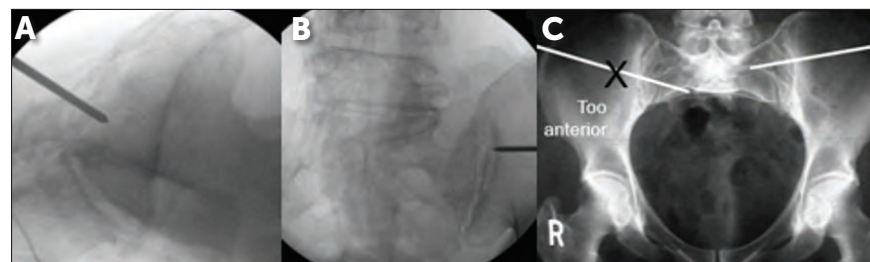
#### Technique – CT/Stealth Image Guidance

After administration of general endotracheal anesthesia and placement of neuromonitoring leads, the patient is positioned prone on a Jackson table with careful attention to adequately padding pressure points and ensuring the abdomen hangs free. The low back and lateral pelvic area on the side to be fused are prepped and draped according to standard protocol. A small incision is made over the contralateral posterior superior iliac spine (PSIS) with a #10 blade, and the fascia opened sharply with monopolar electrocautery. The pin for the Stealth reference frame is advanced into the PSIS. The O-arm is then draped and brought into the surgical field. After confirmation of appropriate anteroposterior (AP) and lateral views centered over the SI joint to be fused, an intraoperative CT is obtained and transmitted to the Stealth work station. The O-arm is then removed from the field. The passive planar probe is used to mark the location of the sacral ala on the skin, as well as



**Figure 2. Incision Planning**

Incision planning with pins placed along the sacral alae (A) and posterior sacral wall (B). The incision is then created about 3 cm in length along the posterior sacral wall, approximately 1 cm below the sacral alae (C).



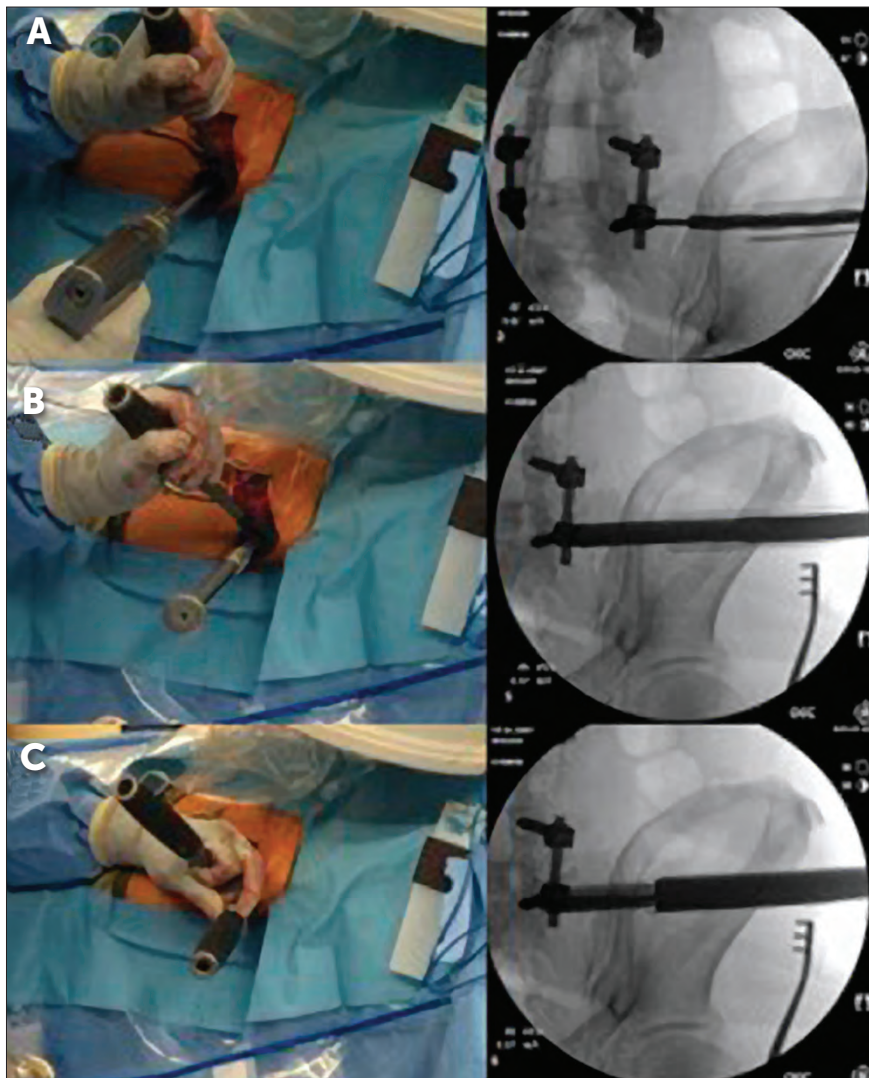
**Figure 3. Pin Placement**

Pin placement about 1 cm below the sacral ala (A). Pelvic outlet views are obtained to advance the pin parallel to the S1 endplate without breaching the sacral foramina (B). Pelvic inlet views are obtained to ensure that the pin placement is appropriate in the anterior-posterior plane (C).

the location of the posterior aspect of the sacral canal on the ipsilateral side. This serves as the incision and reference for graft placement. The skin is then incised with a #10 blade, with dissection carried down through the subcutaneous tissue with monopolar electrocautery. The fascia is opened with a hemostat. The navigated universal drill guide is then placed to the level of the ilium (Figure 5). The first implant is planned and transferred to the work station (Figure 6). The drill guide is then used to place a guidewire through the ilium to the planned depth. A soft tissue dilator is then placed over the wire, followed by a soft tissue protector. The navigated drill is then used to drill over the guidewire across the ilium, the SI joint, and into the sacrum. The drill is removed, and a navigated broach is then advanced and tamped down the same trajectory. Neuromonitoring is then checked and confirmed to be unchanged

from baseline. The soft tissue protector is then removed. A parallel pin guide with a navigated universal drill guide is then used to mark the location for the starting point of the second implant, inferior to the first graft. The process is repeated for the second and third grafts. Neuromonitoring is checked after placement of each graft. Once all grafts have been placed, a second intra-operative CT is obtained to confirm appropriate positioning. The wound is then copiously irrigated with antibiotic solution. The soft tissue is anesthetized with Marcaine solution. The deep dermal layer is closed with 2-0 vicryl suture in an inverted fashion and the skin is closed with a 4-0 monocryl subcuticular suture, followed by skin glue and a sterile dressing. A single monocryl suture is placed in the contralateral PSIS pin site. Figure 7 shows an example of post-operative imaging demonstrating hardware position.





**Figure 4. Implant Placement**

On pelvic outlet views, the drill is advanced over the pin (A), followed by broach placement (B) followed by seating the final implant (C).

## RESULTS

A total of 70 procedures were performed on 67 patients. Baseline characteristics and demographics are shown in Table 1. The average age was 50.4, with a male:female ratio of 49:21. BMI averaged 30.2. Co-morbidities of interest included 9 patients with diabetes, 13 with lumbosacral scoliosis, 5 with confirmed osteoporosis, 29 with a history of smoking, 5 active smokers, and 37 with prior lumbar surgery. Follow-up averaged 7.6 months. A total of 5 cases

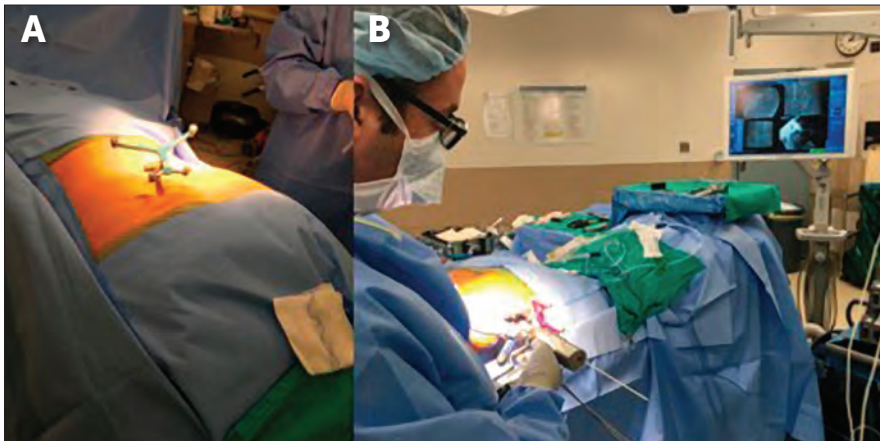
were revision procedures. Forty-six procedures were performed utilizing fluoroscopy, while 24 utilized CT with Stealth navigation. Complications for the entire cohort are demonstrated in Table 2. There was a total of 7 complications noted: 2 neurologic complications (both S1 radiculopathies), two cases of pseudarthrosis, 2 hematomas, and one washout that revealed only "thickened subfascial tissue". Overall 7 patients underwent revision surgery. Table 3 shows comparisons in terms of

baseline demographic and co-morbidities between the fluoroscopy and CT groups, while Table 4 shows complications between the two groups. Baseline demographics were notable for a trend towards a higher proportion of females and a higher proportion of revision surgery in the CT cohort. Complications were overall fairly rare and did not reach statistical significance between groups. There were 5 total complications in the fluoroscopy group compared to two in the CT cohort. There were 4 combined cases of neurologic deficit and pseudarthrosis, all of which occurred in the fluoroscopy group. Revision procedures were required in 5 procedures utilizing fluoroscopic guidance, compared to one in the CT group.

## DISCUSSION

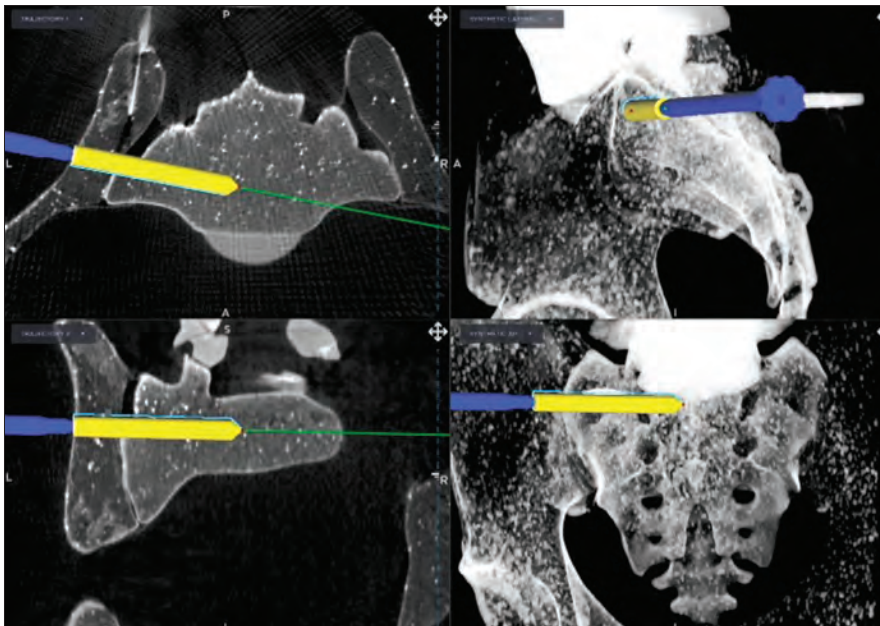
Sacroiliac joint dysfunction is an increasingly-recognized source of low back pain. This patient population has historically been very difficult to treat, with an extremely high burden of cost on both a direct and indirect basis, often with frustrating outcomes and high rates of persistent disability.<sup>3-5</sup> The traditional focus of back pain has been on diagnosis and managing lumbosacral pathology as well as neuropathic pain. Sacroiliac evaluation is only more recently gaining traction. Given that the SI joint is the largest articular surface in the human body, with fairly complex biomechanics central to force transmission across the complicated lumbosacral-pelvic anatomy, it is not surprising that this may be another source of pain.

Previous estimates of up to 30% of chronic back pain being referable to the SI joint have been published by numerous authors.<sup>3-7</sup> Recognition of this pathology has been limited in the past by a lack of clear diagnostic criteria. With increasing focus on this clinical entity, there is starting to be more consensus on appropriate means of diagnosing SI joint dysfunction. Patient history will often reveal pain in the gluteal region, located in the region of the PSIS. This may or may not be associated with a radiating component down the lower extremity and/or into the hip and groin. Pain is often worse in the sitting position. Physical examination is typically notable for positive findings on the Fortin's Finger test, as well as



**Figure 5. CT/Stealth Setup**

A navigation pin is advanced into the contralateral PSIS and an intraoperative CT scan is obtained (A). The navigated drill guide can then be advanced to the level of the ilium after an appropriate incision has been made, and implant planning can proceed (B).



**Figure 6. Implant Planning**

(Implant planning using the Stealth workstation).

reproduction of pain in at least three of five provocative SI joint testing maneuvers including pelvic distraction, thigh thrust, direct compression, flexion/abduction/external rotation (FABER), and Gaenslen's maneuver. Intra-articular SI joint injections with local anesthetic are used to confirm the diagnosis. Diagnostic injections relieve

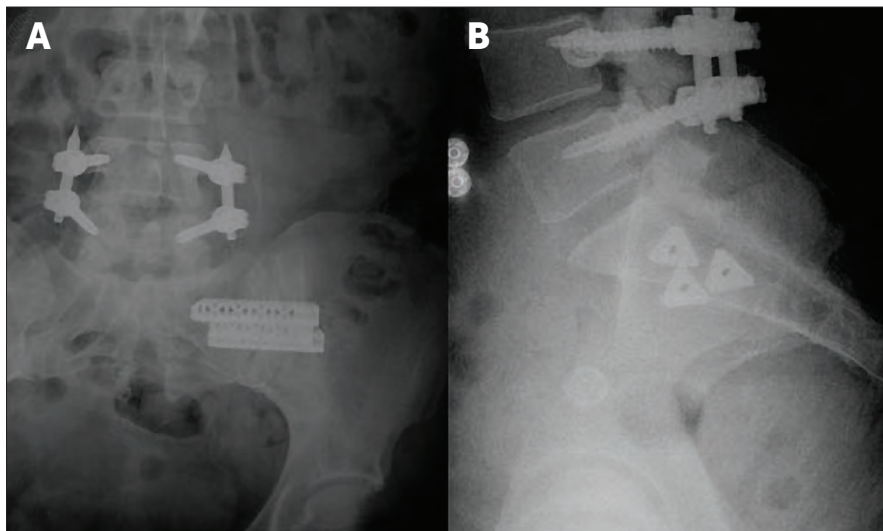
patient pain by at least 50-60% prior to considering surgical fusion of the joint. Therapeutic injections with steroid can be used to try to provide longer lasting relief.

Evidence in favor of minimally invasive SI joint fusion has largely been limited to retrospective studies or smaller prospective cohort studies.<sup>8-11,14-17</sup> Recently two

large prospective, randomized controlled trials (RCT) have been published lending further support to the benefit of SI joint fusion in carefully selected patients. Polly et al<sup>20,21</sup> performed an industry-sponsored trial of minimally invasive SI fusion compared to best medical management. A total of 148 patients were randomized (102 to SI fusion, 46 non-surgical). The primary endpoint was pain as measured by VAS, with secondary endpoints including disability on ODI, health-related quality of life on the EuroQoL-5D (EQ5D) and Short Form 36 (SF 36). At 24-month follow-up, VAS improved from 82.3 to 26.7 in the surgical group, compared to 82.2 to 70.3 in the non-surgical group. Similar disparity was noted on ODI, EQ5D, and SF-36. At the 6-month time point crossover was allowed, and 39/44 patients in the non-surgical group elected for surgery and enjoyed similar benefit as those originally randomized to surgery. Overall complication rates were not significantly different between groups. Dengler et al<sup>8</sup> performed a prospective randomized trial, again industry sponsored, that randomized 103 patients to minimally invasive fusion (n=52) or conservative therapy (n=51). The primary endpoint was back pain on the VAS scale, with secondary endpoints including leg pain VAS, ODI, EQ-5D, and SI joint function via straight leg raise. At 12-month follow-up there was significant benefit of surgery compared to conservative management across all of these measures. Again, crossover was allowed at 6 months. Crossover rates were high, and benefits were similar to those originally randomized to surgery. The authors documented 6 procedure-related complications, of which two required revision surgery.

The focus of this study was complication avoidance and safety. This has been explored by previous authors, but to our knowledge no data is available comparing fluoroscopic versus CT -based techniques. Schoell et al<sup>18</sup> performed the largest evaluation of safety for SI fusion, reporting complication rates in a minimally-invasive SI joint fusion patient population. They used CPT and ICD-9 codes to identify primary (non-revision) minimally invasive SI fusion procedures in a large nationwide insurance database. They





**Figure 7. Post-Operative Imaging**

Postoperative AP and lateral films showing final implant placement

**Table 1. Baseline Characteristics**

Age	50.4
M:F	49:21:00
BMI	30.2
Diabetes	9
Scoliosis	13
Osteoporosis	5
Prior Smoker	29
Current Smoker	5
Revision	5
Prior Lumbar Surgery	37
Fluoro:Nav	46:24:00
Baseline demographics and co-morbidities for patients undergoing SI fusion.	

**Table 2. Complications for the Entire Cohort**

	Value
Sacral radiculopathy	2
Pseudoarthrosis	2
Other	3
Revision	7
This table demonstrates complication profiles for the entire cohort.	

identified a total of 469 patients and noted an overall complication rate of 13.2% within 90 days, and 16.4% within 6 months. Notable complications at 90 days and 6 months respectively included new lumbar pathology (3.6% and 5.3%), infection (3.6% and 4.1%) "nervous system" complications (4.3% and 6.2%), and chronic pain (2.6% and 4.1%). These rates of complications are somewhat higher than compared to previously published RCT and prospective cohort studies, particularly in regard to infection with has often been quoted around 1% for minimally invasive SI fusion.<sup>8-11,14-17,20,21</sup>

Review of our complication data confirms the safety of the procedure, with an overall complication rate of 10% at mean follow-up of 7.6 months. Of note, we had no cases of infection. There were 3 washouts performed (2 hematoma, one which noted only "thickened subfascial tissue"). Our transition to O-arm image guidance appears to have had a positive impact on the complication profile, although the overall low patient numbers and complication rate has prevented this difference from reaching statistical significance as yet. Of particular interest to this study was our rate of neurologic deficit and symptomatic pseudarthrosis; two cases of each occurred, both in the fluoroscopic group. While rare, when such complications occur, they almost invariably result in revision surgery with possible long-term implications for patient outcome. Proper implant placement is critical to avoiding such complications and should be improved with more precise image guidance. While fluoroscopy is a useful adjunct in this regard, the need for sophisticated understanding of sacro-pelvic anatomy on pelvic inlet, pelvic outlet, lateral, and other views can present a steep learning curve. Revision surgery and transitional anatomy can make the procedure more difficult, even in very experienced hands. Three-dimensional image guidance such as CT with Stealth navigation is helpful in this regard, and the lack of implant misplacement in our cohort of 24 navigated cases, even with a significantly higher proportion of revision cases in this group, is a testament to that. An additional consideration in terms of complications and safety worth mentioning is successful fusion across the joint. Our study is limited in that we do not have routine post-operative References



**Table 3. Baseline Characteristics Between Groups**

	Fluoro (n=46)	CT (n=24)	P-Value
<b>Age</b>	50.6	49.9	*
<b>M:F</b>	17:29	4:20	0.078
<b>BMI</b>	30.5	29.5	*
<b>Diabetes</b>	5	4	*
<b>Scoliosis</b>	9	4	*
<b>Osteoporosis</b>	4	1	*
<b>Prior Smoker</b>	18	11	*
<b>Current Smoker</b>	4	1	*
<b>Revision</b>	1	4	<0.05
<b>Prior Lumbar Surgery</b>	24	13	*

This table demonstrates baseline characteristics and comorbidities between the two groups. \* denotes a p-value > 0.1.

**Table 4. Baseline Characteristics Between Groups**

	Fluoro (n=46)	CT (n=24)	P-Value
<b>Sacral radiculopathy</b>	2	0	*
<b>Pseudoarthrosis</b>	2	0	*
<b>Other</b>	1	2	*
<b>Revision</b>	5	2	*

This table demonstrates complication profiles for both groups. \* denotes a p-value > 0.1.

CT scans to evaluate bony bridging across the SI joint. Previous studies have quoted fusion rates at 1-2 years postoperative in the range of 80-97%.<sup>15,17,19</sup> Two of our patients had documented symptomatic pseudarthrosis requiring revision, both in the fluoroscopy group. However, overall statements regarding solid fusion across the SI joint are difficult to generate with our data given the lack of protocolized follow-up CT imaging.

This study has limitations. Most notable is the retrospective nature of the analysis, and relatively low patient numbers. Furthermore, the duration of follow-up in this cohort is short, and longer-term follow-up would be helpful. Fusion across the SI joint was difficult to assess, and a standardized protocol for post-operative CT imaging to formally evaluate this would be helpful to get a better understanding of pseudarthrosis rates.

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# Spinal Cord Injury: Current and Novel Treatment Strategies

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## INTRODUCTION

The care and treatment of spinal cord injury (SCI) patients has significantly evolved over the last several decades. There has been great interest and promising research conducted over this period resulting in advancement of our understanding of the pathophysiology of SCI on both a biochemical and biomolecular level. Concurrently, there has also been rapid clinical advancements in treating spinal fractures with improvement in the understanding of the biomechanics of injuries, as well as improvements in spinal fixation techniques and devices. In addition, there have been great strides made in the collaborative care and treatment efforts of SCI patients particularly in the fields of radiology, rehabilitation, trauma, and intensive care.

The developments in SCI treatment have led to a decrease in the overall incidence of traumatic injuries, particularly in the younger populations. This is mainly a result of preventative measures and education by the various foundations who focus on the treatment of SCI patients such as CSRS, ASIA, AAOS, CNS, and AANS. In addition, there has been a greater emphasis in society on limiting catastrophic injuries such as through the use of: airbag immobilization in motor vehicles, helmets, and the overall reduction of high-risk activities.

To provide some background information on the pathophysiology of a traumatic SCI, it is believed that SCI is multifaceted, with the initial force or compression of the cord resulting in the primary injury. This is then followed by an inflammatory or biochemical response that results in further injury to the cord over the subsequent days to weeks. This is referred to as the secondary injury, and it is this stage of injury that has been the target of intense research. Currently, there exists multiple novel strategies in dealing with this secondary injury component including surgical techniques, medical management, pharmacology, and cell-based therapies which will be discussed below.

## SURGICAL TECHNIQUES

Over the last century, it has been established that early decompression of the spinal cord results in improved neurologic outcomes. However, not until the publication of the STASCIS study (PLoSOne. 2013 Aug 23;8(8):e72659) has clinical data significantly demonstrated that early decompression does, indeed, improve neurological outcome. This study, in which Jefferson Health was the highest enrolled center, showed that surgical decompression and stabilization in less than 24 hours gave the patient the greatest chance of improving by up to two neurologic grades in the ASIA scale.

Another area of exciting research has been the use of a biocompatible scaffold polymers for acute spinal cord injury, which is also an option for patients at Jefferson Health. This scaffold is surgically inserted into the spinal cord at the site of injury and will break down over several weeks. It is postulated that this polymer modulates the healing environment in acute injury and provides the structural support in both acute and chronic injury necessary to promote a local environment supportive of cell survival and growth within the spinal cord. The INSPIRE trial, a study from InVivo therapeutics (<http://www.invivotherapeutics.com>) examined the potential benefit of this Neuro-Spinal Scaffold (TM) for safety and neurologic recovery in patients with complete



**Figure 1.**

Sagittal T2-weighted MRI demonstrating post spinal cord injury with increased signal and edema within the cervical cord (arrow) along with superimposed cervical stenosis

thoracic (T2-T12) spinal cord injury. This study is currently being analyzed and there appears to be a neurologic benefit with use of this polymer scaffold. Larger and more comprehensive studies will likely take place following final analysis of the data from this trial.

## MEDICAL MANAGEMENT

The medical intensive care treatment of the patients after their traumatic SCI is also extremely important in overall recovery and prognosis. It has been determined throughout the last several decades that increased blood flow to the spinal cord by maintaining patients with an elevated mean arterial pressure significantly improves neurologic recovery. This is akin to elevating the blood pressure in an acute stroke patient so as to perfuse the brain penumbra that has not yet reached



**Figure 2.**

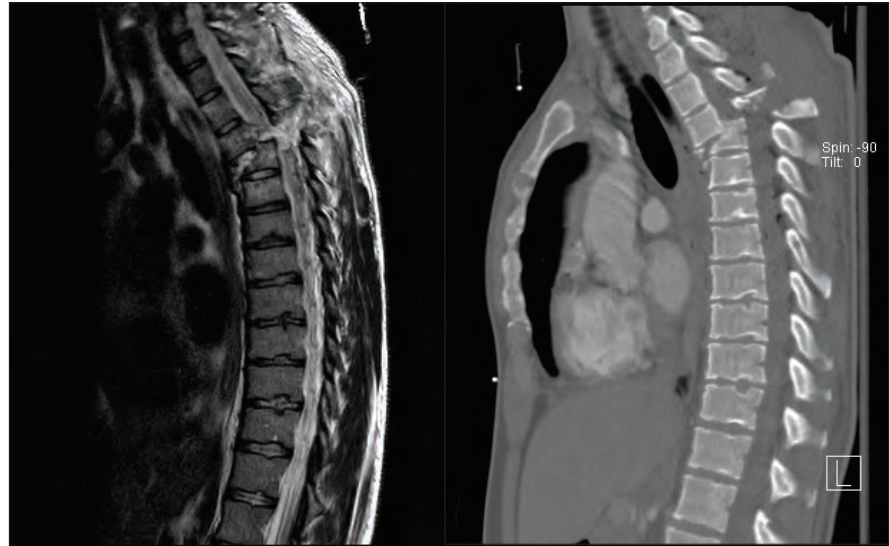
Intraoperative lateral radiograph demonstrating post-surgical instrumented posterior cervical fusion hardware

terminal ischemia. In addition, there is interest in the use of hypothermia to decrease the metabolic demands of the spinal cord during the acute phase of injury to help aid in recovery. Jefferson is currently involved in this study through a grant from the Department of Defense.

## PHARMACOLOGY

The largest international SCI pharmacological multicentered prospective randomized controlled study is presently being run through the AO Foundation. Jefferson is currently the largest clinical enrolling site in North America. This study is investigating the drug, Riluzole, which is approved for patients with ALS, and its effect on reducing excitatory apoptosis (cell-initiated death) after an injury to the spinal cord. This is a continuation of a phase 1 study, also done at Jefferson, which showed safety of the medication.

Unfortunately, not all promising initial studies are confirmed during their phase 3 trials. Recently, Jefferson was involved with the Vertex SCI trial which examined a medication to prevent cell apoptosis

**Figure 3.**

(Left) Sagittal T2-weighted MRI and (Right) CT scan demonstrating a thoracic flexion-distraction injury (fracture dislocation) causing severe spinal cord compression

by blocking the rho activation system. In the initial phase 1 study, which compared the medication to case controls, not only was the medication safe, but it also showed to be efficacy. Unfortunately, when the medication was compared to placebo there was no significant improvement, so the trial was ultimately halted. However, the study did result in greater interest in the investigation of drugs to treat and modulate injuries to the spinal cord.

## CELL-BASED THERAPIES

There is a good deal of excitement about the possibility of cell mediated interventions being used to improve neurologic outcomes after SCI. We are very fortunate at Jefferson to have been asked to participate in many studies investigating this topic and strategy. The first stem cell spinal cord injury trials were performed by Geron Corporation, although, they were eventually halted and sold to a secondary company that became known as Asterias (<https://asteriasbiotherapeutics.com>). Asterias has been a proponent of intraparenchymal spinal cord injection of stem cells. Unlike some other cell-based strategies, these do not target the neurons directly but rather the

oligodendrocytes, which function to provide support and myelin production in the central nervous system.

In another trial, named the StemCell Inc trial, HuCNS stem cells were implanted through direct spinal cord parenchymal injections within one year of the injury. Despite showing promising improvements in neurologic recovery, the study was unfortunately halted due to financial issues.

Currently, there is an active trial investigating the use of Schwann cell transplants being performed at the University of Miami. This study uses Schwann cells harvested from the patient and transfers them directly into spinal cord injury site. The results of the phase 1 portion of this trial were published in 2017 and showed the safety of this treatment, noting that there were no adverse events or serious adverse events related to the cell therapy.

It is important to realize, however, that that with any new treatment, there can be significant complications. Particularly related to cell-based therapies, such as implantation of stem cells, there is the possibility for inducing aberrant growth of non-spinal cord tissue which has potential to harm the surrounding neural structures.

## CONCLUSION

Although the overall incidence of spinal cord injury is decreasing in our population, it is still a major public health concern. The costs associated with treating and caring for patients with spinal cord injuries is quite significant. Currently, there is no "cure" that exists which allows the spinal cord to regenerate and heal completely after a traumatic injury, making many of these injuries devastating to the patients and their families. However, with advancements in surgical, medical, and pharmacological research coming to fruition at a rapid pace, the outlook on evolving the care of these patients and their injuries is promising.

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# Multiple Contiguous-Level Cervical Disc Arthroplasties: Unique Considerations

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## ABSTRACT

Arthroplasty is an established treatment for single and multiple level cervical disc disease. Multiple contiguous arthroplasties introduce unique changes in spinal kinematics that warrant study independent of single-level surgery. The literature regarding the biomechanics, indications, outcomes and complications specific to multiple level arthroplasties was reviewed. Appropriate application of this technology has been shown to be a safe and potentially advantageous alternative to arthrodesis.

## INTRODUCTION

Cervical disc arthroplasty (CDA) is an alternative to anterior cervical discectomy and fusion (ACDF) for the treatment of cervical disc disease. Developed with the intention of preserving or restoring motion of a degenerated disc, CDA has been proposed to reduce rates of adjacent segment degeneration and disease.<sup>1-4</sup>

A single-level ACDF reduces the cervical range of motion approximately 7 degrees, while CDA preserves or may even increase motion at that segment.<sup>5-10</sup> The benefit of replicating physiologic motion to prevent adjacent segment disease has been the subject of debate, with several current meta-analyses advocating the use of CDA over ACDF for single level disease for this reason.<sup>11-13</sup> Evidence includes a randomized control trial reporting a significant decrease in the rate of subsequent surgery at 7 years follow up for single level CDA compared to ACDF.<sup>14</sup>

The generalizability of these data to multilevel disease is unclear. Inclusion criteria for many randomized controlled trials excluded multilevel treatments or, if multilevel CDA was included, those data were often not analyzed independently of single-level results. The purpose of this review is to examine the unique considerations and literature of multilevel CDA.

## BIOMECHANICS

Adjacent segment disease (ASD), defined by Hilibrand as new and symptomatic degenerative changes after fusion,<sup>15</sup> has been attributed to compensatory biomechanical stresses at levels above and below a fusion,<sup>16</sup> which approximately 25% of patients who undergo ACDF will experience within 10 years from surgery.<sup>17</sup> Most biomechanical studies on multilevel CDA were designed to investigate this phenomenon.

The degree of additional stress at adjacent levels is commonly quantified by measurements of intradiscal pressure and mobility.<sup>16,18</sup> In multilevel ACDF, adjacent discal pressures have been shown to increase by 3-6.7 fold, while CDA either maintains or even decreases adjacent level pressures.<sup>19-22</sup>

In a cadaveric load-control study, Phillips found that a single CDA at C5/6 increased flexion-extension of that motion segment by 4 degrees but did not significantly change rotation or lateral bending. The adjacent segments' motions were unchanged. Upon implanting a second CDA at C6/7, lateral bending of the superior adjacent level (C4/5) increased. A single CDA at C6/7 did not reproduce the increase in flexion-extension

or adjacent level mobility. This suggests that multilevel arthroplasty introduces unique spinal kinematics and that the effects may be level-dependent. In vivo, multilevel arthroplasty has demonstrated no significant difference from pre-operative motion at the operated levels.<sup>23, 24</sup>

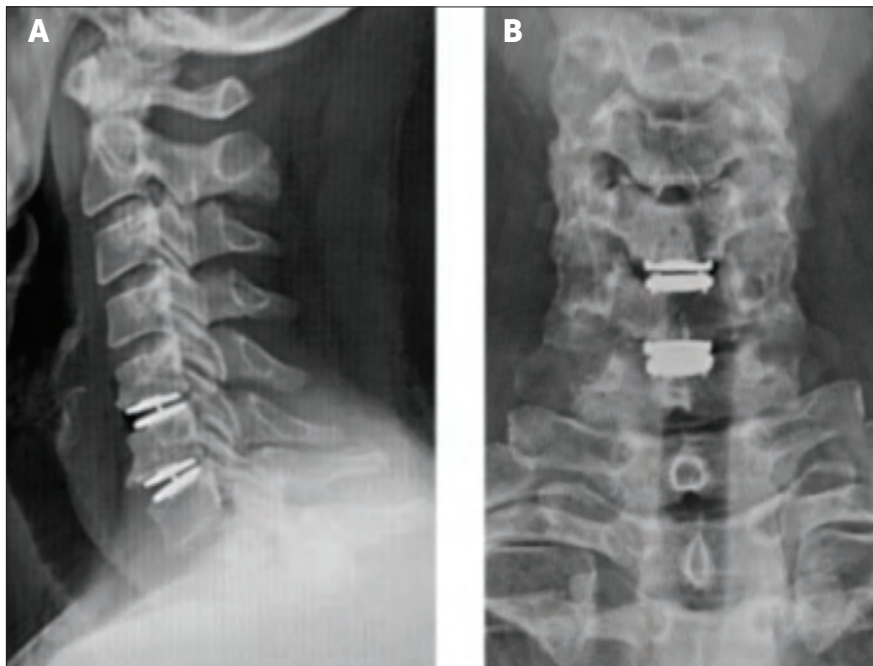
Authors have proposed that biomechanical stresses are additive with consecutive levels of arthrodesis due to increased constraint and suggest that arthroplasty may help defray the mechanical disadvantages of a multilevel fusion;<sup>16</sup> however, a recent meta-analysis reported that the highest prevalence of ASD was in single level ACDF, significantly more than in multilevel fusion.<sup>25</sup> This contradicts finite element analyses wherein longer segment anterior fusions have been shown to increase adjacent level intradiscal stresses.<sup>26</sup> While the authors of the meta-analysis suggest that multilevel procedures might have already addressed the most at-risk levels, the etiologies of ASD and how the biomechanics of arthroplasty affect them have not been fully reconciled with clinical data.

## INDICATIONS/PATIENT SELECTION

Multiple devices have FDA approval for single and multilevel cervical disc arthroplasty. Randomized controlled trials on multilevel arthroplasty selected for patients with degenerative disc disease causing radiculopathy or myelopathy and excluded patients with pathology outside of C3-7.<sup>23, 24, 27</sup> Expanded indications have been reported, including acute traumatic disc herniations<sup>28</sup> and use in upper thoracic levels.<sup>29</sup>

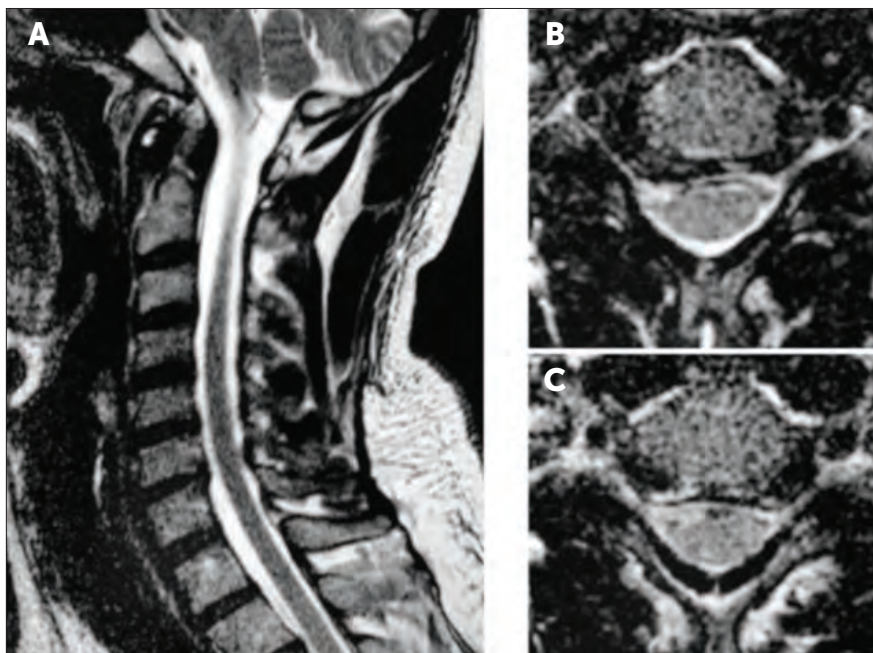
Contraindications include less than three millimeters of available disc space to avoid excessive loading of the posterior elements by overdistracting anteriorly.<sup>30</sup> Kyphotic deformity of greater than 15 degrees may indicate concomitant posterior element pathology that could be exacerbated by increasing motion at that segment. Other





**Figure 1.**

Post-operative lateral (A) and anterior/posterior (B) radiographs showing stable cervical alignment and adequate positioning of consecutive cervical arthroplasties.



**Figure 2.**

Sagittal T2 MRI showing multi-level spondylotic changes without disc space collapse or kyphotic deformity (A). Axial MRI through the C5/6 (B) and C6/7 (C) disc spaces demonstrating broad based disc bulging that results in right foraminal stenosis at C5/6 and bilateral foraminal stenosis at C6/7.

contraindications include active infection, malignancy, and metabolic or inflammatory spine diseases. Osteoporosis may increase the risk for implant migration.<sup>31</sup>

### CASE EXAMPLE

A 45-year-old Caucasian male presented with eight months of neck pain with radiation down his right arm to his right thumb, index and middle finger. There was no inciting event or trauma. He was neurologically intact other than a right Spurling's sign. There was no clinical evidence of myelopathy.

On review of his cervical MRI, he had advanced spondylosis with right greater than left neural foraminal narrowing at C5-6. Spondylosis with bilateral foraminal narrowing was also noted at C6-7. (Figure 1)

He was treated with several weeks of physical therapy, cervical traction, and three epidural steroid injections without lasting improvement in his symptoms. Given his failure of conservative treatment, surgical decompression was recommended. The options of arthrodesis and arthroplasty were offered to the patient, who elected to undergo C5/6 and C6/7 arthroplasties.

Post-operatively, he recovered very well with complete resolution of his preoperative neck and arm symptoms. Radiographs confirmed adequate cervical alignment and device placement. (Figure 2) By 8 weeks post-op, he had returned to work without restrictions as an electrician.

### OUTCOMES

Initial trials excluded multiple level arthroplasties or combined them with single level treatments in their analyses. In 2007, Pimenta reported that 2 or 3 level CDA experienced significantly greater improvements in patient outcomes — Neck Disability Index (NDI) and Visual Analogue Score (VAS) — than single level arthroplasty at 3 years from surgery.<sup>32</sup> Subsequent studies addressed multilevel disease independently.

One class-one randomized, controlled trial has been published comparing patients who underwent single and multiple-level CDA. Clinical outcome scores were not significantly different between the two arms: both groups had similar NDI, VAS, Short Form 12 (SF-12 MCS/

PCS), and satisfaction scores. The rate of complications, subsequent surgeries, and heterotopic ossification were also not significantly different.<sup>27</sup>

In a systematic review, Joaquim identified two class-one randomized, controlled trials that compared contiguous multi-level arthroplasties against arthrodesis.<sup>33</sup> In a 330 patient study, Davis found positive patient-reported outcomes with CDA: a significant decrease in NDI and SF-12 PCS that was maintained for 4 years of follow up and improved patient satisfaction scores. Neck pain and arm pain VAS scores were not significantly different, though neck pain scores were transiently lower with arthroplasty. ACDF had a higher rate of subsequent surgery on the index level, 4.0 vs 15.2%, predominantly for symptomatic pseudoarthrosis.<sup>23</sup>

Radcliff conducted a second randomized, controlled trial in 325 patients. Similarly, NDI and SF-12 PCS were significantly lower with arthroplasty at all post-operative time points through 5 years of follow up. There was no difference in VAS scores for arm or neck pain. Again, a lower probability of subsequent surgery on index or adjacent levels was identified with arthroplasty. Range of motion was not significantly changed from pre-operative values by CDA. Rates of adjacent segment degeneration were assessed by the Kellgren-Lawrence scale: CDA had significantly less degeneration (50.7%) than arthrodesis (90.5%). These two studies suggest that ASD is not prevented by CDA, but patients with multilevel arthroplasty may develop radiographic changes and become symptomatic at a slower rate than those with multilevel ACDF for at least five years.<sup>24</sup>

## COMPLICATIONS

Anterior cervical arthroplasty and arthrodesis share a similar complication profile due to their common surgical approach. Xu conducted a systematic review of arthroplasty trials and reported dysphagia/dysphonia at rates of 1.3 to 27.2%, vascular injury including hematoma at 1.1 to 2.4%, dural injury at 0.0 to 7.1%, and wound infection at 1.2 to 22.5%.

Dysphagia is a well-described approach-related complication to anterior cervical surgery. In a cadaver model, placing

three-level anterior cervical plate fixation was found to cause five-fold higher intraesophageal pressures than what is required to place equivalent level arthroplasties due to increased retraction.<sup>34</sup> A prospective, randomized trial showed a decrease in dysphagia on the Bazaz-Yoo scale with zero-profile arthroplasty compared to arthrodesis with plate fixation.<sup>35</sup> The etiology of the dysphagia may be attributable to the increased dissection and retraction required to introduce the plate or from the presence of a foreign body within the retropharyngeal space. Consecutive interbody fixation devices without an anterior plate may obviate this benefit of arthroplasty.

Heterotopic ossification (HO) is a common complication of prosthetic joints, wherein new bony growth may inhibit movement of the prosthesis or cause compression of the neural elements. The McAfee classification divides HO of CDA into grades I/II, which comprise radiographic findings of bony growth and grades III/IV, which have clinical manifestations of limited movement.<sup>36</sup> The pooled prevalence of HO in single and multilevel CDA across multiple studies has been reported as 58.2% at 2 years, with a 16.7% rate of grade III or above.<sup>37</sup> Wu reported higher rates of HO in two-level arthroplasty (75.0%) compared to single level (40.5%), with 14.3% of arthroplasties losing their mobility after multilevel surgery.<sup>38</sup> In prospective trials of two-level arthroplasty, rates of clinically significant HO were 16.6%<sup>23</sup> and 29.7%.<sup>24</sup> Arthroplasties at C3/4 may also have higher levels of HO due to decreased physiologic motion at that level compared to the other subaxial segments.<sup>39</sup>

Implant migration is a rare complication of CDA that may produce iatrogenic injury. The largest report of symptomatic migrations comprised 5 patients who underwent single or multiple-level CDA in a single institution, with an overall rate of 0.4% of all cervical arthroplasties performed.<sup>40</sup> In four cases, the device was explanted and revised with ACDF and in one patient, the implant was simply removed. Zhai reported a case of migration in a two-level arthroplasty that presented with dysphagia and was revised with a corpectomy of the middle vertebra and multilevel fusion.<sup>41</sup> Of the

large prospective trials on multiple level arthroplasties, only one case of migration was reported in a study of 255 patients with 4 years of follow-up.<sup>23</sup>

Sagittal fracture while preparing superior and inferior keels in a single vertebra is a unique complication of subsequent level arthroplasty. The few case reports available suggest that this is a rare phenomenon and may be managed with a rigid cervical collar, though prolonged post-operative pain may occur.<sup>42</sup>

## CONCLUSION

Multilevel CDA has demonstrated unique biomechanics and complication profiles compared to arthrodesis and single-level arthroplasty. Multilevel arthroplasty offers advantages in patient-reported outcome measures to arthrodesis in appropriately selected patients.

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# Minimal Access Expandable Mesh Device for Transforaminal Lumbar Interbody Fusion: A Case Series

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## ABSTRACT

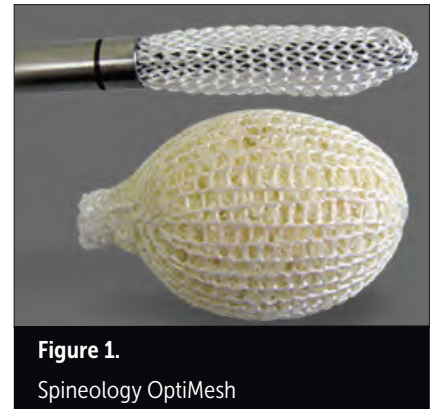
Bone-sparing techniques for transforaminal lumbar interbody fusion (TLIF) are promoted to help maintain spinal stability and to minimize operative time. We present a series of seven patients who underwent TLIF with use of an interbody expandable mesh device and with supplemental instrumentation. This device is deployed and filled with bone through a small cannula. All patients experienced pain relief and suffered no complications. Our results support the data from other centers which have performed similar procedures with this device.

**Keywords:** *transforaminal lumbar interbody fusion, OptiMesh, deployable mesh, minimal access*

## INTRODUCTION

Lumbar interbody devices can be difficult to insert from a posterior approach due to their sizes and shapes, especially when the disc space is significantly collapsed (Figure 5). In addition, stabilizing posterior elements are removed in order to create a clear corridor to the disc space. A less invasive approach to the disc space involves the placement of a collapsed, expandable mesh pouch (OptiMesh by Spineology, St. Paul, MN). The pouch is gradually filled with increasing amounts of allograft bone chips through the small portal. (Figure 1) The mesh itself is made out of polyethylene terephthalate, a non-absorbable and pliable material commonly used in vascular grafts. We describe a series of patients who underwent this procedure with supplemental instrumentation.

Spineology OptiMesh graft containment system has been approved for the treatment of stable vertebral body defects. The device has also been used in the disc space for interbody fusion.<sup>2,5,6,7,8,9</sup> The OptiMesh portal, despite its low profile, allows for an extensive discectomy and with preparation of the endplates, especially when the



**Figure 1.**  
Spineology OptiMesh

cannulas are introduced bilaterally. The bone chips are packed into the mesh until good filling of the disc space is noted on fluoroscopic imaging.

## CASE PRESENTATIONS

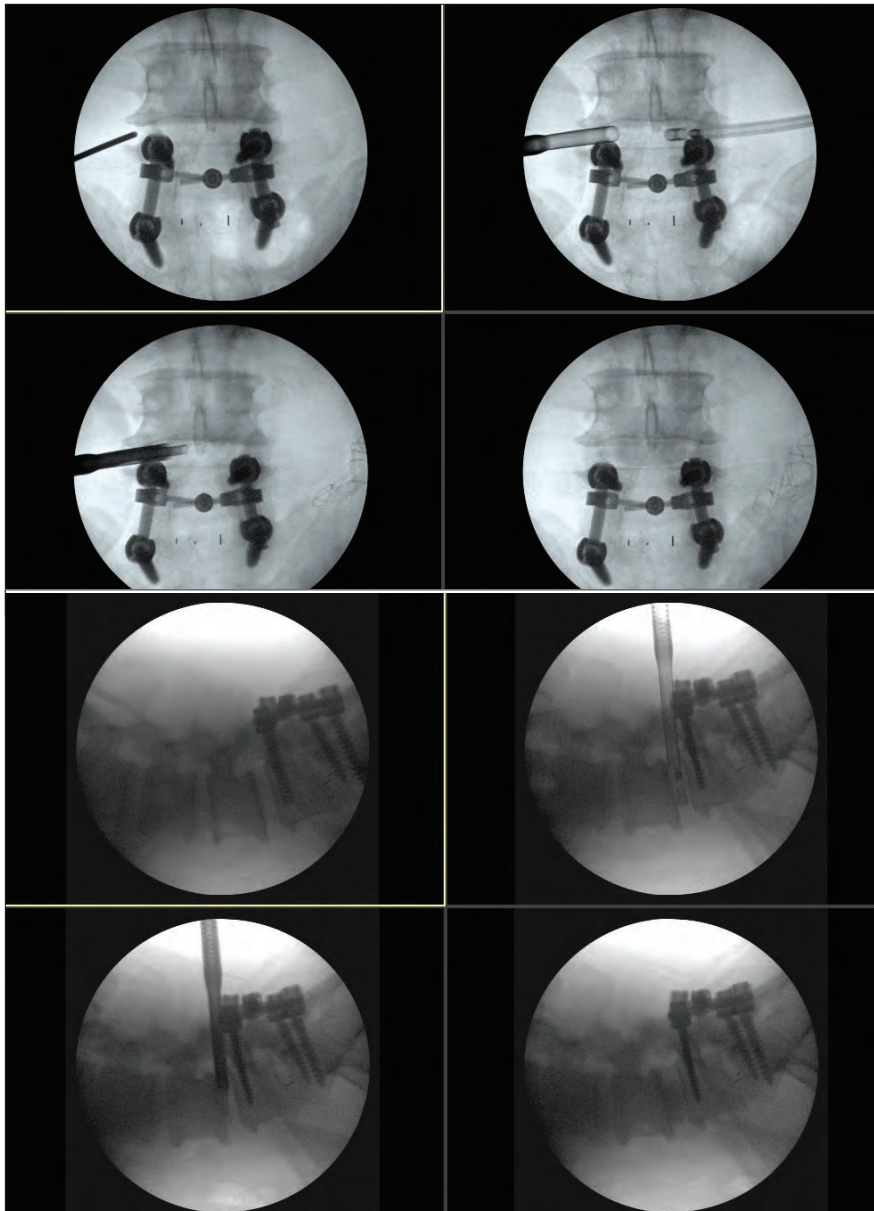
From August 2016 through January 2019, seven patients underwent lumbar transforaminal interbody fusions by the senior author using the mesh containment device with supplemental instrumentation, either interspinous clamps (Patients 2, 3 and 5) or bilateral pedicle screws/rods (Patients 1, 4, 6 and 7). Five patients had the interbody device placed with some minimal bony removal. Two patients had the mesh inserted via a purely percutaneous, bone-sparing approach via Kambin's triangle (Figures 2 and 3).<sup>4</sup> We utilized neuromonitoring for the percutaneous approaches.

Patient 1 was a 66-year-old female who presented with five years of low back pain and one year of right lower extremity pain. An MRI revealed retrolisthesis of L2 on L3, which had progressed slightly over seven years. There were stable findings of anterolisthesis at L4-5 and at L5-S1.

Patient 2 was a 49-year-old male with many years of back pain with one year of paresthesias and numbness in the bilateral lower extremities. An MRI showed

**Table 1.**

Patient Info		TLIF level, type	Follow up	Outcome Compared to Pre-op
1.	66 yo F	L2-3 open	29 months	90% overall pain relief
2.	49 yo M	L3-4 open	24 months	95% overall pain relief
3.	73 yo F	L1-2 open	18 months	90-95% overall pain relief
4.	66 yo M	L4-5 open	17 months	80-85% overall pain relief
5.	42 yo M	L5-S1 open	5 months	50% overall pain relief
6.	57 yo F	L4-5 percutaneous	3 months	95% overall pain relief
7.	46 yo M	L4-5 percutaneous	4 weeks	Preoperative lower extremity pain resolved.



**Figure 2 and 3.**

Intraoperative fluoroscopic images on patient number 7 show the percutaneous instrumentation being placed into the bilateral disc spaces via Kambin's triangle. The disc is removed and the endplates prepared. The OptiMesh is then introduced and filled gradually with granular bone graft.

a moderate left-sided L3-4 disc/osteophyte complex with severe degenerative collapse and Modic changes. Similar findings, to a lesser degree, were seen at L5-S1.

Patient 3 was a 73-year-old female who had undergone an emergent laminectomy at an outside institution for sudden-onset bilateral lower extremity weakness three months earlier. She

regained her strength and sensation but her preoperative, chronic low back pain and left lower extremity pain had worsened after the procedure. An MRI revealed very severe degenerative disc disease at L1-2 with Modic changes. Also noted were postoperative changes at L4 to S1.

Patient 4 was a 66-year-old male with chronic lower back pain which had worsened over six months. He also complained of bilateral lower extremity weakness when going up or down stairs. Physical exam revealed no objective weakness. An MRI revealed a grade I spondylolisthesis at L4-5 with Modic changes and moderate central stenosis.

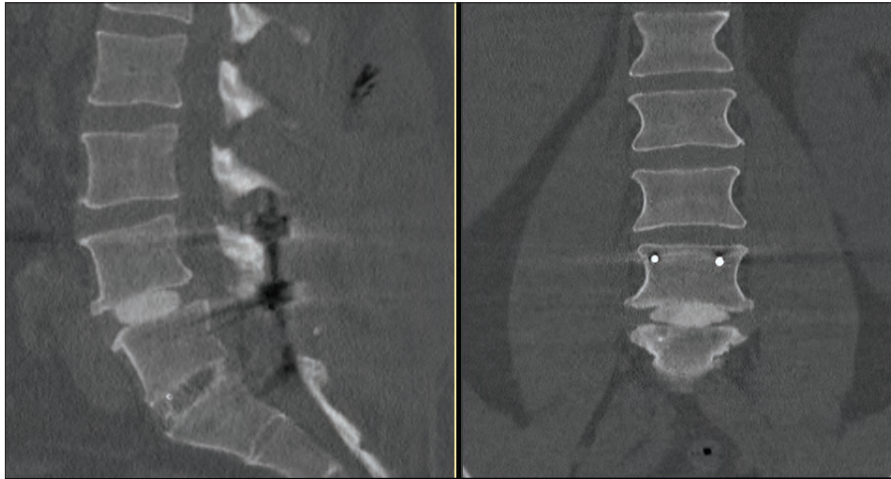
Patient 5 was a 42-year-old male with a history of end-stage renal disease and had presented to the hospital with severe, intractable low back pain radiating into the left lower extremity. An MRI showed evidence of a discitis at L5-S1 and cultures from a needle biopsy by interventional radiology grew *Staphylococcus epidermidis*. Despite initial antibiotic treatment and narcotic medications, he remained in severe intractable pain. He did have a history of chronic low back pain.

Patient 6 was a 57-year-old female who had undergone a right hemilaminectomy and bilateral sublamina decompression at L4-5. She continued to have bilateral lower extremity pain two months after surgery, and dynamic radiographs had demonstrated abnormal motion at L4-5.

Patient 7 was a 46-year-old male who had undergone an L5-S1 instrumented interbody fusion nine years ago. He had developed progressive low back and bilateral lower extremity pain, left greater than right. An MRI showed some mild degenerative disc disease at L4-5 but dynamic radiographs revealed instability at this level with a solid fusion at L5-S1. This particular patient required revision of his existing hardware in order to couple it to the new pedicle screws which were inserted into L4. However, the interbody mesh was delivered via an entirely percutaneous approach.

All patients experienced pain relief compared to preoperatively with no complications (nerve root injuries, durotomies, infections, or hardware failures). All





**Figure 4.**

Postoperative CT on patient number 7 show the interbody graft in good position at L4-5. The previous L5-S1 interbody fusion is also seen.



**Figure 5.**

Preoperative CT on patient number 4. Arrow points to narrow corridor for insertion of a TLIF cage.

patients, except for number 5, had failed conservative management including physical therapy and/or epidural steroid injections. Follow up ranged from 2 weeks to 28 months.

## DISCUSSION AND CONCLUSIONS

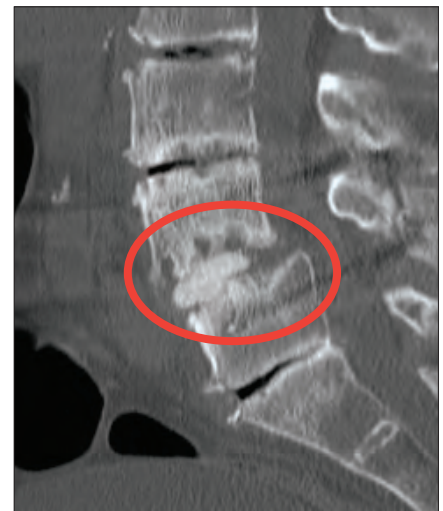
In order to place a typical interbody cage via a TLIF, the unilateral facet joint is generally removed in its entirety. Standard TLIF cages measure from 7 mm to 16 mm in height with 10 to 11 mm width. The Spineology OptiMesh cannula measures 7 mm in diameter; all the bone chips that fill the mesh are delivered through this size portal. The mesh allows for much less bony removal and also the option of a purely percutaneous approach requiring no bony removal via a trajectory through Kammin's triangle.

The rigidity and contour of most interbody devices often causes undesired trauma to the vertebral endplates during insertion. Weakening of the endplates could contribute to settling of bone over the interbody construct. The mesh appears to conform well to a patient's unique endplate shape and integrity (Figure 7). Moreover, the density of the inserted bone chips should more closely match that of a patient's own bone than polyetheretherketone (PEEK) or metal, theoretically reducing the risk of subsidence.



**Figure 6.**

Postoperative CT on patient number 4. The placement of the interbody graft is in the anterior disc space and the lordosis is maintained. Such placement of a graft would be difficult to achieve from a posterior approach with a traditional interbody device due to the narrow entry point through the dorsal disc space. Lordotic cages have a leading edge which are larger than the tail end.



**Figure 7.**

Postoperative CT scan on patient number 6 shows the mottled appearance of the endplates with the OptiMesh device within the disc space. The unhealthy endplates make placement of a very rigid device undesirable.

Various expandable interbody cages are available, but most devices expand only in the sagittal plane, not in the axial and coronal ones. The OptiMesh expands in all planes and, as mentioned, contours to

the shape of the actual disc space. The PEEK or metal used in most interbody devices also occupy significant space, whereas the mesh allows for more surface area contact for bone to remodel



and potentially increase the likelihood of a robust bony fusion.

Based on our limited experience, the mesh device is a safe, effective option for TLIF. Its main advantages appear to be decreased anatomical disruption during delivery and deployment, the ability to expand in all planes with conformity to the endplates, and greater surface area contact of bone for remodeling and fusion. A study involving a larger number of patients and further long-term follow up is warranted.

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# Spinal Cord Stimulation in the 21st Century—Reviewing Innovation in Neuromodulation

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## INTRODUCTION

Low back pain (LBP) is a pervasive problem impacting health systems across the world. In the United States, chronic LBP impacts up to 40% of Americans and results in excessive financial strain on the healthcare budget, estimated at up to \$100 billion annually.<sup>1</sup> Furthermore, treatment results are often disappointing, with the traditional pathway of conservative measures, narcotic pain medication, and surgical decompression and/or fusion leading to both patient and provider frustration, complications, and diminished patient productivity and quality of life. This has naturally led to questions from policy-makers regarding the utility of healthcare dollars spent on back pain. In this milieu, a variety of neuromodulation techniques have found a niche in the management of this patient population, with indications commonly quoted including failed back surgery syndrome (FBSS), chronic neuropathic pain, and complex regional pain syndrome (CRPS), among others.<sup>1,2</sup> From its inception on the basis of Melzak and Wall's gate theory<sup>3</sup>, to its first human trial in the 1960s,<sup>4</sup> and to the modern era, spinal cord stimulation has undergone a series of innovations that have expanded indications and improved patient outcomes. The goal of this study is to summarize the most important clinical trials involving both traditional SCS and newer stimulation paradigms to provide an overview of the current state of affairs of this rapidly-growing field.

## METHODS

We performed a PubMed literature search utilizing the following terms: SCS, spinal cord stimulation, neuromodulation, high frequency stimulation, paresthesia free, HF10, failed back surgery syndrome, and chronic pain. Only English language articles were reviewed. All prospective, randomized controlled trials pertaining to the use of neuromodulation in the treatment of chronic back and limb pain were included. The data extraction was performed by three reviewers (JT, JH, CH), and reviewed by the senior author (CW). The selected studies were analyzed, and relevant results were summarized as follows.

## RESULTS

### Traditional, Low Frequency, Tonic SCS

Several landmark trials paved the way for the widespread use of spinal cord stimulation in the treatment of chronic back and limb pain. These early studies utilized low frequency stimulation generally in the 40-100 Hz range delivered in a tonic manner, producing paresthesias that overlap the areas where the patient experiences pain. North et al<sup>5</sup> randomized 51 FBSS patients with chronic lower limb pain with or without back pain to initial treatment with a low frequency stimulator or re-operation. The primary endpoint was "success", defined as > 50% reported pain relief and patient satisfaction with treatment at 2-years post-operatively or at last follow-up. Secondary end points included treatment crossover, success at last follow-up, and improvement in medication use, daily activities, and neurologic status. At mean three-year follow-up, "success" was achieved in a significantly higher proportion of patients

randomized to SCS (47%) compared to those randomized to reoperation.<sup>5,6</sup> These findings remained statistically significant even after worst-case analysis which assumed patients unavailable for long-term follow-up in the SCS group were all treatment failures. Further, a significantly higher proportion of patients in the reoperation arm crossed over to SCS (54%) compared to only 21% of SCS patients who elected to undergo reoperation. While patient reported functional capacity didn't reach a significant difference, SCS patients did require significantly fewer opiate equivalents for pain control. Kumar et al<sup>7,8</sup> followed this up with the PROCESS study which randomized 100 FBSS patients with limb>back pain to SCS with medical management (n=52) or medical management alone (n=48). The primary end point of the study was defined as > 50% relief of leg pain, with secondary end points including quality of life, functional capacity as measured by the Oswestry Disability Index (ODI), patient satisfaction, and changes in pain medication usage. At 6-month follow-up, the primary endpoint was achieved in 48% of SCS patients compared to 9% in the medical management alone group. The SCS group also reported significantly greater quality of life, improvement in ODI, treatment satisfaction, and reduced back pain compared to medical management alone. SCS patients were also more likely to reduce drug intake based on morphine equivalents as well as decrease use of non-drug therapies. Similar improvements were maintained at 12 and 24 month follow-up analyses.<sup>7,8</sup>

### Paresthesia-Free SCS

As clinical experience with traditional, paresthesia-based systems grew, interest began to develop in creating new stimulation protocols that would generate pain relief without the need for paresthesia overlap as a significant number of patients found these sensations to be uncomfortable, particularly when there

is significant postural variation which can make certain daily activities, such as driving, difficult or painful. Furthermore, traditional spinal cord stimulation, while relatively successful at treating appendicular neuropathic symptoms, struggled with relief of more nociceptive axial pain where adequate paresthesia overlap is difficult to achieve. Given how common low back pain is in the general population, a more efficient means for targeting this symptom complex was needed. Buyten et al<sup>9</sup> prospectively enrolled 82 patients with back pain with or without associated leg pain in a trial of high frequency, low amplitude, paresthesia free stimulation using the Nevro device. The outcomes of interest were VAS scores, ODI, sleep disturbances per night, and patient satisfaction. The trial to conversion rate was 88%. VAS back and leg scores improved at 6 months, <sup>8,4</sup> to 2.7 for back and 5.4 to 1.4 for leg pain. ODI improved by 17 points and patients reported 2.4 fewer episodes of sleep disturbance per night. Similar results were obtained with HF10 therapy in another prospective observational study in patients with a primary complaint low back pain, with back pain and leg pain reduced by 61% and 58%, respectively, based on VAS<sup>10</sup>. While promising, these and other observational studies did not provide a control group to compare against. To that end, De Andres et al<sup>11</sup> compared high frequency (10 kHz) stimulation to conventional stimulation, randomizing 55 patients with FBSS with neuropathic back or leg pain. The results suggested no significant difference at one year, with both stimulation profiles showing significant benefit compared to baseline values.<sup>11</sup> On the other hand, North et al,<sup>12</sup> in their pilot study randomizing patients with FBSS who had a previously implanted, paresthesia-based system with inadequate pain relief, noted that pain relief via NRS and disability via ODI were significantly improved with 1 kHz stimulation.<sup>12</sup> Perruchoud and colleagues<sup>13</sup> similarly randomized patients with chronic neuropathic back and leg pain, previously stable on a conventional SCS system, to periods of sham and 5 kHz, subthreshold tonic stimulation. The periods of sham and 5 kHz stimulation were separated by a "washout" period during which the

patients reverted to their traditional, paresthesia-based pattern. The primary outcome was the Patient's Global Impression of Change (PGIC), with secondary outcomes including VAS and the Euroqol questionnaire EQ-5D. At the end of the study, the authors noted no difference between sham and high-frequency stimulation, with what appeared to be a "period effect" in that patients tended to respond more favorably to sham or 5 kHz stimulation based purely on which was initiated first and responded less favorably to whichever pattern was tested second. However, the comparison to baseline values is confusing and again the use of previously stabilized tSCS patients is a variable that must be considered. The most robust data in this field came from Kapural and colleagues who explored the ability of low amplitude, high frequency spinal cord stimulation at 10 kHz to provide durable relief of both axial and appendicular pain in the SENZA trial.<sup>14,15</sup> In this prospective, multicenter, randomized trial, the investigators randomized 198 patients with medically refractory back and leg pain to either high frequency stimulation (HF10) or traditional low frequency, paresthesia-dependent treatment (tSCS). The primary endpoint was >50% reduction on the visual analog scale (VAS), with secondary outcomes including opioid use, functional disability as measured by ODI, and percentage change from baseline back and leg symptoms. A total of 171 patients had positive trials and were ultimately implanted (HF10, n=90; tSCS, n = 81). At the initial 3-month evaluation, 84.5% of HF10 patients achieved the primary endpoint for back pain, compared to only 43.8% of tSCS patients. Similarly, for leg pain HF10 success on the primary endpoint was 83.1% compared to 55.5% for tSCS. These values remained similar at 12-month follow-up evaluation, with remission rates (VAS <2.5) for back and leg pain approaching 67% for HF10, compared to 35-40% for tSCS. At 24-month evaluation, the difference in primary endpoint success was still maintained in favor of HF10 for both back and leg pain (76.5% and 72.9% respectively for HF10, compared to ~50% for tSCS). Secondary outcome analysis also favored HF10, with greater overall percentage reduction of back and leg

pain compared to baseline, higher likelihood of achieving minimal disability on ODI, and higher patient reported treatment satisfaction. Additionally, 11.3% of patients in the tSCS group reported uncomfortable paresthesias, with no patients in the HF10 group reporting any paresthesia-related issues.<sup>14,15</sup>

Despite accumulating clinical evidence regarding the efficacy of high frequency SCS, several questions remained. One such issue is the impact of varying frequencies and other stimulation parameters on treatment effect. One study<sup>16</sup> prospectively randomized a cohort of 24 patients into a blinded crossover study, with each patient experiencing 3 weeks at a time of sham stimulation, and stimulation at 1200 Hz, 3030 Hz, and 5882 Hz. The devices were programmed such that amplitude was maintained slightly below threshold level, unique to each patient and frequency. The primary outcome was the reduction of VAS back pain scores. Baseline VAS was reported at 7.75, with improvement to 4.83, 4.51, 4.57, and 3.22 for the trial groups (sham, 1200 Hz, 3030 Hz, and 5882 Hz, respectively). All comparisons to baseline were significant, but within the treatment groups only 5882 Hz had a significantly greater impact on outcome. The authors argued that while designed as a study on frequency, the impact of pulse width on allowable amplitude without generating paresthesia yielded higher charger-per-second dosing with higher frequency stimulation, which may have played a role in the results. The results also questioned to what degree pain relief afforded by spinal cord stimulation is a result of placebo, as at the end of the study 12.5% of patients preferred the sham stimulation protocol. A similar study also explored the impact of varying degrees of high-frequency stimulation on treatment effect, noting the unclear mechanism of HF10 and the unclear impact of frequency on clinical outcome. In this study, Thomson et al<sup>17</sup> randomized 21 patients with chronic back>leg pain who had passed a trial of 10 kHz stimulation and were implanted with permanent devices. Each patient experienced four weeks of stimulation, in random order, at 10 kHz, as well as 1-, 4-, and 7 kHz. At each frequency, pulse width and amplitude were adjusted to optimize therapy. The impact on the



primary outcome, NRS for back, leg, and overall pain, was similar between groups with all frequency groups showing about 50% reduction in each category. There were no between-group differences. There was significantly less charge delivered in the 1 kHz stimulation than in the other three groups. Interestingly, the calculated charge delivered per second showed a non-linear relationship with frequency, suggesting that frequency modification in isolation may not deliver appropriate symptom relief, highlighting the importance of the interplay between frequency, pulse width, and amplitude.

As interest in paresthesia-free stimulation grows, other investigators are exploring novel stimulation protocols. Burst stimulation, a technique based on short intervals of high-frequency, low amplitude stimulation followed by periods of inactivity, is one such protocol thought to work in at least two mechanisms: 1) more closely mimic neuronal firing in the central nervous system with impacts on higher-order thalamo-cingulate pathways, and 2) provide inhibition of A $\delta$  and c fibers via subthreshold antidromic A $\beta$  activation with resultant activation of inhibitory interneurons. De Ridder et al<sup>18</sup> performed an early trial with this technology, randomizing 15 patients undergoing a trial of spinal cord stimulation to 7 days each of burst, tonic, and sham stimulation. Primary endpoints included VAS for back, limb, and general pain, with secondary endpoints including the pain vigilance and awareness scale (PVAQ), and worst/best pain levels during a given trial week. They noted that burst stimulation did not induce more paresthesias than sham stimulation. The primary outcome measure showed significant improvements in back, limb, and general pain comparing burst stimulation to placebo. Because burst stimulation produced no noticeable paresthesias, this marked the first time in a randomized trial that spinal cord stimulation could be proven better than control/sham treatment, an important landmark in SCS research. Not surprisingly, tSCS showed significant improvement in limb and general pain, but not back pain, compared to placebo. Comparing burst to tSCS, the mean change in back pain favored burst (-3.8 on VAS compared to -2.2), but this did not reach significance. Limb pain between the two protocols was the same (both -3.9 on VAS). General

pain was significantly reduced with burst therapy (-4.5 VAS) compared to tSCS (-2.5). Regarding the PVAQ, tonic and placebo stimulation showed no impact on attention to pain or attention to changes in pain, whereas burst stimulation significantly improved these parameters, suggesting an impact on affective and attentional components of pain. Schu et al<sup>19</sup> compared high frequency stimulation to a burst protocol, randomizing 20 patients with FBSS and a previously implanted, burst-capable system to separate, one week periods of placebo stimulation, 500 Hz tonic stimulation, and burst stimulation (5 pulses at 500 Hz, delivered 40 times per second), with the primary outcome of interest the impact on the numerical rating scale (NRS) for pain intensity. Baseline values were obtained prior to entering the protocol, with the device programmed for standard, paresthesia-based stimulation. While burst stimulation was the only pattern to significantly reduce the NRS score, the magnitude of the treatment effect was modest (5.6 at baseline, 4.7 for burst stimulation), and disability as measured by ODI showed only a non-significant decrease. However, it is worth reiterating that the "control" values in this study were based on patients stabilized on a paresthesia-based system, and thus treatment effects can be expected to be blunted, and the fact that at the end of the trial 80% of the patients preferred the burst protocol is also significant. More recently, Deer et al<sup>20</sup> published results of the SUNBURST trial, which randomized patients with refractory back and leg pain to tSCS or burst stimulation. The trial was conducted in two phases. First patients were randomized to a 12-week period of a given stimulation treatment, and then switched to the other stimulation method for the next 12 weeks. Thereafter, the patients were allowed to choose their preferred stimulation method and were assessed every 6 months for two years. The primary endpoint was change in VAS. A total of 100 patients were randomized, with 45 entering tSCS first followed by burst, and 55 vice versa. At 12- and 24-week analyses, both non-inferiority and superiority of burst stimulation as compared to tSCS were established via the primary endpoint of VAS reduction. Secondary endpoint analyses revealed that 61.6% of patients were paresthesia-free

with burst compared to only 2.7% of tSCS patients. While 78.1% of patients were satisfied overall with both stimulation methods, 70.8% reported preferring burst stimulation with lack of paresthesia being the most common reason cited. This preference was maintained at one-year follow-up with 68.2% of patients continuing to prefer burst therapy. Much like high frequency stimulation, as the clinical efficacy became clear, more questions emerged regarding mechanisms and the impact of various stimulation parameters. One study<sup>21</sup> randomized 15 patients previously implanted with a burst-capable device in the setting of FBSS to one of two stimulation patterns: 1) 5 pulses delivered at 500 Hz with a 1000  $\mu$ sec pulse width, 40 times per second or 2) 5 pulses delivered at 1000 Hz, 1000  $\mu$ sec pulse width, 40 times per second. The amplitude, and thus the total electrical dose delivered remained the same. Clinical outcomes were not significantly different.

## DISCUSSION

Spinal cord stimulation was first put into clinical practice in the 1960s for an attempt at palliation in a patient with terminal cancer pain.<sup>4</sup> The momentum behind its initial development was the ubiquitous Gate Control Theory put forth by Melzack and Wall.<sup>3</sup> While generally accepted that this theory is overly simplistic regarding the mechanism of action in the various spinal cord stimulation techniques, it did inspire generations of physicians and scientists to develop new means of tackling medically refractory chronic pain syndromes.<sup>22</sup> Traditional, low-frequency, suprathereshold tonic spinal cord stimulation has been postulated to work via several mechanisms. Most commonly cited includes selective activation of large, myelinated A $\beta$  fibers with subsequent inhibition of smaller, pain-mediating A $\delta$  and c fibers via inhibitory interneurons. Other postulated contributors include dorsal horn wide dynamic range neurons, thought to develop a hypersensitivity in neuropathic injury states with resultant increased basal glutamate release and subsequent glutamate:GABA imbalance. Supraspinal mechanisms are also thought to be at play although the exact brainstem-spinal

circuitry activated by spinal cord stimulation remains largely theoretical.<sup>22</sup> Regardless of the inner workings of the therapy, spinal cord stimulation has proven to be an important development in the management of an otherwise frustrating patient population. Medical management in chronic pain conditions often fails and is associated with high rates of narcotic medication use with their associated complications. Futile treatment regimens, although inexpensive in isolation, become expensive when applied indefinitely, and costly revision surgeries without clearly rectifiable structural or compressive pathology are not only low yield, but very expensive and potentially dangerous. Spinal cord stimulation has provided an opportunity to attain symptom relief, limit disability, and improve patient productivity. And although the upfront investment is large, there is an increasing amount of evidence suggesting that the long-term cost-effectiveness profile is positive and that spinal cord stimulation should be considered earlier in the broader treatment paradigm for chronic pain.<sup>1,2</sup> With all of this said, spinal cord stimulation is certainly no panacea. One of the most important limiting factors is the requirement for a high-degree of overlap between induced paresthesia and the patient's baseline pain. This becomes a problem for patients that can't tolerate even mild paresthesia. Furthermore, positional differences in the intensity of elicited paresthesia have been reported by some patients, and occasionally even limit participation in important day-to-day activities such as driving. The requirement for paresthesia overlap also makes the treatment of axial symptoms particularly challenging, as effective paresthesia coverage in this region remains elusive even with today's technology. Given that chronic back pain is one of the most common problems in modern medical systems, achieving efficient low back coverage is a priority for next generation models.

With these challenges in mind, innovation in spinal cord stimulation has moved towards paresthesia-free systems. Burst patterns were developed as a means of subthreshold stimulation that would more closely resemble central nervous system neuronal firing. Furthermore,

simultaneous SCS/EEG studies have suggested that burst stimulation impacts cortical medial pain pathways, with De Ridder et al<sup>18</sup> showing an effect on connectivity involving dorsolateral prefrontal, dorsal anterior cingulate, and parahippocampal regions. In other words, burst stimulation may impact affective and attentional components to pain in addition to pain transmission. High-frequency, low-amplitude stimulation patterns have been developed ranging up to 10,000 Hz. Again, the exact mechanism of action of these systems remains elusive, but several hypotheses have been put forth, including production of a local sodium channel blockade with inhibition of depolarization within the dorsal columns, desynchronization of neuronal messaging from the periphery, and inhibition of wide dynamic range neuronal sensitization, among others.<sup>22</sup> What is clearer is that the clinical benefit has been demonstrated in several randomized controlled trials, most notably the SENZA trial<sup>14,15</sup> where both axial and limb pain response rates approached 70% up to two years after implantation. From a surgical perspective, the purely anatomic placement of HF10 leads creates additional benefit in terms of ease of placement for the surgeon, without the need for uncomfortable wakeup testing for the patient and likely shorter overall anesthesia time. However, such systems are not without their limits, as well. There is a certain subset of patients that prefer paresthesias, ostensibly as a reassuring cue that there is in fact a therapy being provided. Furthermore, very high frequency systems such as HF10 deliver much more charge per second, which can lead to short internal pulse generator (IPG) lifetime, or in the case of rechargeable IPGs, significant charging burden for the patient. Additionally, the exact impact of frequency, amplitude, and pulse width, and thus total charge delivery, are unclear and have not been systematically accounted for in the available literature. It is highly likely that simple frequency modulation is not by itself responsible for the clinical benefit of this technique, and a clearer understanding of how these parameters come together for therapeutic effect will be critical if we are to maximize the potential benefit.

## CONCLUSION

Chronic back pain remains a highly prevalent clinical problem in modern society. This patient population has historically been very challenging to treat. Spinal cord stimulation has helped to bridge the treatment gap in these patients, and while progress so far has been encouraging, there remains much research to be done to fully understand the mechanisms and potential therapeutic reach of this modality.

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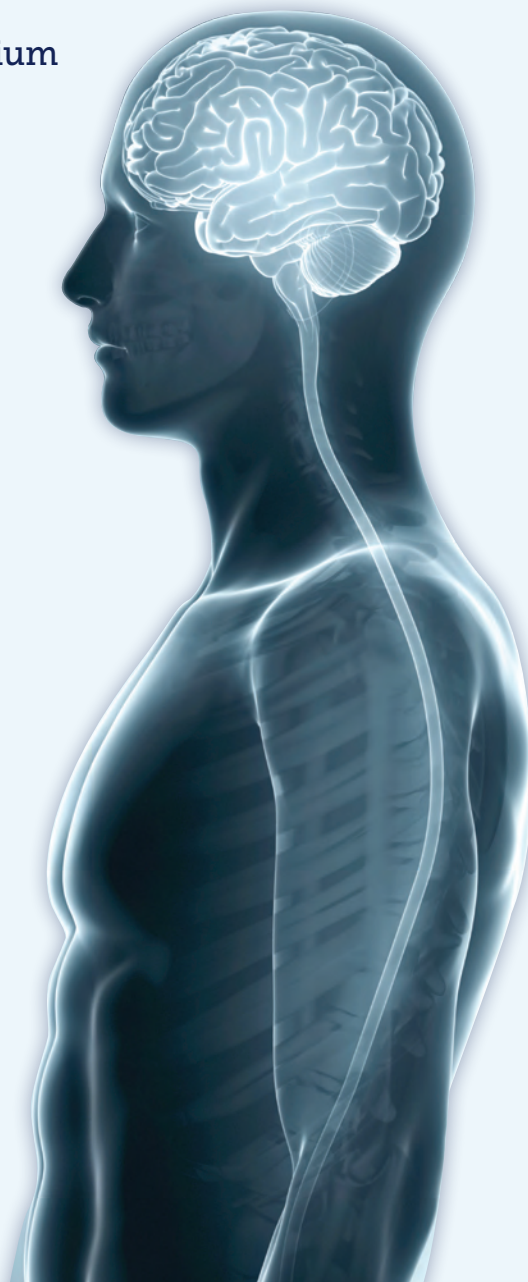
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