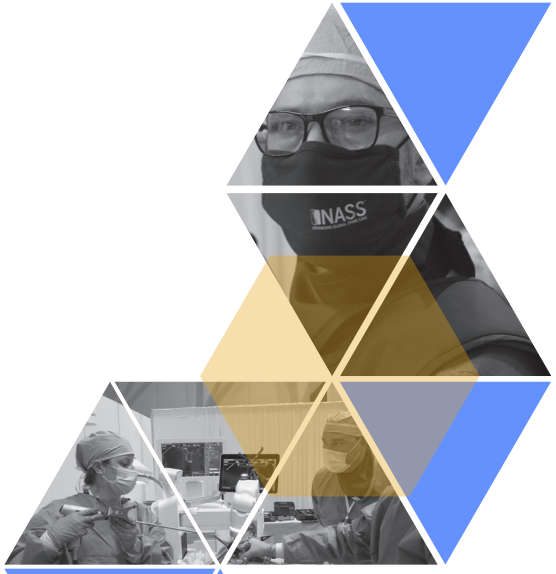
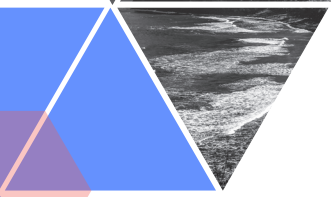




Best of NASS 2021

SpineLine

The Spine Journal

NASS Journal

Coverage Recommendations

NASS Daily News

Hematogenous Septic Spondylodiscitis: Current Concepts

Panagiotis G. Korrovessis, MD, PhD
Orthopedic Department,
General Hospital "Agios Andreas"
Patras, Greece

Synopsis

Hematogenous septic spondylodiscitis (HSD) is a rare but serious infectious disease. The most frequent causative agent is *Staphylococcus aureus* with gram-negative bacteria being the second most common. The most common clinical symptom in HSD is a constant and increasing axial spine pain, along with varying degrees of neurological symptoms from nerve roots and/or spinal cord. Because the disease course can be chronic and lacks specific symptoms, surgeons should be aware of potential delays between its onset and diagnosis.

MRI is most commonly used for early diagnosis for HSD; however, F-18 FDG PET has recently been shown to be more accurate than MRI in detection of HSD. A delay in diagnosis of HSD can potentially result in high morbidity and mortality. The diagnosis is mainly made on the basis of biopsy and blood culture results.

Conservative treatment is the mainstay in cases without neurological symptoms, and consists of antibiotic therapy and immobilization. Surgical treatment comprises conventional approaches (anterior, posterior or combined), and minimally invasive surgery (MIS) is necessary in patients with neurological deficit, spinal instability or is resistant to antibiotic treatment.

The overall mortality rate ranges between 1.5% and 38%. Rates of disability of up to 31% have been reported with residual spinal dysfunction or persistent pain after recovery following spondylodiscitis. The outcome of treatment is influenced by the type of infection, age and comorbidities and by the degree of neurologic compromise before treatment.

Introduction

Hematogenous septic spinal infection includes several pathologies (spondylodiscitis, primary epidural abscess and pyogenic facet arthropathy) with characteristic clinical presentations and courses.[1] It is an uncommon disease with an estimated incidence of 0.2 to 2.4 cases per 100,000 population per year.[1]

Structural localization of primary spinal pyogenic infection has been identified as hematogenous septic spondylodiscitis (95%), discitis (1%), pyogenic facet arthropathy (6%) and primary epidural abscess (2%).[1] The incidence of HSD, however, has increased in recent years mainly because of the aging population, malnutrition, immunosuppression (AIDS, chemotherapy, diabetes mellitus, chronic renal failure, etc).[2] Nosocomial infection is considered a common source of HSD, with up to one-third of these infections being catheter-related and when present, are associated with higher mortality and relapse rates.[3]

Causes of HSD

The main causative microorganisms are gram-positive bacteria, especially *Staphylococcus aureus*, which account for 40%-60% of total cases, followed by gram-negative bacilli that account for approximately 15–23% of cases of HSD.[1] *Staphylococcus aureus* was reported to be the main causative agent that promotes abscess formation[1,4-11] and methicillin-sensitive *Staphylococcus aureus* (MSSA) is more likely than gram-negative bacilli to be associated with epidural abscess in patients suffering from HSD.[4,6,7,10] Enterococcal HSD is frequently (26%) associated with endocarditis and therefore, patients with enterococcal

HSD should have an appropriate cardiac work-up and evaluation. In countries with increased frequency of brucellosis, Brucella varies from 33-44% of HSD cases.[1,12]

Despite the significant incidence of HSD caused by gram-negative bacteria, very few studies have reported clinical characteristics and outcomes of HSD caused by gram-negative bacilli. Gram-negative bacteremia was much more common in the elderly than in younger patients mainly because of increased urinary tract infections in the elderly.[11] Although most of the HSD are caused by a single organism, polymicrobial infection was reported in 1%-10% of the patients.[13]

Clinical Picture of HSD

The clinical symptoms of HSD are nonspecific and include axial spine pain and paravertebral muscle spasm. The rate of patients with neurological involvement on presentation ranges from 10%-50%. The reported delay between the onset of initial symptoms of HSD and the diagnosis ranges from 2-6 months.[3,13]

Clinical manifestations of HSD in elderly or immunocompromised patients may be associated with absence of localizing symptoms.[14] Therefore, these patients, who are more likely to have the early warning signs of drowsiness and fever, should seek immediate medical attention. Diabetes mellitus is a well-recognized risk factor for sepsis, mainly due to sustained hyperglycemia retarding neutrophil chemotaxis. Patients of chronic renal failure are well-recognized to be at an increased risk of bacteremia due to their uremia-induced immunosuppression and possible dialysis and hospitalizations.

Imaging for HSD Diagnosis

Hadjipavlou et al[3] reported that the most frequent anatomical location of spondylodiscitis is the lumbar spine (49.7%) followed by the thoracic (25.7%) and cervical spine (11.6%).[13]

Plain radiographs have low sensitivity in the early stages of HSD, as abnormalities usually develop later on. Computed tomography scans (CT scans) are sensitive in detecting signs of HSD but do not demonstrate the soft tissue accurately. Abnormalities in CT scans are visible in the first two weeks in about 50% of the patients. Magnetic resonance imaging (MRI) is the most sensitive imaging modality for confirming an early diagnosis for HSD. With 96% sensitivity, 94% specificity and 92% accuracy, MRI shows detailed anatomically pathological alterations.[15,16] However, disadvantages of MRI are artifacts due to metallic implants, occasional similarities between spondylodiscitis and degenerative disease, and reduced sensitivity in patients with short duration of symptoms.[15-17] A recent meta-analysis concluded that F-18 FDG PET has better diagnostic accuracy than MRI for the detection of HSD and may be recommended in difficult diagnosis cases.[18]

Laboratory Findings and Biopsy in HSD

Increased ESR and CRP are common findings and seen in >90% of HSD cases. Leukocytosis occurs in <50% of the cases. CRP is superior to ESR in the evaluation of HSD as it rises more quickly and is less influenced by other plasma factors.[3] Blood culture can be very useful in the diagnosis of HSD and positive identification in about 50% of the cases.[3]

Open and needle biopsy provide positive cultures in >75% of the cases,[3,13] however, the proportion of HSD with negative culture result ranges from 21%-34 %.[13] False-negative blood culture or biopsy results are frequently found in patients who are treated with empirical antibiotics before microbiological diagnosis; therefore, a second biopsy should be performed when the initial culture results are negative.[13] If polymicrobial infection is suspected in immunocompromised patients with positive blood cultures in more than one bacteria, or in emergency surgery, biopsy is mandatory for diagnosis establishment.[3,13]

Possible complications of HSD are axial pain, instability, segmental kyphotic deformity, neurological impairment (radiculopathy and paraplegia), paravertebral or epidural (primary, secondary) abscess associated with significant morbidity, and mortality.[3,13]

Treatment Algorithm for HSD

To date, there are no evidence-based guidelines addressing the best treatment methods in the management of HSD. Current management of HSD begins with identification of the causative agent and antibiotics administration.[19,20] Early treatment of HSD may decrease morbidity and mortality. Most of the uncomplicated HSD cases can be treated with immobilization and intravenous antibiotics. Most guidelines recommend 6-12 weeks of parenteral antibiotic treatment for HSD.[20-21] Optimal duration of parenteral antibiotic therapy and of subsequent oral therapy remains unclear.[20,22-24]

Surgical Treatment of HSD

Surgical indications include failure of medical treatment, intractable axial pain, instability, neurological deficit, spinal deformity and abscess formation. Anterior, posterior or combined approaches for debridement, decompression and stabilization in single- or two-staged procedures have been described.[25-30]

The most important advantages of the anterior procedure are that it allows radical resection of the infectious focus (disc, endplates, abscess evacuation, etc) and enables satisfactory interbody fusion. Subsequently, patients had rapid infection resolution and early and frequent bony fusions. Laminectomy has a limited role in the decompression of HSD because the pathology is located anteriorly in the vertebral body and accessing the lesion is difficult with a posterior decompression. In fact, laminectomy without stabilization in presence of significant vertebral body involvement form infection may cause instability following removal of the posterior elements and should preferentially be avoided.[1,13,25-30]

The anterior approach decreases postoperative pain, allows early ambulation and protects posterior ligamentous structures. Thoracotomy provides a good exposure from

T5 to T12. A contralateral side approach would generally be chosen in patients who had previous chest operations to prevent approach-related complications (bleeding, atelectasis and pneumothorax).[25] However, some authors reported a 55.5%-87% fusion rate via posterior approach and posterior approach including debridement and posterior-only instrumentation.[13]

Restoration of the anterior spinal column with fusion is paramount for restoring stability and healing infection. Most authors recommend a double approach including anterior debridement with vertebrectomy supplemented with posterior instrumentation and fusion. This combined surgery seems to be well tolerated by HSD patients with comorbidities and results in pain reduction, faster spinal fusion, reduction of associated segmental kyphotic deformity and maintenance of correction, and early patient mobilization.[13]

A recent systematic review[31] including 50 articles and 4,173 patients showed that medical management remains first-line treatment of HSD justifying previous case series. Decompression with instrumented fusion was the most commonly performed intervention reported (79%), compared to decompression alone (22%). Combined anterior and posterior approach was performed in 33% and staged surgery was performed in 26% of surgical patients. Repeat surgery was necessary in 13% of patients among the surgery-specific series. This review concluded that surgery may be indicated for progressive pain, persistent infection on imaging, deformity or neurologic deficits. If surgery is required, reported literature shows potential for significant pain reduction, improved neurologic function and a high number of patients returning to a normal functional/work status.[31]

Biological Grafts Used in Spinal Surgery for HSD

Various biological (autograft, allograft) have been used to reconstruct the anterior column. Because of the complications and morbidity associated with harvesting iliac bone autograft and the recent enthusiastic outcomes with metallic implants, vertebral body replacement with titanium mesh cages with autogenous bone graft has emerged as a viable option for reconstructing a deficient anterior spinal column contributing to infection healing.[13,28,30]

Although spine surgeons were previously reluctant to use instrumentation in presence of an active spine infection due to concerns for hindering the antimicrobial treatment, significant clinical data and evidence from a number of studies have established the usefulness, stability and safety of spinal instrumentation especially with titanium implants patients undergoing surgery for spinal infection.[13,28,30]

Furthermore, rhBMP-2, in conjunction with circumferential instrumented fusion and appropriate antibiotics, has been successfully used without reported infection recurrences and complications.[13]

Minimally Invasive Surgery in HSD

Minimally invasive surgical techniques are also becoming an attractive option for both decompression and stabilization in patients requiring surgery for spinal infection.[26] These techniques diminish the major surgical stress and provide early and safe mobilization avoiding complications related to immobilization of sick and elderly patients.

A recent retrospective study[27] concluded that mini-open anterior debridement and lumbar interbody fusion in combination with posterior percutaneous fixation via a modified ALIF approach results in little surgical trauma and intraoperative blood loss, acceptable postoperative complications, and is effective and safe for the treatment of single-level lumbar pyogenic spondylodiscitis and could be an alternative to conventional open surgery.

Mortality and Functional Outcome

The overall mortality rate of HSD patients ranged from 1.5-38%.[13,32] The large variance in these reported mortality rates may be attributed to different follow-up periods, varying in-hospital 6-month or 1-year mortality rates, and different causative microorganisms such as drug-resistant bacteria.[13,33-36]

Published data regarding the long-term neurologic and functional outcome or quality of life in patients with HSD managed operatively or nonoperatively are scarce. Rates of disability of up to 31% have been reported for residual spinal dysfunction or persistent pain after recovery following spinal infection, with diagnostic delay associated with poor prognostic outcome. Poor functional outcome following HSD is common at long-term follow-up, even in patients with apparent full neurologic recovery. This suggests under-reporting of poor outcomes in series using neurologic deficit alone to qualify as a poor outcome.[33-36]

Conclusion

The incidence of HSD is rising due to frequency and increased availability of imaging and an increase in patient population susceptible to development of HSD (elderly, immunocompromised, etc). Ideal treatment for HSD remains somewhat controversial. Although the mainstay of treatment for HSD is long-term antibiotic therapy and bracing, surgical intervention is recommended in cases of complicated HSD (spinal instability with vertebral destruction, paravertebral and/or epidural abscess formation, spinal deformity and/or associated neurologic deficits). Minimally invasive surgical techniques have been successfully used to provide debridement of infection and stabilization in some cases in elderly and immunosuppressed patients who cannot withstand an open major surgery. Spinal decompression and instrumentation via anterior, posterior or combined approach when indicated can often be performed without any significant risk of worsening of infection even with use of titanium instrumentation. High rates of mortality and disability have been reported in HSD patients with increased comorbidity and preoperatively existed neurologic impairment.

References

1. Cornett CA, Vincent AS, Crow J, Hewlett A . Bacterial spine infections in adults: evaluation and management. *JAAOS.* 2016;1(24):11–18.
2. Nickerson EK, Sinha R. Vertebral osteomyelitis in adults: an update. *Br Med Bull.* 2016;117:121–138.
3. Hadjipavlou AG, Mader JT, Necessary JT, Muffoletto AJ. Hematogenous pyogenic spinal infections and their surgical management. *Spine.* 2000;25(13):1668–79.
4. Cottle L, Riordan T. Infectious spondylodiscitis. *J Infect.* 2008;56:401–412.
5. Hempelmann RG, Mater E, Schon R. Septic hematogenous lumbar spondylodiscitis in elderly patients with multiple risk factors: efficacy of posterior stabilization and interbody fusion with iliac crest bone graft. *Eur Spine J.* 2010;19:1720–1727.
6. Aagard T, Roed C, Dragsted C, Skinhøj P. Microbiological and therapeutic challenges in infectious spondylodiscitis: a cohort study of 100 cases, 2006–2011. *Scand J Infect Dis.* 2013;45:417–424.
7. Pigrau C, Rodrıguez-Pardo D, Fernandez-Hidalgo N, Moretó L, Pellise F, Larrosa MN, et al. Health care associated hematogenous pyogenic vertebral osteomyelitis. A severe and potentially preventable infectious disease. *Medicine*. 2015;94:3.
8. Cheng AG, DeDent AC, Schneewind O, Missiakas D. A play in four acts: *Staphylococcus aureus* abscess formation. *Trends Microbiol.* 2011;19(5):225–32.
9. Cheng AG, Kim HK, Burts ML, Krausz T, Schneewind O, Missiakas DM. Genetic requirements for *Staphylococcus aureus* abscess formation and persistence in host tissues. *FASEB J.* 2009;23(10):3393–404.
10. Al-Nammari SS, Lucas JD, Lam KS. Hematogenous methicillin resistant *Staphylococcus aureus* spondylodiscitis. *Spine.* 2007;32:2480–2486.
11. GraSham SM, Fishlock A, Millner P, Sandoe J. The management gram-negative bacterial haematogenous vertebral osteomyelitis: a case series of diagnosis,treatment and therapeutic outcomes. *Eur Spine J.* 2013;22(8):1845–53.
12. Sakkas LI, Davas ME, Kapsalaki E, et al. Hematogenous spinal infection in central Greece. *Spine.* 2009;34:E513–E518.
13. Korovessis P, Vardakastanis K, Fennema P, Syrimbeis V. Mesh cage for treatment of hematogenous spondylitis and spondylodiskitis. How safe and successful is its use in acute and chronic complicated cases? A systematic review of literature over a decade. *Eur J Orthop Surg Traumatol.* 2016;26(7):753-61.
14. Park KH, Cho OH, Jung M, Suk KS, Lee JH, Park JS, et al. Clinical characteristics and outcomes of hematogenous vertebral osteomyelitis caused by gram-negative bacteria. *J Infect.* 2014;69(1):42–50.
15. Ledermann HP, Schweitzer ME, Morrison WB, Carrino JA. MR imaging findings in spinal infections: rules or myths? *Radiology.* 2003;228:506–514.
16. Dunbar JA, Sandoe JA, Rao AS, Crimmins DW, Baig W, Rankine JJ. The MRI appearances of early vertebral osteomyelitis and discitis. *Clin Radiol.* 2010;65:974–81.
17. Carragee EJ. The clinical use of magnetic resonance imaging in pyogenic vertebral osteomyelitis. *Spine.* 1997;22:780–5.
18. Kim S-J, Pak K, Kim K, Lee JS. Comparing the diagnostic accuracies of F-18 fluorodeoxyglucose positron emission tomography and magnetic resonance imaging for the detection of spondylodiscitis. A meta-analysis. *Spine.* 2018; 44 E414–E422.
19. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362(11):1022–9.
20. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomized, controlled trial. *Lancet.* 2015;385:875–82.
21. Walters R, Vernon-Roberts B, Fraser R, Moore R. Therapeutic use of cephazolin to prevent complications of spine surgery. *Inflammopharmacology.* 2006;14(3–4):138–43.
22. Al-Nammari SS, Lucas JD, Lam KS. Hematogenous methicillin-resistant *Staphylococcus aureus* spondylodiscitis. *Spine.* 2007;32(22):2480–6.
23. Khan IA, Vaccaro AR, Zlotolow DA. Management of vertebral discitis and osteomyelitis. *Orthopedics.* 1999;22:1668–1679.
24. Shiban E, Janssen I, Wostrack M, et al. Spondylodiscitis by drug-multiresistant bacteria: a single-center experience of 25 cases. *Spine J.* 2014;14(12):2826–34.
25. Fukuta S, Miyamoto K, Masuda T. Two-stage (posterior and anterior) surgical treatment using posterior spinal instrumentation for pyogenic and tuberculotic spondylitis. *Spine.* 2003;28:e302–e308.
26. Oh HS, Kim JS, Lee SH, Liu WC, Hong SW. Comparison between the accuracy of percutaneous and open pedicle screw fixations in lumbosacral fusion. *Spine J.* 2013;13:1751–1757.
27. Lin Y, Li F, Chen W, Zeng H, Chen A, Xiong W. Single-level lumbar pyogenic spondylodiscitis treated with mini-open anterior debridement and fusion in combination with posterior percutaneous fixation via a modified anterior lumbar interbody fusion approach. *J Neurosurg Spine.* 2015;23:747–753.
28. Korovessis P, Repantis T, Iliopoulos P, Hadjipavlou A. Beneficial influence of titanium mesh cage on infection healing and spinal reconstruction in hematogenous septic spondylitis: A retrospective analysis of surgical outcome and twenty-five consecutive cases and review of literature. *Spine.* 2009;33:759–767
29. Pee YH, Park JD, Choi YG, Lee SH. Anterior debridement and fusion followed by posterior pedicle screw fixation in pyogenic spondylodiscitis: autologous iliac bone strut versus cage. *J Neurosurg Spine.* 2008;8:405–412.
30. Bydon MD, De la Garza-Ramos R, Macki M, Naumann M, Sciubba DM, Wolinsky JP. Spinal instrumentation in

patients with primary spinal infections does not lead to greater recurrent infection rates: an analysis of 118 cases. *World Neurosurg.* 2004;82:e807–e814.
31. Taylor GD, Buchholz LA, Sure RD, Buell JT, Nguyen HJ, Chen C-J. Presentation and outcomes after medical and surgical treatment versus medical treatment alone of spontaneous infectious spondylodiscitis: a systematic literature review and meta-analysis. *Global Spine J.* 2018; 8(4S)49S-58S.
32. Kehrer M, Pedersen C, Jensen TG, Hallas J, Lassen AT. Increased short- and long-term mortality among patients with infectious spondylodiscitis compared with a reference population. *Spine J.* 2015;15(6):1233–40.
33. Rutges JP, Kempen DH, van Dijk M, Oner FC. Outcome of conservative and surgical treatment of pyogenic spondylodiscitis: a systematic literature review. *Eur Spine J.* 2016;25(4):983–992.
34. O'Daly JB, Morris FS, O'Rourke KS. Long-term functional outcome in pyogenic spinal infection. *Spine.* 2008;33:E246–E253.
35. McHenry M, Easley KA, Locker GA. Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. *Clin Infect Dis.* 2002;34:1342–50.
36. Solis Garcia del Pozo J, Vives Soto M, Solera J. Vertebral osteomyelitis: long-term disability assessment and prognostic factors. *J Infect.* 2007;54:129–34.

Author Disclosure

P Korovessis: Nothing to disclose.

Cannabinoid Use in the Perioperative Period

Ken Finn, MD
Springs Rehabiliation, PC
Colorado Springs, CO

Introduction

Pre– and postoperative pain control in the surgical patient is an important aspect of effective patient care and has a direct bearing on outcome. In patients with noncancer (benign) pain, surgery is typically not emergent, unless associated with trauma. In the midst of the opioid epidemic, effective pain management is challenging.

Pain management before surgery may impact preoperative assessment and care. Patients on chronic or high dose opioids may not be good surgical candidates, due not only to issues with pain control and dosing, but to inactivity-related deconditioning. On the contrary, patients with adequate pain control may be able to participate in a rehabilitative program pre– and postoperatively. Prior to surgery, non-opioid medications such as nonsteroidal anti-inflammatory medications and acetaminophen, and non-pharmacologic interventions, such as physical therapy, chiropractic and alternative treatments may be helpful in avoiding opioid-related issues.

Discussion

Approximately one-third of patients use opioids chronically before lumbar arthrodesis and nearly half of preop opioid users will continue to take opioids at one year postsurgery.[1] Other studies have demonstrated similar findings for pre– and postsurgical opioid use. For instance, people who took prescription opioid medications for six months or longer before undergoing lumbar spine surgery were more likely to continue taking opioids after surgery. The primary risk factor for continued opioid use after surgery was the duration of opioid use presurgery of six months or longer.[2] A recent literature review concluded that preoperative opioid use in patients with spinal pain is overwhelmingly associated with negative surgical and functional outcomes, including postoperative opioid use, hospitalization duration, health care costs, risk of surgical revision and several other negative outcomes.[3] Other studies have also concluded the use of opioid medications to control pain before patients underwent lumbar fusion for degenerative lumbar conditions was associated with less favorable clinical outcomes postoperatively.[4]

Data related to the use of cannabis-based medicines for pain management has evolved over the past several years. In 2015, Whiting reported moderate-quality evidence supporting the use of cannabinoids for the treatment of chronic pain; however, cannabinoids were associated with an increased risk of short-term adverse effects.[5] In 2017, the National Academies of Science, Engineering, and Medicine reviewed the health effects of cannabis and cannabinoids and reported substantial evidence for cannabis as an effective treatment for chronic pain in adults.[6] It is critical to understand that the data evaluated for these papers included products not available in the United States (nabiximols) or synthetic cannabis-based medications (dronabinol) and in less common pain conditions (neuropathic and cancer pain). The products from domestic dispensaries have not been evaluated thoroughly or proven efficacious. As an example, nabiximols, which are natural, purified and regulated cannabinoids, have failed Phase III clinical trials in cancer patients who have maximized opioid use and have persistent severe pain.[7]

A significant amount of data refutes the usefulness of cannabinoids in chronic noncancer pain. In 2018, a four-year, prospective cohort Australian study noted that cannabis use is common in people with chronic non-cancer pain who had been prescribed opioids.[8] The study showed no evidence that patient outcomes were improved in this population

and no evidence that cannabis use reduced pain severity or exerted an opioid-sparing effect.

Patients who use cannabis have an increased likelihood of developing opioid use disorder and nonmedical prescription opioid use based on a large study by Olfson et al. The authors followed >30,000 cannabis users in two separate waves between 2001 and 2005 (wave 1) and 2004-2005 (wave 2).[9] Among adults with nonmedical opioid use in wave 1, cannabis use was associated with an increase in nonmedical opioid use. Further meta-analysis and review of controlled and observational studies concluded that the effectiveness of cannabis-based medicine in chronic noncancer pain is limited.[10] The number to treat benefit ratio is high and the number needed to harm is low. These data suggest that cannabinoids are not effective medicines for chronic noncancer pain. The European Pain Federation position paper on cannabis-based medicine did not recommend use of cannabis-based medicine in patients utilizing opioids or benzodiazepines.[11] They also cautioned use while driving and in the elderly, recommended screening for anxiety and depression and did not recommend use of cannabis flower >12.5% tetrahydrocannabinol (THC) content to avoid intoxication and cognitive impairment.

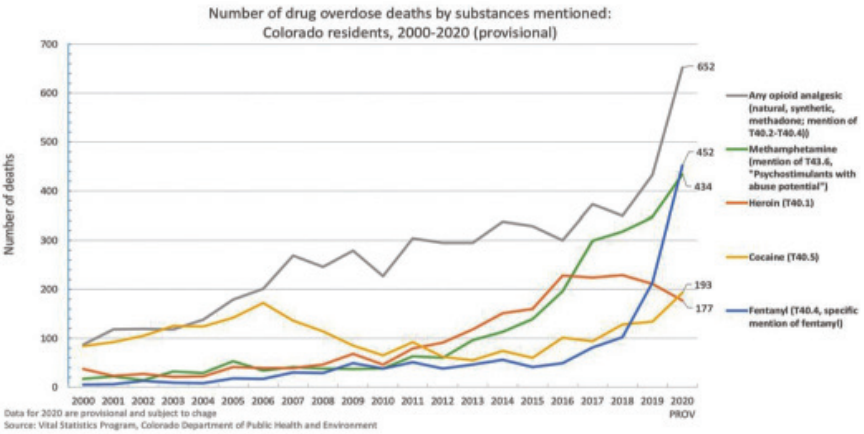


Fig 1. Number of drug overdose deaths by substances mentioned: Colorado residents, 2000-2020 (provisional). Source: Vital Statistics Program, Colorado Department of Public Health and Environment.

Potencies in the US can reach 100% THC and there is large-scale evidence that first episode psychosis (FEP) patients with a history of daily use of high-potency cannabis (defined as >10% THC) present with more positive symptoms of psychosis compared with those who never used cannabis or used low-potency types.[12,13] The availability of high potency cannabis resulted in a greater proportion of FEP cases being attributed to cannabis use.

In patients who may be using medical cannabis or a cannabis-based medication, drug interactions should be discussed. For instance, cannabidiol (CBD), a nonpsychoactive cannabinoid isolated from the marijuana plant, has over 500 drug interactions. Buprenorphine, the medication used to treat opioid use disorder, has a major drug interaction with ingested CBD and interacts with dozens of common prescribed and over-the-counter medications.[14] CBD has been shown to cause hepatic impairment; patients utilizing CBD should have transaminases followed.[15] It can cause suicidal ideation and behavior, somnolence, sedation, irritability and agitation. Recently, the US FDA issued a warning regarding the use of CBD while driving due to possible sedative side effects.[16] Compared with drivers testing negative for marijuana, those testing positive were 28% more likely to test positive for prescription opioids based on Fatality Analysis Reporting System data. In a National Road Survey of Alcohol and Drug Use by Drivers, those testing positive for marijuana were twice as likely to test positive for prescription opioids.[17]

Given this information, the concept of substituting opioids with cannabinoids is attractive but questions remain as to efficacy. Cannabis and its constituents are considered by the general public and many in health care to be benign, harmless and a reasonable alternative to opioids for pain control. Opioids are powerful analgesics which carry serious, sometimes fatal, risks related to addiction and overdose. Respiratory depression is generally less likely with cannabis than with opioids. This, however, does not include the pediatric population, where children exposed to marijuana may have respiratory impairment, occasionally to the point of requiring ventilatory support including intubation.[18] According to one study, naloxone, the opioid overdose reversal agent, also interacts with the cannabinoid system.[19]

Current evidence does not support the substitution of opioids with marijuana. Recent data reviews suggest that enactment of medical marijuana laws was not associated with a reduction in nonmedical prescription opioid use.[20]

In those states with medical marijuana programs, pain is the most frequent reason for use (not otherwise specified). In Colorado, 93% of medical marijuana cards are used to obtain cannabis for pain.[21] Colorado has had a medical marijuana program since 2001, and in 2019, had a record number of opioid overdose deaths. Between 2018 and 2019 alone, prescription opioid overdose deaths increased by 24% and fentanyl-related deaths increased by 115%.[22] (**Figure 1**). Cannabinoid-related deaths have also been noted to be increasing in Colorado as well. However, the state health department has been unable to verify whether or not these deaths were attributed to synthetic cannabinoids, regulated market products, or marijuana use as a co-drug.

In Colorado, other drug-related deaths have continued to climb over the past 20 years, with overall upward trends in multiple drug categories, despite having medical marijuana which recommended for pain relief.

Similar patterns can be seen in other states such as Califor-

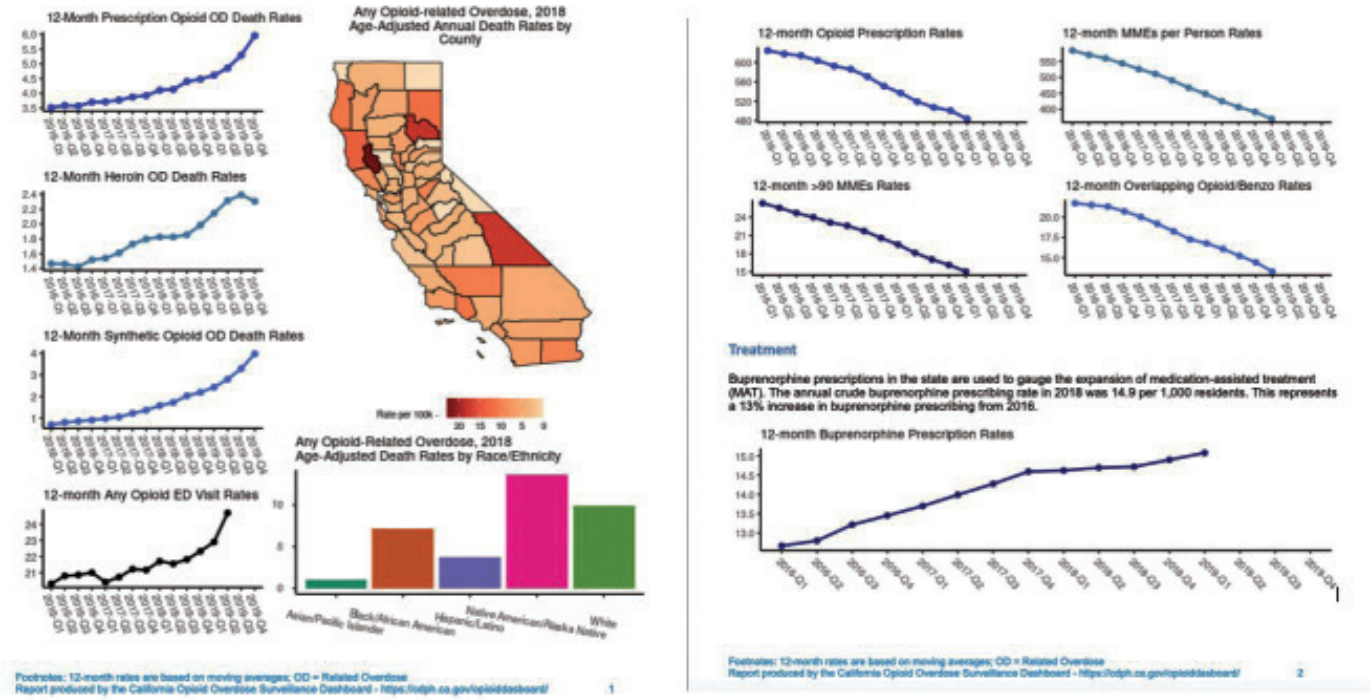


Fig 2. California Opioid Overdose Surveillance, Source: California Department of Public Health

nia (**Figure 2**) where there has been significant push back on the opioid epidemic with fewer overall prescriptions, decreasing daily morphine equivalents, less co-prescribing of opioids and benzodiazepines, and increases in the use of buprenorphine which is used for treatment of opioid use disorder.[23]

For patients who have failed nonsurgical care and are surgical candidates, anesthesia factors need to be considered. Due to lipid solubility, cannabinoids can be rapidly accumulated in fatty tissue which can prolong elimination up to several days or more after use. The systemic effects as well as interactions with anesthetic agents may have significant consequences. It may be challenging to determine cannabinoid exposure in the pre-anesthesia assessment. For example, researchers found that compared with people who did not regularly use cannabis, people who regularly used cannabis required an amount of sedation for endoscopic procedures that was significantly higher than those who did not (P=.05). The statistical significance persisted when adjusted for age, sex, and use of alcohol, benzodiazepines and opiates.[24]

Echeverria-Villalobo et al[25] reviewed pharmacologic and anesthetic considerations in the perioperative care of cannabis users. Identifying baseline cannabinoid use may have implications in presurgical anesthesia planning. Identifying exposures to synthetic cannabinoid should also be part of the anesthesia assessment. Recreational versus medicinal use of cannabis, frequency of use, potency of products used and last time of exposure should be part of anesthesia planning. Elective surgeries should be avoided for at least 72 hours from last exposure due to accumulation in fatty tissue and long elimination time.

New users may experience tachycardia, systolic hypertension within two hours of consumption, malignant arrhythmias (atrial fibrillation, ventricular fibrillation, ventricular tachycardia), coronary spasm and airway hyper-reactivity (uvulitis). Chronic users may show bradycardia followed by tachycardia, orthostatic hypotension, sinus arrest, hyper-reactive airway, intraoperative hypothermia, coronary vasospasm or myocardial infarction. Patients with a history of cannabinoid hyperemesis syndrome (CHS) may need to be addressed by anesthesia due to possible postoperative nausea and vomiting (PONV). Chronic users may develop cannabis withdrawal syndrome in the immediate to short-term postoperative period and anesthesia should be aware of the patient's use patterns. Risk factors for cannabis withdrawal syndrome include amount and potency of cannabis used, female gender and environmental and genetic factors.[26]

History of CHS, hyperactive airway or severe shivering with prior surgeries should be obtained as well. Ingestion route, such as vaping, smoking or ingestion. Ingested cannabinoids will likely have a longer onset and duration of action, and there may be high interpatient variability[27] effect. There may be serious pulmonary sequelae related to the vaping of marijuana products. E-cigarette or vaping product use-associated lung injury (EVALI) is a known outcome of the vaping of legal and illegal marijuana products, and there is some association with these lung injuries.[28] There is evidence that there was a significant effect on the bispectral index (BIS) after controlling for minimum alveolar concentration (MAC).[29] The average BIS

values, measured during steady state anesthesia, were significantly higher in the high dose cannabis treatment group. In patients who use cannabis prior to general anesthesia induction, BIS monitoring in determining the patient's sedative state may not be reliable.

Patients using cannabis may experience serious cardiovascular effects. Regular cannabis use was associated with larger indexed left ventricular end diastolic volume, end systolic volume, and impaired global circumferential strain compared with rare/no cannabis use, even after adjustment for potential confounders (age, sex, body mass index, systolic blood pressure, use of cholesterol medication, diabetes, smoking, and alcohol consumption).[30] It is important to consider episodic marijuana use as a significant risk factor for acute coronary syndromes, particularly in individuals with no cardiac risk factors, as delay in management can result in fatal outcomes.[31] Cannabis consumption has been shown to cause arrhythmia including ventricular tachycardia and potentially sudden death, and to increase the risk of MI. Acute cannabis consumption has been shown to cause an increase in blood pressure, specifically systolic blood pressure (SBP), and orthostatic hypotension. Cannabis use has been reported to increase risk of ischemic stroke, particularly in healthy young patients.[32,33] Patients with reversible cerebral vasoconstriction syndrome (RCVS) secondary to marijuana were more often male ($p = 0.05$) and younger ($p = 0.02$) compared to those who did not use marijuana; no differences were observed in the outcomes. These findings were consistent when examining marijuana versus other vasoactive substances.[34]

Pulmonary concerns also need to be taken into consideration. Some evidence in large studies indicates that inhaled marijuana has adverse effects on the respiratory system and, conversely, bronchodilatory effects.[35] The data indicate a risk of lung cancer from inhaled marijuana as well as an association with spontaneous pneumothorax, bullous emphysema and COPD. A variety of symptoms have been reported by inhalation marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation and other symptoms.

Interactions between cannabinoids and anesthetics have not been thoroughly investigated, but there are enough data to cause concern. For instance, THC has been shown to prolong the action of some intravenous anesthetics such as ketamine, pentobarbital, thiopental and others.[36-38] The endocannabinoid, anandamide, may be associated with severe hypotension via inhibition of the sympathetic response mediated by the CB1 and vanilloid receptor-type 1 in animal models.[39,40] Cannabis smokers required significantly higher doses of propofol during the induction of general anesthesia when compared to non-cannabis users, likely due to the overlap of general anesthetics and endocannabinoids via modulation of gamma-aminobutyric acid (GABA).[41] Similar higher tolerance to inhaled anesthetics such as isoflurane and sevoflurane was linked to cannabis users.[42] The effects of neuromuscular blockers have not been well studied in the human population, but based on animal models, cannabinoids may potentiate or prolong the effects of non-depolarizing neuromuscular blockers.

Chronic cannabis users may have higher opioid requirements post vehicular trauma. Salottolo et al[43] report that marijuana users who did not use other drugs consumed significantly more opioids (7.6 mg vs 5.6 mg, $p < 0.001$) and reported higher pain scores (4.9 vs 4.2, $p < 0.001$) than non-marijuana users. There is also evidence there may be an increased risk of perioperative MI in patients with active cannabis use disorder.[44]

More recent data demonstrated higher anesthetic requirements for patients who used marijuana undergoing surgery for tibial fracture, compared to those who did not.[45] These patients also had higher pain scores while in recovery and received 58% more opioids per day while in the hospital.

Patients on preoperative cannabinoids had significantly higher pain scores and poorer quality of sleep in the early postoperative period compared to patients who did not have a history of cannabinoid use.[46] Medical marijuana users are also more likely to use prescription drugs, including opioids, medically and nonmedically.[47]

Conclusion

Patients who are using cannabinoids, either medicinally or recreationally, need to be thoroughly evaluated prior to surgery. Anesthesia considerations are paramount, due to multiple physiologic effects, depending on the patient, products used and method of delivery. Knowledge of potential drug-drug interactions pre– and postoperatively with cannabinoids and commonly prescribed medications and anesthetic agents is vital in the comprehensive care of the patient. Current evidence does not show dispensary cannabis to be effective for chronic non-cancer pain, or for marijuana as an opioid substitute. Medical providers should support FDA drug development protocols of cannabinoids for use in particular medical conditions guided by scientific rigor.

References

1. Kalakoti P, Hendrickson N, Bedard N, Pugely A. Opioid utilization following lumbar arthrodesis trends and factors associated with long-term use. *Spine.* 2018;4(17):1208-1216.
2. Schoenfeld A, Belmont P, Blucher J, et al. Sustained preoperative opioid use is a predictor of continued use following spine surgery. *J Bone Joint Surg Am.* 2018;100(11):914-921.
3. Yerneni K, Nichols N, Abecassis Z, Karras C, Tan L. Preoperative opioid use and clinical outcomes in spine surgery: a systematic review. *Neurosurgery.* 2020;86(6):E490–E507.
4. Villavicencio A, Nelson E, Kantha V, Burneikiene S. Prediction based on preoperative opioid use of clinical outcomes after transforaminal lumbar interbody fusions. *Neurosurg Spine. 2017;*26:144–149.

5. Whiting P, Wolff R, Deshpande S, et al. Cannabinoids for medical use. A systematic review and meta-analysis. *JAMA.* 2015;313(24):2456-2473.
6. National Academies of Sciences, Engineering, and Medicine. 2017. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.
7. Fallon MT, Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *Br J Pain.* 2017;11(3):119–133.
8. Campbell G, Hall W, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health.* 2018;(3);e342-e350.
9. Olfson M, Wall M, Liu SM, Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. *Pain*. 2018;159:1932–1954.
10. Stocking E, Campbell G, Hall, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain.* 2018;159:1932–1954.
11. Hauser W, Finn D, Kalso E, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. *Eur J Pain.* 2018;22:1547–1564.
12. Quattrone D, Ferraro L, Tripoli G, et al. Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case-control study. *Psychol Med.* 2020;18;1-9.
13. DiForti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry.* 2015;2:233–38.
14. Drugs.com. Interactions between cannabidiol and buprenorphine. Available at: https://www.drugs.com/drug-interactions/cannabidiol.html, Accessed July 9, 2020.
15. Epidiolex, Full Prescribing Information; Warnings and Precautions. https://www.epidiolex.com. Accessed July 9, 2020.
16. US Food and Drug Administration. Some Medicines and Driving Don't Mix. Available at: https://www.fda.gov/consumers/consumer-updates/some-medicines-and-driving-dont-mix. Accessed July 22, 2020.
17. Li G, Chifuri S. Is marijuana use associated with decreased use of prescription opioids? Toxicological findings from two US national samples of drivers. *Substance Abuse Treatment, Prevention, and Policy.* 2020;15:12.
19. Richards JR. Treatment of acute cannabinoid overdose with naloxone infusion. *Toxicology Communications.* 2018;2(1):29-33.
20. Segura LE, Mauro C, Levy N, et al. Association of US medical marijuana laws with non-medical prescription opioid use and prescription opioid use fisorder. *JAMA Network Open.* 2019;2(7):e197216.
21. Colorado Department of Public Health and Environment. Medical Marijuana Registry Statistics. Available at: https://drive.google.com/file/d/18DaudmBYMzTtijhBXbPz1nrdD63_p6gX/view. Accessed July 8, 2020.
22. Colorado Department of Public Health and Environment; Colorado Drug Overdose Dashboard. Available at: https://cohealthviz.dphe.state.co.us/t/PSDVIP-MHPPUBLIC/views/DrugOverdoseDashboard/LandingPage?iframeSizedToWindow=true&:embed=y&:showAppBanner=false&:display_count=no&:showVizHome=no&:origin=viz_share_link. Accessed July 8, 2020.
23. California Department of Public Health. California Opioid Overdose Surveillance Dashboard. Available at: https://skylab.cdph.ca.gov/ODdash/. Accessed July 8, 2020.
24. Twardowski MA, Link MM, Twardowski NM. Effects of cannabis use on sedation requirements for endoscopic procedures. *J Am Osteopath Assoc*. 2019;119(5):307-311.
25. Echeverria-Villalobos M, Todeschini A, Stoicea N, et al. Perioperative care of cannabis users: a comprehensive review of pharmacological and anesthetic considerations. *J Clin Anesth*. 2019;57:41–49.
26. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abus Rehabil.* 2017;8:9.
27. Borgelt L, Franson K, Nussbaum A, Wang G. The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy.* 2013;33(2):195-209.
28. Centers for Disease Control and Prevention. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. February 25, 2020. Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed July 22, 2020.
29. Ibera C, Shalom B, Saifi F, et al. Effects of cannabis extract premedication on anesthetic depth. *Harefuah.* 2018;157(3):162-166.
30. Khanji M, Jensen M, Kenawy A, et al. Association between recreational cannabis use and cardiac structure and function. *JACC Cardiovasc Imaging.* 2020;13(3):886-888.
31. Patel RS, Kamil SH, Bachu R, et al. Marijuana use and acute myocardial infarction: A systematic review of published cases in the literature. *Trends in Cardiovascular Medicine.* 2019;21:33.
32. Goyal H, Awad H, Ghali J. Cannabis consumption has been shown to cause arrhythmia including ventricular tachycardia, and potentially sudden death, and to increase the risk of myocardial infarction (MI). *J Thoracic Disease.* 2017;9(7):2079-2092.
33. Rumalla K, Reddy A, Mittal M. Recreational marijuana use and acute ischemic stroke: a population-based analysis of hospitalized patients in the United States. *J Neurological Sciences.* 2016;364:191–196.
34. Jensen J, Leonard J, Salattolo K, et al. The epidemiology of reversible cerebral vasoconstriction syndrome in patients

at a Colorado comprehensive stroke center. *J Vasc Interven Neurol.* 2018;10(1):32-38.
35. Martinasek M, McGrogan J, Maysonet A, et al. A systematic review of the respiratory effects of inhalational marijuana. *Respiratory Care.* 2016;11(61):1543-1551.
36. Frizza J, Chesher G, Jackson D, Malor R, Starmer G. The effect of delta 9, cannabidiol, and cannabinol on the anaesthesia induced by various anaesthetic agents in mice. *Psychopharmacology.* 1977;55(1):103–7.
37. Chesher G, Jackson D, Starmer G. Interaction of cannabis and general anaesthetic agents in mice. *Br J Pharmacol.* 1974;50(4):593–9.
38. Karam K, Abbasi S, Khan FA. Anaesthetic consideration in a cannabis addict. *J Coll Physicians Surg Pak.* 2015;25(S1):S2–3.
39. Varga K, Wagner JA, Bridgen DT, Kunos G. Platelet-and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. *FASEB J.* 1998;12(11):1035–44.
40. García MDC, Adler-Graschinsky E, Celuch SM. Hypotensive effect of anandamide through the activation of CB 1 and VR 1 spinal receptors in urethaneanesthetized rats. *Naunyn Schmiedeberg's Arch Pharmacol.* 2003;368(4):270–6.
41. Flisberg P, Paech M, Shah T, Ledowski T, Kurowski I, Parsons R. Induction dose of propofol in patients using cannabis. *Eur J Anaesthesiol.* 2009;26(3):192–5.
42. Georg R, Götz B, Arlt F, Heymann CV. Cannabis consumption before surgery may be associated with increased tolerance of anesthetic drugs: a case report. *Int J Case Rep Images.* 2015;6(7):436–9.
43. Salottolo K, Peck L, Tanner A, et al. The grass is not always greener: a multi-institutional pilot study of marijuana use and acute pain management following traumatic injury. *Patient Saf Surg.* 2018;12:16.
44. Goel A, McGuiness B, Jivraj N, et al. Cannabis use disorder and perioperative outcomes in major elective surgeries: a retrospective cohort analysis. *Anesthesiology.* 2020;132(4):625-635.
45. Liu C, Bhatia A, Buzon-Tan A, et al. Weeding out the problem: the impact of preoperative cannabinoid use on pain in the perioperative period. *Anesth Analg.* 2019;129(3):874-881.
46. Caputi T, Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and non-medically. *J Addict Med.* 2018;12(4):295-299.

Author Disclosure

K Finn: Board of Directors: American Board Of Pain Medicine (Nonfinancial, Exam Council); Scientific Advisory Board: Colorado Department Of Public Health And Environment (Nonfinancial, Reviewed RFP for scientific research on cannabis for the State of Colorado).

ASK! Preoperative Safety Checklist Protocol in Interventional Spine Procedures: A Quality Improvement Study

Akhil Chhatre, MD
Johns Hopkins School of Medicine and Sinai Hospital Physical Medicine & Rehabilitation Residency
Hanover, MD

Adam Amir, DO
Johns Hopkins Hospital
Department of Physical Medicine and Rehabilitation
Baltimore, Maryland

Laryssa Richards, DO
Johns Hopkins Hospital
Department of Physical Medicine and Rehabilitation
Baltimore, MD

Synopsis
Human error is inevitable, even in medicine. Performing a surgical procedure on the incorrect side or leaving a surgical instrument inside a wound can have dire consequences and cause substantial harm. One way to avoid mistakes is to use rigorous checklists that are carefully designed to target areas with higher probabilities of human error, keeping in mind that each procedure type has its specific set of error probabilities. In 2003, The Joint Commission implemented the Universal Protocol and in 2008, the World Health Organization (WHO) developed the Surgical Safety Checklist. Both of these checklists were developed to help prevent wrong-site surgeries, near misses and other surgical never events. Multiple studies have shown that time-outs and checklists help prevent some of the human errors. The purpose of this quality improvement (QI) study is to assess the efficacy of newly implemented preoperative safety checklist that is specific to interventional spine procedures. Our preliminary six-month results showed a statistically significant decrease in the number of incidents and near misses after the implementation of this new protocol.

Introduction
Mistakes are inevitable. However, in medicine, doing a surgical procedure on the incorrect side or leaving a piece of equipment in a wound has potentially dire consequences for both the patient and the physician. The Joint Commission implemented the Universal Protocol in 2003, which consists of three key steps: conducting a preprocedure verification process, marking the procedure site and performing a time-out.[1] The World Health Organization (WHO) Surgical Safety Checklist (**Figure 1**) developed in 2008 is also intended to improve patient safety, preventing wrong site surgeries, near misses, and other surgical never events.[2]

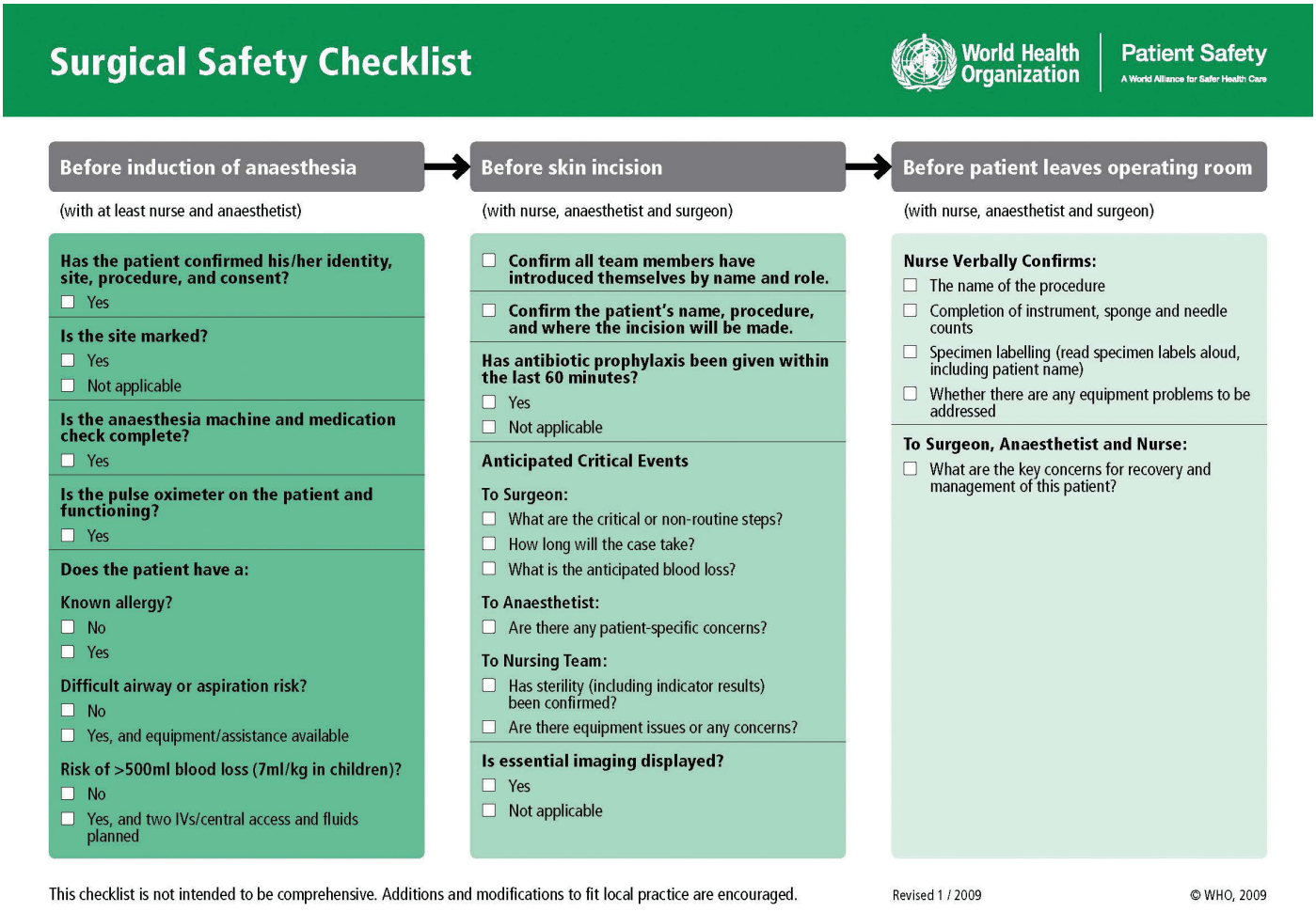
Using a systematic time-out has greatly reduced these rates. Yoon et al[3] collected data on 12,215 cases where 6,126 were "pre-education" and 6,089 were "post-education." They found that the monthly rate of incorrectly booked cases was 0.75% before the intervention and 0.41% after the intervention. They also found that improperly performed time-out procedures decreased from 18.7% to 5.9% after the educational interventions. Another study done by Neily et al[4] created a unique surgical checklist with the goal of including the patient and family members or caregivers in the preoperative time-out process to reduce near misses and wrong-site surgeries. They found that after implementing a total surgical checklist, there were zero discrepancies between team members and zero wrong-site, wrong-side, or wrong-patient surgeries.

Furthermore, Henshaw et al[5] collected data on the incidence of wrong-site nerve blockade over eight years. The first two years included a retrospective review to compare the incidence of wrong-side nerve blockade to the following six years after implementation of a preprocedural checklist. They found that four events occurred before checklist imple-

mentation during 10,123 procedures and that zero occurred after checklist implementation during 35,890 procedures. This appears to be true across specialties. Robert et al[6] measured the effects of a WHO presurgical checklist for laser vision correction. They found that two serious errors occurred in the pre-checklist cohort and none occurred following a safety checklist protocol.

A time-out does not require any qualifications and can be done by any member of the surgical team, is easily performed, and costs nothing. However, despite the effectiveness, compliance issues remain a problem. According to Neily et al[7] and Rydenfält et al,[8] time-out related issues are shown to be the most common root cause of adverse events, whether it was conducted incorrectly or incomplete in some way. Papadakis et al[9] suggested educational strategies to help with compliance, as the most important reason for low compliance rates was the lack of awareness of the importance of time-outs among health care professionals. Nelson et al[10] found that compliance with time-outs required considerable education as staff can easily revert to "old ways." They developed ongoing monitoring, training modules and yearly education for staff members. Since implementing these changes, they had no incidents of wrong-site, wrong-procedure or wrong-patient surgery in the OR. Interestingly, Freundlich et al[11] found that at least one member of the OR team was actively distracted in 10% of time-out procedures observed and despite distractions, no wrong-site or wrong-person surgeries were reported during this study period during which a time-out was done in 100% of the cases.

To our knowledge, no study has been done on interventional spine procedures. Therefore, our study was introduced as a QI project in interventional spine procedures at Johns Hopkins Greenspring Station ASC and Johns Hopkins Knoll North ASC from August 2020 through August 2021. The results discussed here are from August 1, 2020 through February 28, 2021. The aim of this study was to implement a 30-second time-out performed by the attending physician, interventional spine fellow, radiologist technician, nurse and anesthesiologist, if present, and collect data on wrong-site, wrong-procedure, and/or wrong-patient surgeries.



Surgical Safety Checklist

World Health Organization | Patient Safety
A World Alliance for Safer Health Care

Before induction of anaesthesia → **Before skin incision** → **Before patient leaves operating room**

(with at least nurse and anaesthetist) | (with nurse, anaesthetist and surgeon) | (with nurse, anaesthetist and surgeon)

Has the patient confirmed his/her identity, site, procedure, and consent?
- ☐ Yes

Is the site marked?
- ☐ Yes
- ☐ Not applicable

Is the anaesthesia machine and medication check complete?
- ☐ Yes

Is the pulse oximeter on the patient and functioning?
- ☐ Yes

Does the patient have a:

Known allergy?
- ☐ No
- ☐ Yes

Difficult airway or aspiration risk?
- ☐ No
- ☐ Yes, and equipment/assistance available

Risk of >500ml blood loss (7ml/kg in children)?
- ☐ No
- ☐ Yes, and two IVs/central access and fluids planned

Confirm all team members have introduced themselves by name and role.

Confirm the patient's name, procedure, and where the incision will be made.

Has antibiotic prophylaxis been given within the last 60 minutes?
- ☐ Yes
- ☐ Not applicable

Anticipated Critical Events

To Surgeon:
- ☐ What are the critical or non-routine steps?
- ☐ How long will the case take?
- ☐ What is the anticipated blood loss?

To Anaesthetist:
- ☐ Are there any patient-specific concerns?

To Nursing Team:
- ☐ Has sterility (including indicator results) been confirmed?
- ☐ Are there equipment issues or any concerns?

Is essential imaging displayed?
- ☐ Yes
- ☐ Not applicable

Nurse Verbally Confirms:
- ☐ The name of the procedure
- ☐ Completion of instrument, sponge and needle counts
- ☐ Specimen labelling (read specimen labels aloud, including patient name)
- ☐ Whether there are any equipment problems to be addressed

To Surgeon, Anaesthetist and Nurse:
- ☐ What are the key concerns for recovery and management of this patient?

This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged.

Revised 1 / 2009

Figure 1. World Health Organization (WHO) Surgical Safety Checklist. Reprinted with permission from WHO Safe Surgery: Tools and Resources: https://www.who.int/teams/integrated-health-services/patient-safety/research/safe-surgery/tool-and-resources. Accessed 8 June 2021.

Methods

This is a prospective QI study assessing every interventional spine procedure done by a PM&R spine specialist at Johns Hopkins Greenspring Station ASC and Johns Hopkins Knoll North ASC from August 1, 2020 through February 28, 2021. The sign-in process began with obtaining patient demographics and medical and surgical history by the medical assistant. Once the procedure details were posted, members of the different interdisciplinary team—the charge nurse, radiology technician, interventional spine fellow and the anesthesiologist—created separate checklists. The patient's laterality was marked by the attending physician. The patients were then brought back to the procedure room and prepped on the exam table. A standard time-out was performed by the nurse. Immediately prior to the start of the procedure, the attending performed an ASK (Ascertain Site Knowledge). He stated the laterality and pointed at the marking on the patient and asked every team member if they are in agreement. After affirmation from each team member, the procedure can be started. The number of incorrect markings of laterality or incorrect procedures site was documented into two categories as near miss or incident, depending on the situation. A near miss is defined as an error, which does not have the potential to cause harm, while an incident is an error which causes potential harm.

Results

From August 1, 2020 through February 28, 2021, 1,106 interventional spine procedures were completed. During this time period, the different interdisciplinary team checklists were done, the laterality marked by the attending, a standard time-out took place, as well as the ASK as described in the methods section. These actions were done in all the cases, and there were zero near misses or incidents.

Discussion

Procedure checklists are an integral part of efforts to do no harm to the patient. The WHO procedural checklist was created as a general guide and is not meant to be used without procedure-specific modifications. Studies have shown centers that relied solely on the WHO checklist had more incidents of errors compared to those that implemented a secondary checklist that was specific to their practice.[12]

Procedural errors can occur at any part between the sign-in and sign-out; however, some procedures can carry disproportionate risks of error at different parts of the safety checklist. For example, the possibility for an error to occur during the time-out part of an epidural injection procedure is higher simply because of the three different possibilities for how this procedure may be done based on the patient's diagnosis (right side, left side, or bilateral injection). Conversely, procedures like open-heart surgery can carry increased risk of error during the sign-out part when counting the fine instrumentation and surgical gauze before incision closure requires close attention. A carefully tailored checklist specific to the task performed has been shown to reduce chances of errors.[13]

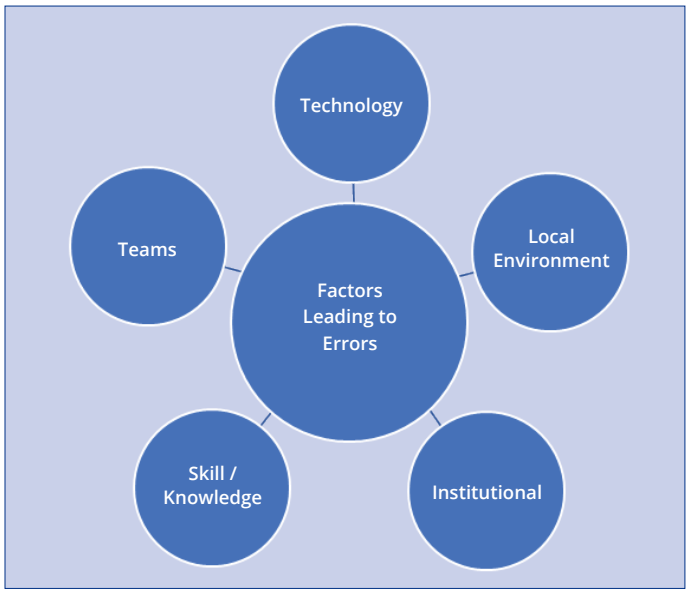


Figure 2. Factors leading to surgical errors.

Multiple factors could contribute to error, as demonstrated in **Figure 2**, with team dynamic and skill/knowledge being the highest source of errors.[14] A 2019 retrospective study of videos of 24 procedures found the incision site was checked in only 25% of the time.[5] In a cohort of 72 subjects, surgical site was confirmed by one member of the team in 91% of the cases and only validated by another member in 37% of the cases.[15] Based on previous data, we modelled this QI project around creating parallel checklists that require team members to include the side of procedure, as well as having the attending perform a mandatory 30-second time-out with laterality check to compare against those of the other team members. This model resulted in a statistically significant reduction of incidents, especially wrong-side procedures.

Conclusion

In summary, our results showed a decreased rate of error in interventional spine procedures when the procedural safety checklist was carried out as a team effort with parallel checklists along with an attending-led time-out. This preliminary data is not designed to draw conclusions, rather to raise the need for a more comprehensive randomized controlled trial to create a standardized protocol specific to interventional spine procedures checklists.

References

1. The Joint Commission. The Universal Protocol for preventing wrong site, wrong procedure, wrong person surgery. 2003. Available at: https://www.jointcommission.org/standards/universal-protocol/. Acessed: Feb 20, 2021.
2. WHO Surgical Safety Checklist. 2008. Available at: https://www.who.int/teams/integrated-health-services/pa-

tient-safety/research/safe-surgery/tool-and-resources. Acessed: Feb 20, 2021.
3. Yoon RS, Alais MJ, Hutzler LH, et al. Using "near misses" analysis to prevent wrong-site surgery. *J Healthc Qual.* 2015;37(2):126-132.
4. Neily SD, Elkwood L, Gaynor D, et al. An innovative approach to the surgical time out: a patient-focused model. *AORN J.* 2016;103(6): 617-622.
5. Henshaw DS, Turner JD, Dobson SW, et al. Preprocedural checklist for regional anesthesia: impact on the incidence of wrong site nerve blockade (an 8-year perspective). *Reg Anesth Pain Med.* Jan 13, 2019. DOI: 10.1136/rapm-2018-000033.
6. Robert MC, Choi CJ, Shapiro FE, et al. Avoidance of serious medical errors in refractive surgery using a custom preoperative checklist. *J Cataract Refract Surg.* 2015;41(10): 2171-2178.
7. Neily J, Soncrant C, Mills PD, et al. Assessment of incorrect surgical procedures within and outside the operating room: a follow-up study from US Veterans Health Administration Medical Centers. *JAMA New Open,* 2018; 1(7):e185147.
8. Rydenfält C, Johansson G, Odenrick P, et al. Compliance with the WHO Surgical Safety Checklist: deviations and possible improvements. *Int J Qual Health Care.* 2013;25(2):182-187.
9. Papadakis M, Meiwandi A, Grzybowski A. The WHO safer surgery checklist time out procedure revisited: Strategies to optimise compliance and safety. *Int J Surg.* 2019;69:19-22.
10. Nelson PE. Enhanced time out: an improved communication process. *AORNJ.* 2017;105(6): 564-570.
11. Freundlich RE, Bulka CM, Wanderer JP, et al. Prospective investigation of the operating room time-out process. *Anesth Analg.* 2020;130(3)725-729.
12. Saxena S, Krombach JW, Nahrworld DA, et al. Anaesthesia-specific checklists: a systematic review of impact. *Anaesth Crit Care Pain Med.* 2020;39(1):65-73.
13. Raman J, Leveson N, Samost AL, et al. When a checklist is not enough: How to improve them and what else is needed. *J Thorac Cardiovasc Surg.* 2016;152(2)585-592.
14. Elbardissi AW, Wiegmann DA, Dearani JA, et al. Application of the human factors analysis and classification system methodology to the cardiovascular surgery operating room. *Ann Thorac Surg.* 2007;83(4):1412-1418; discussion 1418-1419.
15. Cullati S, Le Du S, Raë AC, et al. Is the surgical safety checklist successfully conducted? An observational study of social interactions in the operating rooms of a tertiary hospital. *BMJ Qual Saf.* 22013;2(8):639-646.

Author Disclosures

A Chhatre: Nothing to disclose
A Amir: Nothing to disclose
L Richards: Nothing to disclose

Hip-Spine Syndrome: Avoiding the Pitfalls

Rhett MacNeille, MD,
Omar Ramos, MD,
Thomas Donaldson, MD,
Olumide Danisa, MD
Department of Orthopedic Surgery, Loma Linda University Medical Center
Loma Linda, CA

Synopsis
Hip-spine syndrome is a common but challenging clinical condition involving the overlapping presentation of groin, hip, buttock and thigh pain in patients with both hip and spine pathologies. Increased costs have been associated with delayed or incorrect diagnosis. History, physical findings and appropriate workup are critical. Understanding the framework for managing the various presentations of hip-spine syndrome will help to avoid misdiagnosis or delayed diagnosis and improve outcomes.

Introduction
Hip and lumbar spine pathologies are often present in combination and can lead to significant disability.[1] (**Figure 1**) Complaints of pain in the hip, lower back, buttock and thigh are common in patients with degenerative changes of the hip and/or the lumbar spine.[2-4] Such symptomology can also lead to presentation or referral to various health care providers: primary care, emergency room physicians, physical therapists, chiropractors, orthopedic surgeons (general, spine, joint reconstruction), neurological surgeons, pain management specialists and physiatrists. Within each specialty, there may be biases which can affect workup and treatment focus. Osteoarthritis (OA) is the most common musculoskeletal disease associated with aging and patients often present with imaging showing degenerative changes consistent with hip OA, lumbar spine degeneration and/or stenosis.[5] Imaging findings do not always correlate with symptomatology.[6] This overlapping clinical picture has been recognized for decades and continues to challenge providers.

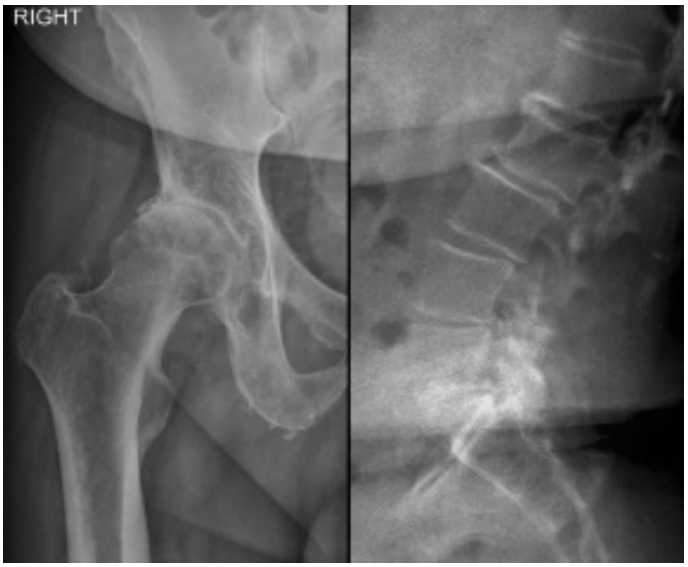


Figure 1. Patient with coexisting hip and spine pathology.

Hip-spine syndrome was first described in 1983 by Offierski and MacNab.[4] They described four different clinical presentations of hip-spine syndrome. **Simple hip-spine syndrome** is present when there are pathologic changes in both the hip and the lumbar spine, but one is the clear source of pain and/or disability. In **complex hip-spine syndrome**, there are pathologic changes in both the hip and the lumbar spine, but the primary source of disability is not clear. In **secondary hip-spine syndrome**, the pathologic changes in the hip and the lumbar spine are interrelated, with

one exacerbating the other. Lastly, **hip-spine syndrome can be misdiagnosed** when the source of pain is mistakenly attributed solely to the hip or the lumbar spine.

Failure to recognize and appropriately treat hip-spine syndrome and its subtypes can result in excessive imaging, interventions and unnecessary surgery.[7,8] Understanding how to recognize and differentiate hip and spine pathology through a complete evaluation is key to managing these patients.[9]

History

Obtaining a detailed and thorough history is extremely important when trying to differentiate hip pathology from lumbar spine pathology.

Pain from hip OA is most commonly localized to the groin and is associated with a limp, referred knee pain, and pain with range of motion of the hip.[1,10] Other frequently reported locations of pain in patients with hip OA include the buttock, anterior thigh, posterior thigh, anterior knee, anterior leg and calf (**Table 1**).[10] The presence of a limp, groin pain or limited internal rotation of the hip has been shown to be predictive of a primary hip pathology or hip and spine pathology rather than a spine pathology only. Brown et al[11] reported that patients with a limp and groin pain were 7 times more likely to have a hip disorder only, or a hip and spine disorder than a spine-only disorder. Patients with groin pain and limited internal rotation were 7 and 14 times, respectively, more likely to have a hip disorder only, or a hip and spine disorder than a spine-only disorder. Pain, clicking and popping symptoms during hip movement are also indicative of hip pathology.

Pain secondary to lumbar stenosis commonly presents with lower extremity pain and/or neurogenic claudication, an achy, cramping pain with leg heaviness or weakness. Symptoms are worse standing and/or during ambulation, and are relieved by sitting down and a forward-bending posture (shopping cart sign).[9,12] Patients with lumbar stenosis have higher relative frequencies of calf and leg pain, and lower relative frequencies of groin pain and gluteal pain when compared to hip osteoarthritis.[10] Burning or radicular pain are also associated with lumbar central or neuroforaminal stenosis, particularly when concomitant dermatomal sensory changes are present. Facet mediated pain will primarily present with insidious axial pain but can also radiate to the flank, buttock, groin and/or thigh in a non-dermatomal fashion.[13]

Sacroiliac (SI) pathology localizes to the axial spine (SI region) with radiation to the buttocks 90%-94% of the time, rarely localizing above the L5 spinous process.[14,15] Greater trochanteric bursitis presents with pain localized over the lateral hip (greater trochanter) and complaints of pain with lying on the side.[16]

The timing and frequency are also important considerations of a complete history. Degenerative pathologies of both the hip and spine typically worsen with activity. Lack of symptom relief and/or night pain should increase suspicion for infectious and pathologic etiologies.

While this review focuses primarily on the most common causes of hip and back pain, having a broad initial differential diagnosis is critical for any physician. **Spinal pathologies** to consider include lumbar stenosis, lumbar disc herniation, foraminal stenosis, facet cysts, nerve-root sheath tumor, spondylolysis/spondylolisthesis, sagittal malalignment, spinal malignancy (primary versus metastatic) and psoas pathology (abscess, hematoma, etc.). **Intra-articular hip pathologies** include osteoarthritis, inflammatory arthritis, septic arthritis, osteonecrosis, stress fracture (intracapsular), labral tear, femoroacetabular impingement, loose body and chondral damage/lesion. **Extra-articular hip pathologies** include greater trochanteric bursitis, iliotibial (IT) band tendonitis, stress fracture (extracapsular), gluteus medius/minimus tear, iliopsoas tendonitis, coxa saltans (snapping hip), piriformis syndrome, adductor strain, hamstring pathology and subgluteal space syndromes. **Other pathologies** that should be considered include sacroiliac (SI) joint arthritis, peripheral vascular disease, peripheral neuropathy, sciatic nerve tumor, intrapelvic tumor, sacral insufficiency fracture, osteitis pubis, sports hernia, Paget disease, shingles and meralgia paresthetica.[9]

Table 1. Location of Pain in Hip Osteoarthritis

Pain Location	Sensitivity (%)	Specificity (%)
Groin	84%	70%
Buttock	76%	61%
Anterior Thigh	59%	26%
Posterior Thigh	44%	48%
Anterior Knee	69%	44%
Anterior leg	51%	35%
Calf	30%	41%

Data source: Khan AM, et al. Hip osteoarthritis: where is the pain? *Annals of The Royal College of Surgeons of England*, 2004;86(2):119-121.[11]

Evaluation

Physical examination can quickly provide information including previous surgical scars, posture, coronal/sagittal alignment (aided by forward bend test), leg-length discrepancy, pelvic obliquity, lower extremity hair loss and skin discoloration (peripheral vascular disease) and gait abnormalities. Observation of the gait is also essential. The Trendelenburg gait was originally described for and is commonly observed in hip pathology, but this finding can also be seen in spine pathologies. A Trendelenburg gait from hip pathology is typically associated with pain with an antalgic component, while a Trendelenburg gait from spine pathology (L5 radiculopathy) is secondary to painless abductor weakness. Palpation may help identify the source of pain (eg, greater trochanter, SI joint, groin and paraspinal vs midline lumbar spine). Hip range of motion (ROM) should be assessed with attention to

loss of internal ROM and pain at terminal motion as these findings have a strong association with hip pathology.[11,17]

Motor and sensory findings of myotomal and/or dermatomal deficits suggest lumbar spine pathology. **Tables 2** and **3** describe important physical exam maneuvers for hip and spine pathologies which are particularly important when distinguishing between less obvious sources of pain about the spine and hip. In most patients with lumbar stenosis, the physical exam is normal.[18]

Imaging and Other Diagnostic Tests

Plain radiography is the first line of testing that should be obtained. Dunn or frog leg lateral views are the most helpful to assess asphericity of the femoral head as seen in femoroacetabular impingement (FAI). Standing AP and lateral radiographs of the lumbar spine are also the first line for evaluation of back pain and can show degenerative change, disc space narrowing, neuroforaminal stenosis, pars defects, listhesis, etc. Flexion-extension views are particularly helpful to assess sagittal stability. Full-length standing X-ray imaging of the spine should be obtained if evaluation of spinal deformity/malalignment is required. Spinopelvic parameters can also be measured on these radiographs. It is important to note that degenerative findings and OA of the lumbar spine are present in more than 50% of adult patients.[19] Similarly, 27% of adults ≥45 years have radiographic findings of hip OA but only 9.2% have symptomatic hip OA.[6]

MRI of the lumbar spine may be obtained to diagnose lumbar stenosis, infection and malignancy. CT scan is most helpful for close evaluation of bony anatomy as in subtle fractures, spondylolysis, evaluation of prior fusion and assessment of bony destruction related to malignancy. CT myelogram is also an option in patients where MRI is contraindicated. MRI of the hip, in combination with history and exam findings, has utility to assess for labral tears, tendonitis, early osteonecrosis, infection and malignancy. Arthrogram can improve the evaluation of labral tears.

Electrophysiologic studies are important in differentiating radiculopathy from peripheral neuropathy but cannot be used to reliably exclude radiculopathy when the findings are within normal limits.[20] Ankle-brachial index (ABI) and ultrasound duplex studies can help to evaluate for the presence of peripheral vascular disease.

Fluoroscopically guided anesthetic injections can be very useful in differentiating the source of pain. Intra-articular hip injections, selective nerve-root injections, and epidural injections can be used not only as a diagnosis tool but can also be therapeutic. Intra-articular hip injections have an 87% sensitivity and 100% specificity for hip pathology.[21-24] Injections in the lumbar spine as a diagnostic test in patients with hip-spine syndrome are neither as sensitive nor specific. Saito et al[7] reported on four patients with lumbar stenosis and hip osteoarthritis in whom the anatomic source of pain was unclear. In all patients, the symptoms resolved after an L5 spinal nerve lock, but remained after an intra-articular hip injection. The patients then underwent a lumbar decompression but had unresolved leg pain and all had a total hip arthroplasty, which resolved their pain.

Management

Management should be directed at the primary source of pain. It is important, however, to appropriately counsel pa-

Table 2. Spine Exam

Exam Maneuver	Description	Associated Pathology
Straight Leg Raise	Radicular pain in the ipsilateral leg when raised 30°-60° with the knee in extension	Lumbar radiculopathy
Contralateral Straight Leg Raise	Radicular pain the ipsilateral leg when the contralateral leg is raised 30-60 degrees with the knee in extension	Lumbar radiculopathy
Femoral Nerve Stretch Test	Hip extended and knee flexed with patient in supine position	Upper Lumbar radiculopathy
Trendelenburg Test	Contralateral drop in the hemipelvis when standing one-legged on the ipsilateral leg	Abductor weakness (often L5 radiculopathy)

Table 3. Hip Exam

Exam Maneuver	Description	Associated Pathology
Thomas Test	Lack of full hip extension when contralateral hip is brought into full flexion with patient supine (lumbar spine must remain flat on the examination table)	Hip flexion contracture
Ober Test	Lack of hip adduction with the patient laying on the unaffected side (knee held in 90 degrees of flexion)	Iliotibial (IT) band tightness (associated with greater trochanteric bursitis)
Anterior Impingement Test (FADIR)	Hip Flexion to 90 degrees with hip internal rotation and adduction	FAI, Hip labral tears, Hip OA
Posterior Impingement Test (FABER)	Hip Flexion to 90 degrees with hip external rotation and abduction	SI joint pathology with posterior/buttock pain Hip pathology/FAI with groin pain
Piriformis Stretch Test	Posterior pain at piriformis upon flexion, adduction and internal rotation with patient in seated position	Piriformis Syndrome (sciatic nerve impingement)

tients with hip-spine syndrome that complete resolution of pain is not always possible due to multiple etiologies that may be contributing to the pain in various degrees. Nonsurgical and surgical management strategies will be discussed based on the four described categories/presentations of hip-spine syndrome.

Simple Hip-Spine Syndrome: Hip Pathology

In younger patients, FAI and/or labral tears are more common than symptomatic OA.[25] These can be more accurately diagnosed with MRI arthrogram. Nonsurgical treatment involves a multimodal approach consisting of patient education, activity modification, oral anti-inflammatories, physical therapy and intra-articular injection(s).[26] If nonsurgical treatment fails, then surgery (often arthroscopic) is indicated to correct any morphological changes and address any underlying soft tissue injuries.[26]

For symptomatic OA, treatment guidelines from multiple professional organizations suggest an initial core set of nonpharmacological interventions including education, weight loss (if overweight) and exercises.[27-30] Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line pharmacologic treatment for OA.[28] There is strong evidence supporting the use of intra-articular corticosteroids to improve function in the short term.[28] Hip corticosteroid injections have at least an 87% sensitivity and 100% specificity for hip pathology and can predict success of total hip arthroplasty.[21,23] Total hip arthroplasty is an excellent option for patients with osteoarthritis who are no longer tolerating nonoperative treatment.[31] McNamara et al demonstrated that "simple" hip-spine syndrome may not always be straightforward, reporting nine patients who presented with isolated symptoms of hip/lower extremity pain and loss of range of motion but then subsequently developed symptoms related to lumbar stenosis after total hip arthroplasty was performed.[3]

In the case of greater trochanteric bursitis, corticosteroid injection is both diagnostic and therapeutic. Surgical intervention in these patients is rarely required.

Simple Hip-Spine Syndrome: Spine Pathology

Nonoperative treatment is attempted first in the absence of progressive neurologic deficits. Physical therapy or chiropractic manipulation and epidural steroid injections have been shown to provide short- to medium-term pain relief in the setting of lumbar stenosis.[32] Decompression with or without fusion as indicated can be offered to patients who have failed nonoperative management.[33] Mokhtar et al[34] showed significant quality-of-life improvement after lumbar decompression and fusion comparable to total hip arthroplasty.

Complex Hip-Spine Syndrome

Managing complex hip-spine syndrome requires clear communication with the patient as well as between the spine surgeon and orthopedic hip specialist. The aforementioned hip and epidural corticosteroid injections can be valuable tools in this setting to help provide clinical clarity as to which pathology is the most significant source of pain. Surgical intervention can be pursued based on the worst pain generator with cautionary discussion with the patient that complete pain relief cannot be reliably predicted.

In 1979, Bohl and Steffee[35] reported their case series of eight patients who had resolution of the groin pain but worsening of the posterior thigh pain after total hip arthroplasty, six of the eight subsequently requiring decompression. McNamara et al[3] reported five patients with concomitant symptoms of hip OA and lumbar stenosis undergoing total hip arthroplasty first, two of which required subsequent lumbar decompression. Worsening hip pain and OA has also been reported after a lumbar decompression and fusion resulted in improved activity levels.[1] Conversely, the secondary pain source often improves after the primary source is treated. Parvizi et al[36] reported 170 of 344 patients undergoing total hip arthroplasty with back pain preoperatively, 113 of which had resolution of their back pain following arthroplasty surgery.

Secondary Hip-Spine Syndrome

Patients with secondary hip-spine syndrome have both hip and spine pathology that are inter-related and exacerbating one another. Offierski and MacNab[4] described two classic examples. The first is the development of a hip flexion contracture which is common in hip pathologies such as OA. The flexion contracture leads to increased pelvic tilt and subsequent hyperlordosis which results in increased stress and subluxation of the facet joints causing foraminal stenosis. This may resolve with resolution of the flexion contracture by osteotomy or total hip arthroplasty. The other example is scoliosis which can cause pelvic tilt, uncovering of the femoral head, and increase contact forces that result in accelerated OA of the joint. Hip flexion contractures are common in patients with sagittal spine deformities. In most cases, the hip pathology and hip flexion contracture can be addressed first with total hip arthroplasty in order to improve sagittal alignment. Failure to restore sagittal alignment is associated with poor outcomes after lumbar fusion.[37] Rates of dislocation after total hip arthroplasty have been shown to be significantly higher in patients with spinal fusions.[38,39] For hip surgeons considering total hip arthroplasty in patients with sagittal spine deformity, it is important to consider the pelvic tilt when planning acetabular component version to prevent excessive component anteversion.[40,41] (**Figure 2**)

Should total hip arthroplasty or deformity correction and spinal fusion be done first? Ultimately, joint decision-making and surgical management of the more severe pain generator and/or deformity should be the primary determinant. In cases where significant spinal deformity corrections will be required, resulting in a significant change in acetabular positioning, spinal correction should be considered prior to total hip arthroplasty.[40,42]

Conclusion

Hip-spine syndrome can be a challenging condition for patients and physicians. Specialists such as spine surgeons, joint reconstruction surgeons or pain specialists may have treatment biases related to training.

Regardless of the specialty, however, proper identification of both hip and spine pathologies is critical to avoiding delayed diagnosis or worse, misdiagnosis. Thorough history, physical examination and workup can optimize the identification of the primary pain generator, which, in turn, guides appropriate counsel and treatment. Surgical management should focus on treating the primary source of pain with the understanding that a second surgery may eventually be required in the case of incomplete pain resolution. Preemptively recognizing and establishing expectations for treatment will put these patients on the smoothest road to pain relief and function.

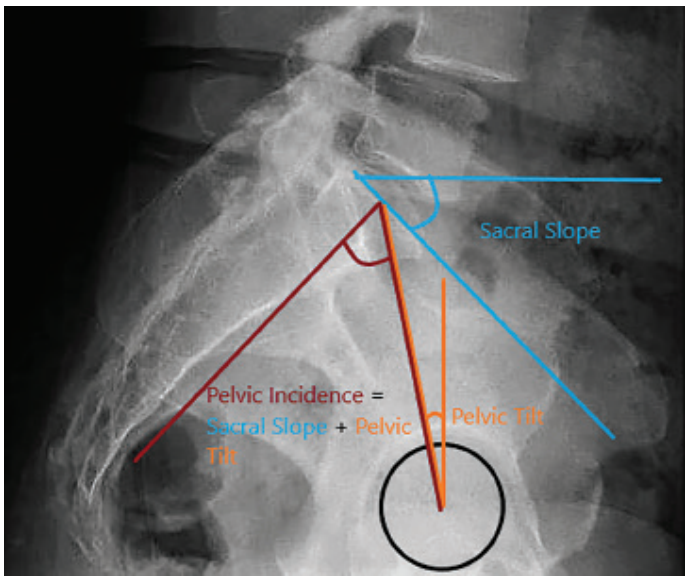


Figure 2. Spinopelvic parameters.

References

1. Devin CJ, McCullough KA, Morris BJ, Yates AJ, Kang JD. Hip-spine syndrome. *J Am Acad Orthop Surg.* 2012;20(7):434-442.
2. Fogel GR, Esses SI. Hip spine syndrome: management of coexisting radiculopathy and arthritis of the lower extremity. *Spine J.* 2003;3(3):238-241.
3. McNamara MJ, Barrett KG, Christie MJ, Spengler DM. Lumbar spinal stenosis and lower extremity arthroplasty. *J Arthroplasty.* 1993;8(3):273-277.
4. Offierski CM, MacNab I. Hip-spine syndrome. *Spine (Phila Pa 1976).* 1983;8(3):316-321.
5. Dagenais S, Garbedian S, Wai EK. Systematic review of the prevalence of radiographic primary hip osteoarthritis. *Clin Orthop Relat Res.* 2009;467(3):623-637.
6. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58(1):26-35.
7. Saito J, Ohtori S, Kishida S, et al. Difficulty of diagnosing the origin of lower leg pain in patients with both lumbar spinal stenosis and hip joint osteoarthritis. *Spine (Phila Pa 1976).* 2012;37(25):2089-2093.
8. Swezey RL. Overdiagnosed sciatica and stenosis, underdiagnosed hip arthritis. *Orthopedics.* 2003;26(2):173-174; discussion 174.
9. Buckland AJ, Miyamoto R, Patel RD, Slover J, Razi AE. Differentiating Hip Pathology From Lumbar Spine Pathology: Key Points of Evaluation and Management. *Instr Course Lect.* 2017;66:315-327.
10. Khan AM, McLoughlin E, Giannakas K, Hutchinson C, Andrew JG. Hip osteoarthritis: where is the pain? *Ann R Coll Surg Engl.* 2004;86(2):119-121.
11. Brown MD, Gomez-Marin O, Brookfield KF, Li PS. Differential diagnosis of hip disease versus spine disease. *Clin Orthop Relat Res.* 2004(419):280-284.
12. van Kleef M, Vanelderen P, Cohen SP, Lataster A, Van Zundert J, Mekhail N. 12. Pain originating from the lumbar facet joints. *Pain Pract.* 2010;10(5):459-469.
13. de Schepper EI, Overdevest GM, Suri P, et al. Diagnosis of lumbar spinal stenosis: an updated systematic review of the accuracy of diagnostic tests. *Spine (Phila Pa 1976).* 2013;38(8):E469-481.
14. Slipman CW, Jackson HB, Lipetz JS, Chan KT, Lenrow D, Vresilovic EJ. Sacroiliac joint pain referral zones. *Arch Phys Med Rehabil.* 2000;81(3):334-338.
15. Young S, Aprill C, Laslett M. Correlation of clinical examination characteristics with three sources of chronic low back pain. *Spine J.* 2003;3(6):460-465.
16. Mulligan EP, Middleton EF, Brunette M. Evaluation and management of greater trochanter pain syndrome. *Phys Ther Sport.* 2015;16(3):205-214.
17. Almeida GP, de Souza VL, Sano SS, Saccol MF, Cohen M. Comparison of hip rotation range of motion in judo athletes with and without history of low back pain. *Man Ther.* 2012;17(3):231-235.
18. Egli D, Hausmann O, Schmid M, Boos N, Dietz V, Curt A. Lumbar spinal stenosis: assessment of cauda equina involvement by electrophysiological recordings. *J Neurol.* 2007;254(6):741-750.
19. Scavone JG, Latshaw RF, Rohrer GV. Use of lumbar spine films. Statistical evaluation at a university teaching hospital. *JAMA.* 1981;246(10):1105-1108.
20. Cho SC, Ferrante MA, Levin KH, Harmon RL, So YT. Utility of electrodiagnostic testing in evaluating patients with lumbosacral radiculopathy: An evidence-based review. *Muscle Nerve.* 2010;42(2):276-282.
21. Crawford RW, Gie GA, Ling RS, Murray DW. Diagnostic value of intra-articular anaesthetic in primary osteoarthritis of the hip. *J Bone Joint Surg Br.* 1998;80(2):279-281.

22. Yoong P, Guirguis R, Darrah R, Wijeratna M, Porteous MJ. Evaluation of ultrasound-guided diagnostic local anaesthetic hip joint injection for osteoarthritis. *Skeletal Radiol.* 2012;41(8):981-985.
23. Kleiner JB, Thorne RP, Curd JG. The value of bupivicaine hip injection in the differentiation of coxarthrosis from lower extremity neuropathy. *J Rheumatol.* 1991;18(3):422-427.
24. Maldonado DR, Mu BH, Ornelas J, et al. Hip-Spine Syndrome: The Diagnostic Utility of Guided Intra-articular Hip Injections. *Orthopedics.* 2020;43(2):e65-e71.
25. Haldane CE, Ekhtiari S, de Sa D, Simunovic N, Ayeni OR. Preoperative physical examination and imaging of femoroacetabular impingement prior to hip arthroscopy-a systematic review. *J Hip Preserv Surg.* 2017;4(3):201-213.
26. Trigg SD, Schroeder JD, Hulsopple C. Femoroacetabular Impingement Syndrome. *Curr Sports Med Rep.* 2020;19(9):360-366.
27. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 2019;27(11):1578-1589.
28. Rees HW, Barba M. AAOS Clinical Practice Guideline: Management of Osteoarthritis of the Hip. *J Am Acad Orthop Surg.* 2020;28(7):e292-e294.
29. Piuzzi NS, Manner P, Levine B. American Academy of Orthopaedic Surgeons Appropriate Use Criteria: Management of Osteoarthritis of the Hip. *J Am Acad Orthop Surg.* 2018;26(20):e437-e441.
30. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis.* 2005;64(5):669-681.
31. Williamson OD. Measuring the success of joint replacement surgery. *Med J Aust.* 1999;171(5):229-230.
32. Kreiner DS, Shaffer WO, Baisden JL, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). *Spine J.* 2013;13(7):734-743.
33. Chan AK, Sharma V, Robinson LC, Mummaneni PV. Summary of Guidelines for the Treatment of Lumbar Spondylolisthesis. *Neurosurg Clin N Am.* 2019;30(3):353-364.
34. Mokhtar SA, McCombe PF, Williamson OD, Morgan MK, White GJ, Sears WR. Health-related quality of life: a comparison of outcomes after lumbar fusion for degenerative spondylolisthesis with large joint replacement surgery and population norms. *Spine J.* 2010;10(4):306-312.
35. Bohl WR, Steffee AD. Lumbar spinal stenosis. A cause of continued pain and disability in patients after total hip arthroplasty. *Spine (Phila Pa 1976).* 1979;4(2):168-173.
36. Parvizi J, Pour AE, Hillibrand A, Goldberg G, Sharkey PF, Rothman RH. Back pain and total hip arthroplasty: a prospective natural history study. *Clin Orthop Relat Res.* 2010;468(5):1325-1330.
37. Kwon BK, Elgafy H, Keynan O, et al. Progressive junctional kyphosis at the caudal end of lumbar instrumented fusion: etiology, predictors, and treatment. *Spine (Phila Pa 1976).* 2006;31(17):1943-1951.
38. Anderson PM, Arnholdt J, Rudert M. Total Hip Arthroplasty After Spinal Fusion Surgery. *Zeitschrift für Orthopädie und Unfallchirurgie.* 2020;158(03):333-341.
39. Sing DC, Barry JJ, Aguilar TU, et al. Prior Lumbar Spinal Arthrodesis Increases Risk of Prosthetic-Related Complication in Total Hip Arthroplasty. *J Arthroplasty.* 2016;31(9 Suppl):227-232 e221.
40. Buckland AJ, Vigdorchik J, Schwab FJ, et al. Acetabular Anteversion Changes Due to Spinal Deformity Correction: Bridging the Gap Between Hip and Spine Surgeons. *J Bone Joint Surg Am.* 2015;97(23):1913-1920.
41. Legaye J. Influence of the sagittal balance of the spine on the anterior pelvic plane and on the acetabular orientation. *Int Orthop.* 2009;33(6):1695-1700.
42. Zheng GQ, Zhang YG, Chen JY, Wang Y. Decision making regarding spinal osteotomy and total hip replacement for ankylosing spondylitis: experience with 28 patients. *Bone Joint J.* 2014;96-B(3):360-365.

Author Disclosures

R MacNeille: Nothing to disclose.
O Ramos: Nothing to disclose.
T Donaldson: Consulting: Zimmer/Biomet (not relevant to this manuscript, amount not disclosed at press time).
O Danisa: Board of Directors: Musculoskeletal Transplantation Foundation (B, Paid directly to institution/employer); Consulting: Spineart (B); Royalties: Globus Medical (E); Trips/Travel: American Board of Orthopaedic Surgeons (B).

Basivertebral Nerve Ablation: Pearls and Pitfalls

William D. Summers, MD
University of Colorado School of Medicine, Department of PM&R
Aurora, CO

Ryan Russell, BS
Rocky Vista University College of Osteopathic Medicine
Parker, CO

Eduardo J. Carrera, MD
University of Colorado School of Medicine, Department of PM&R
Aurora, CO

Gregory Moore, MD
Pacific Sports and Spine
Eugene, OR

Synopsis

Many potential pain generators can lead to chronic low back pain. Vertebrogenic pain—pain originating from the vertebra itself—has been successfully treated by basivertebral nerve ablation. This article reviews such a case treated with basivertebral nerve (BVN) ablation. The background, current evidence and a description of the procedure are discussed below. We also highlight common pearls and pitfalls of the procedure.

Case Description

A 46-year-old female with a history of depression and asthma presented with 17 months of axial low back pain. This pain began after a weightlifting injury and significantly worsened after a golfing injury three months later. She described the pain as a stabbing, sharp pain located along the lumbar spine at approximately the L5 spinous process, worse on the left. The pain was a 6/10 on average, and was worse with activity, bending forward, sneezing and coughing. The patient denied symptoms of radiculopathy or myelopathy.

Physical exam was remarkable for pain with lumbar flexion and rotation. Patient otherwise had a full spine range of motion, normal strength, sensation, reflexes and gait. Straight leg raise, SLUMP and Patrick's test were negative.

She had been evaluated by nonoperative spine specialists about six months after symptom onset. She had tried physical therapy, weight loss, Pilates, TENS, acupuncture, Tylenol and NSAIDs. None of these treatment modalities provided adequate pain relief. Work-up included lumbar X-ray and MRI remarkable for multilevel degenerative disc disease most severe at L5-S1, facet arthropathy at L4-5 and L5-S1, L4-5 annular tear with small L5-S1 disc extrusion, and significant Modic changes at the L5-S1 endplates (**Figure 1**).

The patient underwent several procedures with the referring provider, including interlaminar epidural steroid injection (ILESI), transforaminal epidural steroid injection (TFESI), medial branch blocks (MBB), intradiscal injections with platelet-rich plasma (PRP) and iliolumbar ligament injections. None of these procedures provided significant long-term relief, though the L5-S1 ILESI and the L4-5, L5-S1 intradiscal PRP did provide some short-term relief. At the time, the decision was made to proceed with an L5-S1 BVN ablation and the patient was referred for the procedure.

The procedure was performed 22 months after the onset of her low back pain. There were no procedure-related complications. The patient reported 80%-85% pain relief at the two-week follow-up visit. She described near-resolution of the stabbing, sharp pain two days after the procedure. Eighteen months after the procedure, she had over 90% improvement in her pain and is now actively training and participating in triathlons, mountain biking and golfing.

Discussion

Chronic low back pain affects up to 13% of the US population. Determining a diagnosis or etiology is difficult, leading to heterogeneity in treatment and outcomes.[1] Vertebrogenic pain appears to be mediated via the BVN. The BVN is a branch of the sinuvertebral nerve that enters the vertebral body via the basivertebral foramen, bifurcates at the terminus and arborizes at the endplates. The BVN is nociceptive, enervating the endplates of vertebral bodies[2] (**Figure 2A**). The basivertebral foramen can commonly be seen on lateral

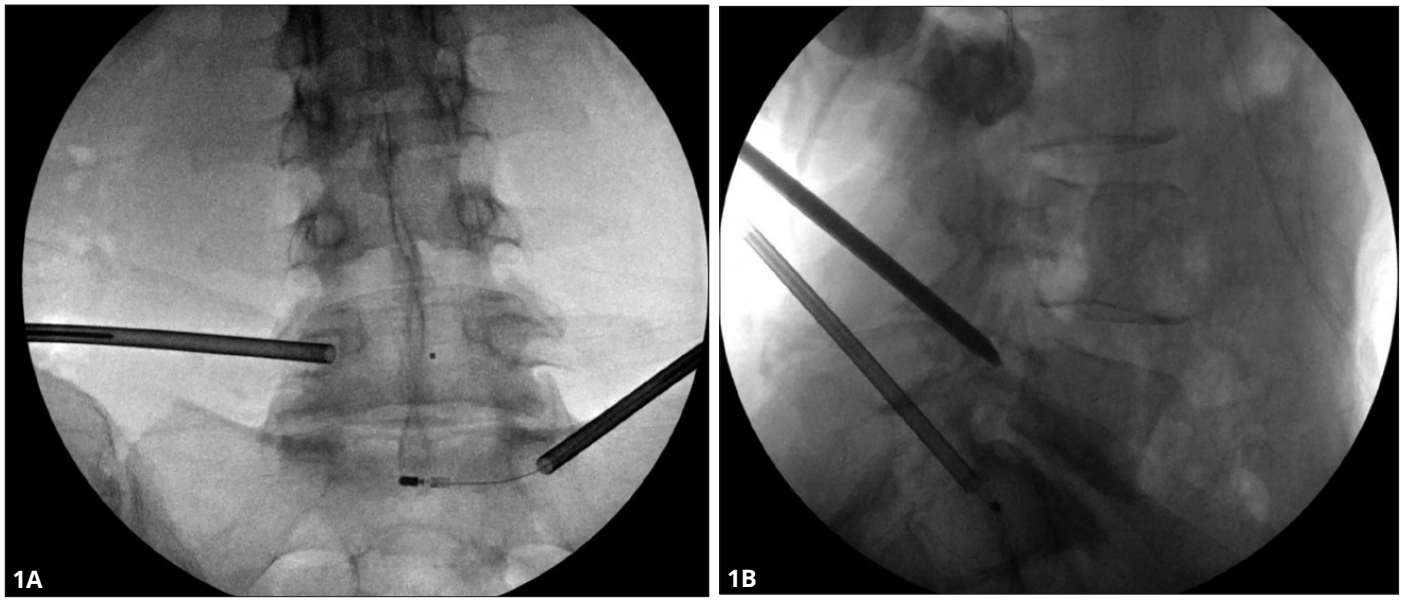


Figure 1A: AP fluoroscopic view of introducer cannulas on left L5 pedicle and right S1 pedicle. Radiofrequency probe at S1 directed at the midline of the vertebral body. **1B:** Lateral fluoroscopic view of introducer cannulas at L5 and at S1, with radiofrequency probe directed to 30%-50% from posterior margin of vertebral body.

lumbar MRI imaging (**Figure 2B**). Endplate damage can trigger chronic inflammation and nerve proliferation, leading to Modic changes seen on MRI and chronic low back pain.[3]

Modic changes are abnormal signals in vertebral bodies adjacent to discs. Type 1 Modic changes are hypointense on T1-weighted and hyperintense on T2-weighted MRI sequences. Type 1 Modic changes represent inflammation and are a marker of endplate disruption. Type 2 Modic changes are hyperintense on both T1 and T2 sequences. Type 2 Modic changes represent fatty infiltration and occur after the acute inflammatory process. Type 3 Modic changes are hypointense in both T1 and T2 sequences. Type 3 Modic changes represent sclerosis of the vertebral body. Type 1 and 2 Modic changes are a marker of back pain with a low sensitivity (0.24) but high specificity (0.83). Furthermore, with a likelihood ratio of 3.4 at identifying the source of pain, MRI offers 69% diagnostic confidence. MRI could offer an alternative to discography, which carries risks such as discitis, disc herniation and possible accelerated degeneration.[4]

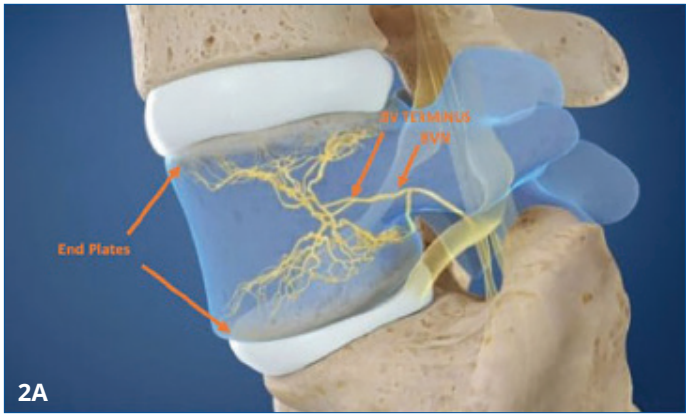
The SMART study was a randomized controlled trial comparing BVN ablation to sham. After three months, there was a statistically greater improvement in the primary outcome of Oswestry Disability Index (ODI) in the BVN arm (20.5 points) compared to sham arm (15.2 point) in the per treatment protocol. There was a statistically significant difference in VAS between the two groups at six and 12 months, but not at three months. There was no difference in ODI between the two groups at six and 12 months.[5] On two-year follow-up of the treatment arm, 76.4% of BVN ablation patients had a ≥10-point ODI improvement, 57.5% had a ≥20-point ODI improvement, and 70.2% had a ≥1.5 cm VAS improvement. On five-year follow-up of the treatment arm, 77% had ≥15-point ODI improvement; 88% had ≥2-point VAS improvement.[6]

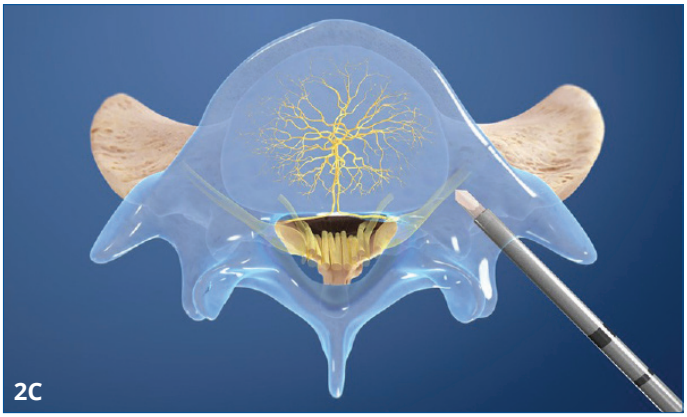
The Intracept trial was a prospective, randomized, controlled, open-label trial examining BVN ablation versus continuation of standard care. At three months, there was a statistically significant difference in the primary outcome of mean ODI (-25.3 vs -4.4), with 74.5% achieving >10-point improvement in ODI compared to 32.7% in the standard care arm. There was also statistically significant reduction in VAS (-3.46 vs -1.02). Given the large difference in treatment response, this study offered crossover to the standard of care group at three months.[7]

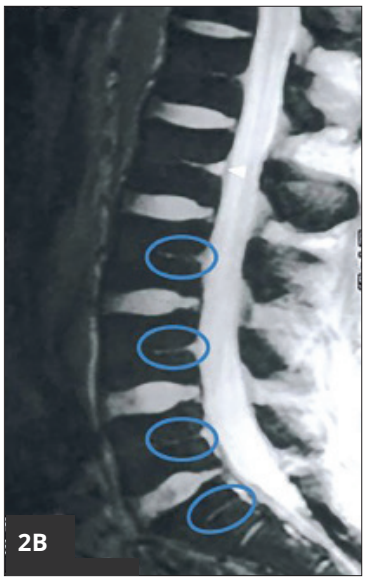
Patient Selection

Patient selection for BVN ablation can be challenging due to a lack of specific physical exam findings that can differentiate vertebrogenic pain from other causes of chronic low back pain. However, the SMART and Intracept trials support prior research that Modic changes act as a marker for vertebrogenic pain. A "typical" BVN ablation candidate may present with unexplained chronic discogenic-like low back pain in addition to Type 1 or 2 Modic changes on MRI.

While the trial of other interventions often occurs prior to BVN ablation, failure of these methods is not required to diagnose and treat vertebrogenic back pain. Patients with Type 1 or 2 Modic changes at L3-S1 and ≥6 months of chronic low back pain who have failed conservative management are candidates for the procedure. Notably, the studies had extensive exclusion criteria, including but not limited to BMI>40, component of radicular pain, previous lumbar spine surgery (discectomy/laminectomy allowed in later studies), symptomatic spinal stenosis, diagnosed osteoporosis, disc extrusion or protrusion >5 mm, spondylolisthesis, significant depression, infection, addiction behaviors, compensated injury and litigation.[5,7]







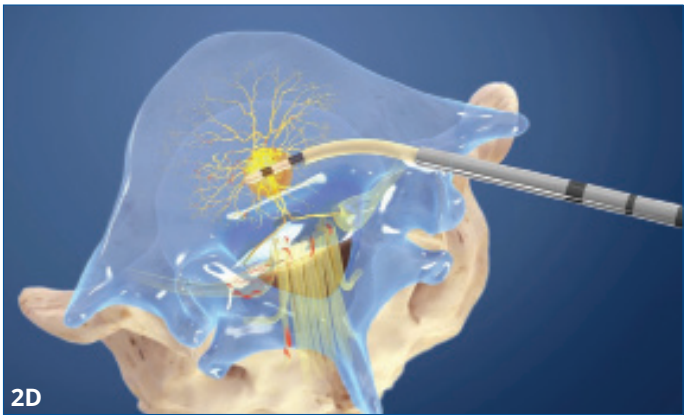


Figure 2A. Anatomy of basivertebral nerve (BVN). Note the bifurcation of the nerve at the terminus. The terminus is located in the posterior one-third of the vertebral body and is the target for ablation proximal to the sprouting of nerves that supply the endplates. **Figure 2B.** Lateral MRI, view of basivertebral nerve foramen (circles). **Figure 2C.** Introducer trocar shown being advanced through the pedicle until it breaches the posterior vertebral wall. **Figure 2D.** Replacement of the introducer trocar shown being replaced with a smaller curved cannula to facilitate a path to the basivertebral nerve ablation.

Technique

This procedure is performed with the patient prone under general anesthesia or conscious sedation. Using a unilateral approach, the introducer cannula is advanced through the pedicle under fluoroscopic guidance until the introducer trocar breaches the posterior vertebral wall (**Figure 2C**). The trocar is then replaced with the smaller curved cannula/nitinol stylet to facilitate a curved path to the BVN terminus (**Figure 2D**). Once the BVN terminus is reached, the stylet is removed and replaced with the radiofrequency (RF) probe. This position is confirmed under AP and lateral views (**Figure 3**). Ablation is performed for 15 minutes at a constant 85°C creating a 1cm spherical lesion within the vertebral body.

Some procedural pearls worth noting:

- A more lateral approach to arrive more medially may provide greater ease of access to the posterior one-third of the vertebral body rather than trying to manipulate the curved cannula to make an early trajectory change to reach the same point. However, an excessively lateral approach may increase the rare risk of a psoas hematoma, as noted in the SMART trial.
- Once inside the pedicle, instead of entering the cortex entirely with the trocar, breach the posterior wall of the cortex and remove the stylet. There is a 10mm safety margin profile for the device.
- Consider variations in bone density between patients when advancing and manipulating the cannula. Maintaining the cannula position can often be more challenging in patients with decreased bone density. Careful considerations are prudent for this population as these were excluded from the SMART and Intracept trials.
- Ablation prior to reaching the BVN terminus may be more beneficial as this will result in a larger nerve bundle eradication.
- When performing BVN ablation on multiple levels, move caudad to cephalad, while transitioning to the contralateral side at ascending levels to avoid fighting against the RF probes already placed, and improve efficiency of the procedure. This is demonstrated in **Figure 2**.

Logistics

BVN ablation does not have a dedicated Current Procedural Terminology (CPT) code and thus requires the use of an

"unlisted procedure, spine" code for billing. The use of Relievant's Patient Access Program can be helpful for getting patients covered.

When performing BVN ablation under general anesthesia, plan for a total procedural time of 45 to 90 minutes depending on the number of levels being treated. Intravenous antibiotics are administered within 30 minutes of the procedure.

Adverse Events

Reported adverse events of BVN ablation have generally been mild and transient in nature. More common events include limited new-onset leg or back pain and transient sensory or motor deficits. Less common events include one case of retroperitoneal hemorrhage and procedure-related complications including incisional pain, urinary retention, corneal abrasion, incisional infection and lateral femoral cutaneous neurapraxia. One compression fracture was reported in the SMART trial in a sham-controlled patient who was later diagnosed with osteopenia on high-dose estrogen therapy. The fracture resolved spontaneously in eight weeks. Otherwise, no serious adverse events were reported at 12-month or five-year follow-up in the Intracept and SMART trials, respectively.[8]

Conclusions

BVN ablation offers a promising and effective treatment for some patients with lumbar vertebrogenic pain with Modic Type 1 or 2 endplate changes. Trials have proven its efficacy and durability for pain relief with improved function and safety up to five years post-procedure. We have described a patient case successfully treated with BVN ablation after failing multiple other treatment modalities and injections. Careful patient selection can improve the chance of therapeutic success. We have provided tips and considerations to optimize care for these individuals.

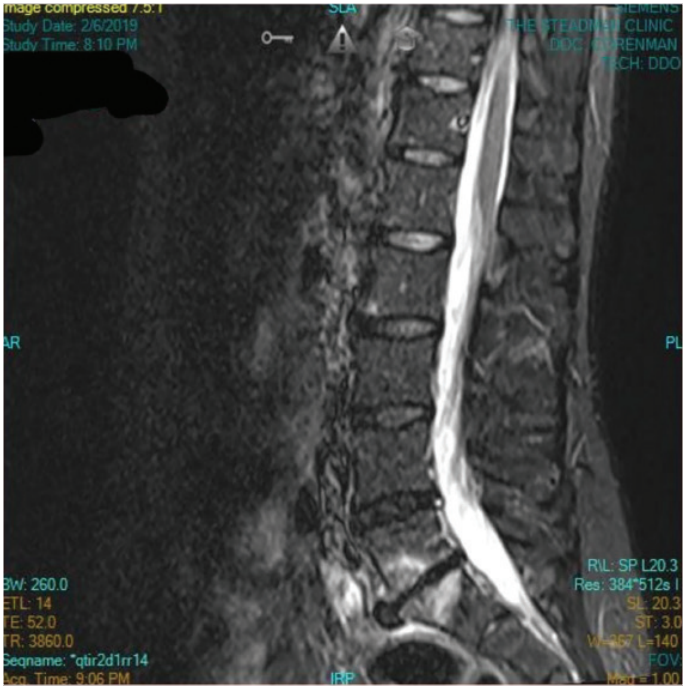


Figure 3. Sagittal Lumbar MRI with STIRsequence. L5 inferior vertebral endplate and S1 superior vertebral endplates are hyperintense, consistent with endplate edema. Disc degeneration of L5-S1 disc. No spinal canal stenosis is visible at these levels.

Acknowledgements

The authors thank Dr. Dustin Anderson for his guidance and manuscript review.

References

1. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med.* 2009;169(3):251-8.
2. Fras C, Kravetz P, Mody DR, Heggeness MH. Substance P-containing nerves within the human vertebral body: an immunohistochemical study of the basivertebral nerve. *Spine J.* 2003 Jan-Feb;3(1):63-7.
3. Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral endplate in low back pain. *Global Spine J.* 2013;3(3):153-64.
4. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: state-of-the-art review. *Pain Med.* 2013;14(6):813-36.
5. Fischgrund, JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 2-year results from a prospective randomized double-blind sham-controlled multicenter study. *Int J Spine Surg.* 2019;13(2)110-119.
6. Fischgrund JS, Rhyne A, Macadaeg K, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J.* 2020;29(8):1925-1934.
7. Khalil JG, Smuck M, Koreckij T, et al. INTRACEPT Trial Investigators. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain. *Spine J.* 2019;19(10):1620-1632.
8. Smuck M, Khalil J, Barrette K, et al. Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results. *Reg Anesth Pain Med.* Published online May 23, 2021. doi:10.1136/rapm-2020-102259.

Author Disclosures

W Summers: Nothing to disclose.
R Russell: Nothing to disclose.
E Carrera: Nothing to disclose.
G Moore: Research Support (Staff and/or materials): Abbott (E, Paid directly to institution/employer), Boston Scientific (G, Paid directly to institution/employer), Relievant (D, Paid directly to institution/employer).

Achieving Value and Effectiveness through ~~a Multidisciplinary~~ an Interdisciplinary Approach to Spine Care

Edward Dohring, MD
President, North American Spine Society
Spine Institute of Arizona
Phoenix, AZ

One of the highlights of being involved in NASS has been exposure to a myriad of approaches to diagnose and treat spine-related problems.

Although predominantly populated by surgeons, one of NASS' main strengths is the multidisciplinary nature of our membership and leadership. This diversity is important in many ways. For example, NASS has considerable credibility with government regulatory agencies and third-party payors because of this breadth of interest, advocating for high-quality patient care that is not limited to a single approach or specialty, but inclusive of many different approaches to spine care.

Indeed, our mission statement includes the term "multidisciplinary." What exactly does that term imply?

NASS Mission Statement

NASS is a global multidisciplinary medical organization dedicated to fostering the highest quality, ethical, value-based and evidence-based spine care through education, research and advocacy.

Interestingly, there is an entire field of study focused on understanding how specialists with different educational backgrounds and expertise can best work together. It turns out that optimal patient care may best be achieved through an interdisciplinary or even transdisciplinary approach, as opposed to a multidisciplinary approach.

Per the experts in this field, the term **multidisciplinary** refers to team members from different specialties working together, but in a manner where each subspecialist only conceptualizes within his/her discipline, really a rather siloed approach. An example would be recommending patient care solutions based on each individual's expertise, and then comparing solutions and choosing the specialty-specific solution as a team; for example, the next step in care being physical therapy (PT) vs injections vs surgery, etc. "Each rock star tries to convince everyone else what the team should do." (Sean Newman Maroni, 2015)

The term **interdisciplinary** refers to team members integrating their expertise and perspectives into a unified plan, taking into account feedback loops between different specialties. An example: discussing individual patient cases and creating a multipronged algorithmic diagnosis and treatment plan for each patient, which might include two or more specialties providing care at once, eg, simultaneous medication and PT and patient education, incorporating injections and cognitive behavioral therapy as needed. In the event that a particular patient remains symptomatic after the initial treatment and goes onto surgery, an integrated postop regimen then follows.

The term **transdisciplinary** implies the inclusion of extra-academic perspectives into patient care, emphasizing the experiential knowledge and values/interests of each individual patient. An example: formally involving the individual patient's work, life goals and cultural expectations in all treatment decision-making.

The experts in this field take things even further as shown in **Figure 1**.

Within spine care, any integration of subspecialties is of great benefit to our patients, and our goal should always be to take into account patient-specific values and needs. The reality of spine care, however, is that true transdisciplinary or even interdisciplinary care is uncommon.

Most surgical and nonsurgical spine and pain specialists traditionally work

in silos: neurosurgeons, orthopedic spine surgeons, anesthesiologists and physiatrists/pain physicians, neurologists, PTs, chiropractors and psychologists all work separately, speaking their own languages, and making diagnoses and treatment choices wholly within their specialty. In some communities, specialists are even business competitors. As specialists, we are largely the product of our subspecialty training and experience, and often do not truly understand other approaches to patient care.

This leads to a profession-centric instead of a patient-centric approach to care. Under this silo model, patient care often depends completely on the background of whichever provider they saw first. This approach has many disadvantages, especially if used to diagnose and treat pain emanating from the spine, which can be caused by anatomical, mechanical, physiological factors, and psychosocial factors. With this silo model, cross-referral primarily occurs when a specific subspecialty approach has little to offer, or the treatment has failed.

No one likes poor outcomes. An awareness of the disadvantages of this "silo" approach has led to the creation of multidisciplinary spine clinics with algorithmic care models, such as a clinic in Italy (**Figure 2**).

Unfortunately, evidence-based studies of interdisciplinary care to guide us toward the best spine care outcomes with the greatest value are scarce. There is quite a bit of research on interdisciplinary models of care for chronic pain and for return-to-work after episodes of surgical and nonsurgical treatment for spine pain, but very little assessment of spine care itself.

Indeed, most multidisciplinary spine care papers only look at sequential unidisciplinary models of care. These papers do show that integrated sequential unidisciplinary care models—indistinguishable from what is commonly referred to as multidisciplinary care—speed up referrals to appropriate specialists, hasten appropriate diagnostic studies and treat-

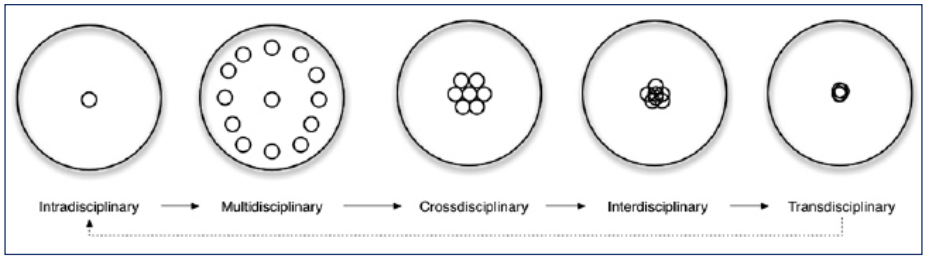


Figure 1. Disciplinarities: Intra, Multi, Cross, Inter, Trans
Source: Alexander Refsum Jensenius. Disciplinarities: intra, cross, multi, inter, trans. March 12, 2012. Available at: https://www.arj.no/2012/03/12/disciplinarities-2/. Adapted from Zeigler 1990.

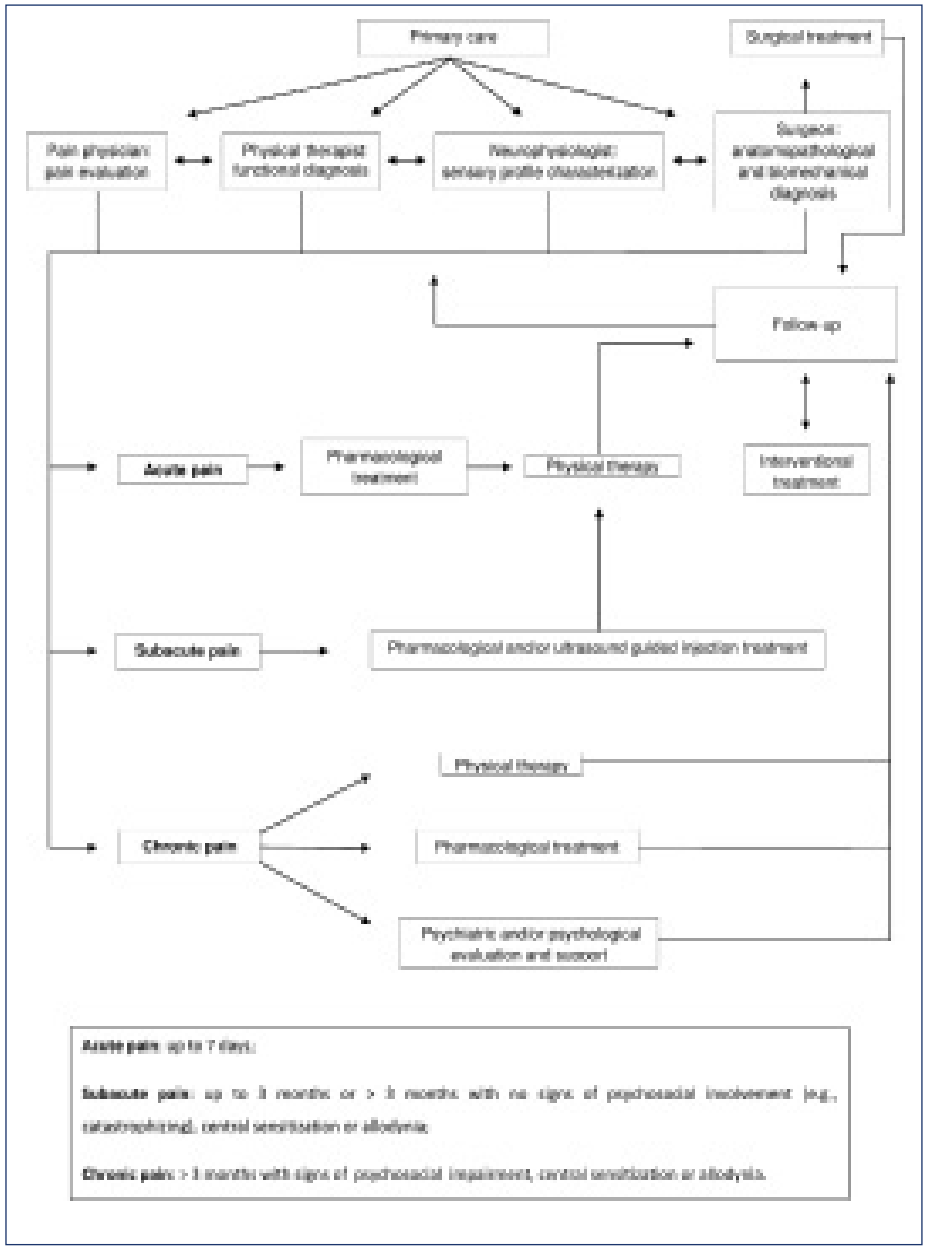


Figure 2. Flowchart for multidisciplinary pain management in a spine center.
Source: Sindaco G, et al. Letter to the editor: The development of a multidisciplinary spine center: a new shared approach for pain care. *Pain Practice.* 2017;17(2):281-283. (CC By-NA-ND 4.0)

ments, reduce the number of nonsurgical patients evaluated by surgeons (a nice benefit!) and reduce the number of surgeries performed, and thus the number of failed spine surgeries. However, this model does not harness the true potential of an interdisciplinary care team.

A few papers have looked at what the experts would call an interdisciplinary approach, and the results are intriguing. Clinical care in the interdisciplinary models usually decreases surgical rates, by as much as 50%, with simultaneous increase in treatment by PT and injections, resulting in fewer failed surgeries and an overall reduction in costs of care. Perhaps even more intriguing, a few studies have looked at incorporating cognitive behavioral therapy into pre– and postoperative care protocols, with distinct improvements in surgical outcomes.

Government and private payors are attracted to predictable patient outcomes and costs for care, especially expensive surgical care. The result: new payment models using "clinical outcome report cards" (vetting performance), and introducing outcomes-based financial risk for health care providers are being introduced.

The future of spine care will depend more and more on optimizing value and on minimizing financial risk. These improvements will be achieved by replacing "silo" cross-referral multidisciplinary models in favor of interdisciplinary team models: surgeons, interventionalists, physiatrists (PMR), neurologists, PTs/DCs and psychologists working together to optimize treatment decision-making to avoid poor outcomes and to provide patients with tools to optimize their personally-valued outcome.

Bringing different specialists together improves the patient experience and creates value: it encourages communication and collaboration between health care professionals to achieve the best outcomes possible, at the lowest cost. And it reduces the burden on patients because they don't need to make multiple trips to multiple appointments weeks apart to see various specialists and obtain different specialty opinions.

Hopefully, we will see the creation of more pilot models of interdisciplinary spine care and more funding directed toward interdisciplinary spine care outcome studies.

What specialist wouldn't want to see fewer patients who have failed their intervention?

What specialist wouldn't want to have a clinic full of satisfied patients?

The future is in our hands.

Suggested Reading List and Notes

"Multidisciplinary" Unidisciplinary Sequential Spine Clinic: Effect on Surgical Indications and Rates, Effect on Treatment Times

Rasmussen C, Nielsen GL, Hansen VK, Jensen OK, Schioettz-Christensen. Rates of lumbar disc surgery before and after implementation of multidisciplinary nonsurgical spine clinics. *Spine.* 2005;30(21):2469-2473.

- Patients with sciatica of 1-3 months' duration
- Annual lumbar disc operations decreased from approximately 60 to 80 per 100,000 to 40 per 100,000 (P = 0.00)

Longo M, Gelfand YJ, Gitkind AI, Yassari R, Yanamadal V. Multidisciplinary spine clinic model significantly reduces lead times for appropriate specialist visit and appropriate intervention in an underserved population: a case control pilot study. *Neurosurgery.* 2019;66(S1). https://doi.org/10.1093/neuros/nyz310_401

- Time to pain specialist visit was reduced by 45 days (P < .001)
- Time to Intervention was reduced by 60 days (P = .007)

Wilgenbusch CS, Wu AS, Fourney DR. Triage of spine surgery referrals through a multidisciplinary care pathway: a value-based comparison with conventional referral processes. *Spine.* 2014;39(22S):S129-S135.

Wu A, Liu L, Fourney DR. Does a multidisciplinary triage pathway facilitate better outcomes after spine surgery? *Spine.* 2021;46(5):322-328.

- Wait times for MRI (16.8 vs 63.0 days, P < 0.001), and for specialist appointment were shorter
- Patients more likely to trial nonoperative treatments
- Patients referred for surgery more likely to be surgical (60% vs 38%)
- Surgical patient satisfaction higher if they used SSP pathway
- Overall surgical outcomes similar

Interdisciplinary

Yanamadala V, Kim Y, Buchlak, QD, et al. Multidisciplinary evaluation leads to decreased utilization of lumbar fusion. *Spine.* 2017;42(17):E1016-E1023(8)

- Multidisciplinary conference: physiatrists, anesthesiologists, pain specialists, neurosurgeons, orthopaedic spine surgeons, physical therapists and nursing staff.
- 100 patients with prior spinal surgery, all proposed for further surgery by outside surgeons:
  - Nonoperative management 58/100 patients (58%) (χ^2 = 26.6; P < 0.01).
  - Surgical plan revised 16/42 patients (28%) (χ^2 = 43.6; P < 0.01)
    - More diverse nonoperative treatment options

Benton J, Weiss BS, Longa M, et al. A multidisciplinary spine clinic reduces spine surgery utilization. *Spine J.* 2020;20(9S): S173.

Benton J, Weiss B, Longo M. Surgical utilization rates and timing of care in a multidisciplinary spine clinic versus a unidisciplinary spine clinic setting. *Neurosurgery.* 2020;67(S1):nyaa447_112. Available at: https://doi.org/10.1093/neuros/nyaa447_112.

- Unidisciplinary neurosurgery spine clinic vs multidisciplinary spine clinic: neurosurgery, orthopedics, interventional pain medicine and physiatry
- 853 outpatients, 397 patients USC & 456 at the MSC
- USC: surgery 23%, PT 13%, injection 12%
- MSC: surgery 11%, PT 23%, injection 17%

- Multidisciplinary clinic visits reduce recommendations for surgical intervention by 50%, increased recommendations for PT & injections
- Same research group: shorter time to injection: 21 vs 32 days

Naidu I, Videlefsky, Ryvlin J. The effect of a multidisciplinary spine clinic on treatment rates and lead times to care. *Spine J.* 2021;21(9S):S102.

Monticone M, Ferrante S, Teli M, et al. Management of catastrophizing and kinesiophobia improves rehabilitation after fusion for lumbar spondylolisthesis and stenosis. A randomized controlled trial. *Eur Spine J.* 2014:23(2)87-94.

Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *BMJ.* 2015;350:h444.

- Behavioral intervention might be more beneficial than an exercise intervention.

Further Reading on Multidisciplinary/Interdisciplinary Care

Maroni, Sean Newman. Interdisciplinary is not multidisciplinary. Aug 22, 2015. Available at: https://seannewmanmaroni.medium.com/interdisciplinary-verses-multidisciplinary-40024faafeee

Rick Szostak/Association for Interdisciplinary Studies. Available at: https://interdisciplinarystudies.org/

Machiel Keestra/Institute for Interdisciplinary Studies. Available at: https://iis.uva.nl/en

Menken S, Keestra M, Rutting L (eds), et al. *An Introduction to Interdisciplinary Research: Theory & Practice.* Amsterdam Universit Press; 2016. Available at: https://philpapers.org/rec/MENAIT-4

ELSEVIER

The SPINE JOURNAL

The Spine Journal 22 (2022) 8–18

2021 Outstanding Paper Award Winner

The effect of ketorolac on posterior minimally invasive transforaminal lumbar interbody fusion: an interim analysis from a randomized, double-blinded, placebo-controlled trial

Chad F. Claus, DO[a,*], Evan Lytle, DO[a], Michael Lawless, DO[a], Doris Tong, MD[a], Diana Sigler, RPh[b], Lucas Garmo, BS[a], Dejan Slavnic, DO[a], Jacob Jasinski, DO[a], Robert W. McCabe, DO[a], Ascher Kaufmann, MD[a], Gustavo Anton, DO[a], Elise Yoon, DO[a], Ammar Alsalahi, MD[a], Karl Kado, MD[c], Peter Bono, DO[a], Daniel A. Carr, DO[a], Prashant Kelkar, DO[a], Clifford Houseman, DO[a], Boyd Richards, DO[a], Teck M. Soo, MD[a]

[a] *Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine, Southfield, MI, USA*

[b] *Department of Pharmacy, Ascension Providence Hospital, Southfield, MI, USA*

[c] *Division of Neuroradiology, Department of Radiology, Ascension Providence Hospital, Michigan State University, College of Human Medicine, Southfield, MI, USA*

Received 25 January 2021; revised 25 August 2021; accepted 30 August 2021

Abstract

BACKGROUND CONTEXT: Postoperative pain control following posterior lumbar fusion continues to be challenging and often requires high doses of opioids for pain relief. The use of ketorolac in spinal fusion is limited due to the risk of pseudarthrosis. However, recent literature suggests it may not affect fusion rates with short-term use and low doses.

PURPOSE: We sought to demonstrate noninferiority regarding fusion rates in patients who received ketorolac after undergoing minimally invasive (MIS) posterior lumbar interbody fusion. Additionally, we sought to demonstrate ketorolac's opioid-sparing effect on analgesia in the immediate postoperative period.

STUDY DESIGN/SETTING: This is a prospective, randomized, double-blinded, placebo-controlled trial. We are reporting our interim analysis.

PATIENT SAMPLE: Adults with degenerative spinal conditions eligible to undergo a one to three-level MIS transforaminal lumbar interbody fusion (TLIF).

OUTCOME MEASURES: Six-month and 1-year radiographic fusion as determined by Suk criteria, postoperative opioid consumption as measured by intravenous milligram morphine equivalent, length of stay, and drug-related complications. Self-reported and functional measures include validated visual analog scale, short-form 12, and Oswestry Disability Index.

METHODS: A double-blinded, randomized placebo-controlled, noninferiority trial of patients undergoing 1- to 3-level MIS TLIF was performed with bone morphogenetic protein (BMP). Patients were randomized to receive a 48-hour scheduled treatment of either intravenous ketorolac (15 mg every 6 hours) or saline in addition to a standardized pain regimen. The primary outcome was fusion. Secondary outcomes included 48-hour and total postoperative opioid use demonstrated as milligram morphine equivalence, pain scores, length of stay (LOS), and quality-of-life

FDA device/drug status: Not applicable.

Author disclosures: ***CFC***: Nothing to disclose. ***EL***: Nothing to disclose. ***ML***: Nothing to disclose. ***DT***: Nothing to disclose. ***DS***: Nothing to disclose. ***LG***: Nothing to disclose. ***DS***: Nothing to disclose. ***JJ***: Nothing to disclose. ***RWM***: Nothing to disclose. ***AK***: Nothing to disclose. ***GA***: Nothing to disclose. ***EY***: Nothing to disclose. ***AA***: Nothing to disclose. ***KK***: Nothing to disclose. ***PB***: Nothing to disclose. ***DAC***: Nothing to disclose. ***PK***: Nothing to disclose. ***CH***: Nothing to disclose. ***BR***: Nothing to disclose. ***TMS***: Nothing to disclose.

*Corresponding author. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine, 16001 W Nine Mile Rd, Southfield, MI 48075, USA.

E-mail address: chadfclaus@gmail.com (C.F. Claus).

https://doi.org/10.1016/j.spinee.2021.08.011

outcomes. Univariate analyses were performed. The present study provides results from a planned interim analysis.
RESULTS: Two hundred and forty-six patients were analyzed per protocol. Patient characteristics were comparable between the groups. There was no significant difference in 1-year fusion rates between the two treatments (p=.53). The difference in proportion of solid fusion between the ketorolac and placebo groups did not reach inferiority (p=.072, 95% confidence interval, -.07 to .21). There was a significant reduction in total/48-hour mean opioid consumption (p<.001) and LOS (p=.001) for the ketorolac group while demonstrating equivalent mean pain scores in 48 hours postoperative (p=.20). There was no significant difference in rates of perioperative complications.
CONCLUSIONS: Short-term use of low-dose ketorolac in patients who have undergone MIS TLIF with BMP demonstrated noninferior fusion rates. Ketorolac safely demonstrated a significant reduction in postoperative opioid use and LOS while maintaining equivalent postoperative pain control.

Keywords: Ketorolac; Lumbar fusion; Minimally invasive surgery; NSAIDs; Opioids; Patient-reported outcomes; Pseudarthrosis; Transforaminal lumbar interbody fusion

Introduction

Posterior lumbar fusion remains one of the most common spinal procedures performed today [1]. Postoperative pain control following posterior lumbar fusion continues to be challenging and often requires high doses of opioids for pain relief. However, opioid analgesia is associated with significant adverse effects such as nausea, vomiting, urinary retention, and respiratory depression. Additionally, patients remain at high risk for continued postoperative opioid use [2]. Studies have demonstrated the use of opioids for acute postoperative pain as an unintended gateway to long-term opioid addiction [3]. As the opioid epidemic continues throughout the United States, strategies to combat and limit opioid use following spinal surgery remain a tremendous public health priority. Ketorolac, a nonsteroidal anti-inflammatory (NSAID) with a well-described opioid-sparing effect, has been used as an effective analgesic for postoperative pain control [4–8]. Yet, historically, NSAID use has been avoided due to concerns related to intraoperative and postoperative bleeding, as well as platelet aggregation inhibition [9]. More importantly, ketorolac has been shown to decrease osteogenesis and inhibit spinal fusion in adults [10–16]. However, these adverse effects may be type-specific, dose, or duration-dependent [12–19]. A recent meta-analysis of retrospective studies demonstrated that ketorolac was associated with pseudarthrosis in adults only when administered for >2 days and/or at a dose of ≥120 mg/d [20]. To date, there has been no randomized controlled trial to evaluate the safety and efficacy of the use of ketorolac following posterior spinal fusion. As spine surgery practice adopts a more patient-centric approach involving patient-reported outcomes, treatment paradigms such as enhanced recovery after surgery (ERAS) protocols have, in large part, continued to limit the use of NSAIDs despite their ostensible benefit [21]. The option to include NSAIDs such as ketorolac in these protocols would prove valuable in the continuing improvement of such protocols. In this randomized, double-blind, noninferiority trial, we aimed to evaluate the early and long-term effects of ketorolac on patients undergoing minimally invasive (MIS) transforaminal lumbar interbody fusion (TLIF) with bone morphogenetic protein (BMP), namely its opioid-sparing effect on postoperative analgesia and effect on fusion, respectively.

Here, we describe the results of our interim 1-year analysis involving 292 patients.

Methods

This is a randomized, double-blind, placebo-controlled, noninferiority trial involving the use of ketorolac for postoperative analgesia for patients who have undergone elective, minimally invasive TLIF with BMP. The study is continuing enrollment. The interim analysis described here involved the first 292 patients enrolled and was conducted to assess ketorolac's safety and efficacy as our recruitment reaches its 50% benchmark. The trial's prespecified endpoints are planned to be reported at trial completion. The data cutoff for this interim analysis was July 2020.

Patients

Following Institutional Review Board approval, consecutive patients scheduled to undergo elective lumbar spinal fusion using a minimally invasive TLIF technique between October 2017 and July 2020 were screened for eligibility. Inclusion criteria were as follows: age 18 and above, elective posterior minimally invasive lumbar fusion, three or fewer levels, use of BMP for the interbody fusion, and consent to participate in the study. The exclusion criteria were: patients with a history of drug-seeking behavior or chemical addiction currently dependent requiring treatment or use, creatinine level greater than 1.5 mg/dL, history of coagulopathy, active tobacco smoker or history in the past 6 weeks, revision of fusion at operative level(s), history of autoimmune/rheumatological condition, oral-systemic steroid use for greater than or equal to 1 week in the last 1 month, auto/workers' compensation-related injury, traumatic pathology at operative level, infection at operative level(s), tumor at operative level(s), patients on

chemotherapeutic agents in the last 6 months, patients who have a history of allergy to ketorolac, history of liver impairment/failure, or uncontrolled cardiovascular disease. All patients included in the study gave written informed consent.

Study design, intervention, randomization, and blinding

This was a randomized, double-blinded, placebo-controlled, noninferiority trial drafted in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines. The study was carried out in secondary and tertiary care settings. The study was funded by the institution's research department and conducted according to the declaration of Helsinki [22], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice [23], and registered at http://www.clinicaltrials.gov (Identifier NCT03278691). CONSORT 2017 guidelines, including the noninferiority extension [24], were used in reporting. The complete study protocol was previously published [25].

This study implemented a two-arm parallel design without crossover with equal randomization per arm. On the day of surgery, patients were randomized with a centralized treatment allocation mechanism and block randomization to ensure the two arms achieve an equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians were blinded to the allocation. Blinding was achieved by concealment of allocation sequence to personnel involved in the enrollment, care, and evaluation of the patient. Each patient received a standardized general anesthesia protocol. Using a standardized surgical technique, the patients underwent a minimally invasive lumbar instrumented interbody fusion using a tubular retractor system for the facetectomy, discectomy, and interbody cage placement. The interbody cage was augmented with locally harvested autograft, cancellous chip allograft, and the minimally effective dose of rhBMP-2 (1.05 mg/level) [26]. The interbody fusion was further supported by percutaneous pedicle screw fixation. Postoperatively, each patient received a standardized analgesic regimen, in addition to their treatment allocation in which the treatment patients received 15 mg (1 mL) of intravenous ketorolac while the control patients received 1 mL of normal saline every 6 hours for 48 hours postoperative (see Supplementary Appendix). While in the hospital, the patients were evaluated daily at 4-hour intervals for any major adverse events, specifically gastrointestinal bleeding, postoperative wound or spinal hematoma, and acute kidney injury (AKI), as defined as an increase in Cr >50% from baseline. Strict trial monitoring and quality control were followed. A data safety monitoring board was established.

Outcome assessment

Our prior protocol mandated that all patients were evaluated at 6-month and 1-year postoperative follow-up visits for the primary fusion outcome by a combination of clinical symptoms and radiographic images, and for secondary outcomes by standardized and validated questionnaires. We evaluated radiographic fusion independently at each interspace. Fusion was determined by two blinded independent neuroradiologists using a combination of static and dynamic anterior-posterior and lateral x-rays (XRs). The Suk diagnostic criteria were used to establish fusion [27,28]. In symptomatic patients with inconclusive or positive XR images, computed tomography (CT) was then used to evaluate fusion using the Christensen criteria and guide clinical management [28]. Those patients assessed at 1 year who were determined to have nonunion had additional follow-up to further evaluate fusion status up to 2 years following their surgery date. The COVID-19 pandemic presented a unique challenge in collecting timely radiographic follow-up. To minimize “lost to follow-up” due to the impact of COVID-19, the follow-up period was extended to 2 years for all patients whose 6-month follow-up dates were supposed to occur after March 2020.

Secondary outcomes included 48-hour and total opioid use during hospitalization recorded as intravenous milligram morphine equivalence (MME), length of stay, pain intensity measured through the visual analog scale (VAS), and patient-reported outcomes (PROs). Pain was assessed every 6 hours following surgery until the discontinuation of the study medication/placebo. PROs were collected via the 12-item short-form, Oswestry Disability Index, at baseline and postoperative intervals (6-months, 1-year, and 2-year).

Statistical analysis

Using clinically and statistically important differences in fusion rate, a noninferiority margin was determined as -0.15. Noninferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) for the difference in fusion rate exceeded -0.15. The sample size of 300 fusion levels per arm was estimated to be sufficient (with a two-sided 95% CI and 95% power) to detect inferiority.

The comparability of the two groups baseline characteristics (age, sex, body-mass index, diabetes mellitus, specific lumbar level, number of operative levels, total dose of Fentanyl during surgery, duration of surgery, estimated blood loss, and opioid tolerance [as defined as any use of opioids for 14 or more days in the 3 months immediately preceding the lumbar fusion]) was evaluated by univariate analyses. The primary outcome, fusion, was analyzed by univariate analysis. Parametric quantitative data were compared using t test, whereas nonparametric quantitative data were compared using the Mann-Whitney U test. A p value <.05 was considered significant. Outcomes were analyzed per protocol.

Results

Participants

A total of 994 patients were assessed for eligibility, with 292 patients randomized to receive either ketorolac or placebo after meeting eligibility and consented to participate (Fig. 1). A total of 140 patients were assigned to the ketorolac group, of which ten did not receive the assigned treatment (Fig. 1). The placebo group comprised 152 patients, of which 14 did not receive the assigned treatment. Eleven patients in each group withdrew their consent after randomization. At the time of this interim analysis, 165 patients and 194 fusion levels were assessed for the primary outcome at 1-year. The per-protocol analysis for secondary outcomes included 246 patients (119 in the ketorolac group and 127 in the placebo group) (Fig. 1).

The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the two treatment groups in any preoperative or perioperative variables (Table 2).

Fusion

A total of 247 levels and 194 levels were assessed for the primary outcome at 6-months and 1-year, respectively.

Table 1
Patient demographics

N=246	Ketorolac(n=119)	Control(n=127)	p value
Age	61.0±10.8	61.4±11.3	.63
Sex (male)	55 (46.2)	56 (44.1)	.74
BMI	31.0±6.0	31.2±6.3	.77
Diabetes mellitus	18 (15.1)	25 (19.7)	.35
Opioid tolerant*	48 (40.3)	50 (39.4)	.88
Disposition	—	—	.79
Home	106 (89.1)	113 (89.0)	—
SAR	11 (9.2)	13 (10.2)	—
IPR	2 (1.7)	1 (0.8)	—

Continuous data presented as mean±SD. Categorical data presented as n (%). p<.05 considered significant. BMI, body mass index; SAR, subacute rehabilitation; IPR, inpatient rehabilitation.

* Opioid tolerant defined as any opioid use for ≥14 days in the last 3 months.

There was no significant difference between the two groups in the primary outcome; the proportion of radiographic nonunion was 9.3% in each treatment group at 1-year (Table 3). The difference in proportion for solid fusion between the ketorolac group and the placebo group was .026 (95% CI, -.010 to .15) and .072 (95% CI, -.07 to .21) at 6-months and 1-year, respectively, which did not cross the specified inferiority margin of -0.15 (Fig. 2). Of the radiographic nonunions, the ketorolac group observed 2 (1.7%) patients who

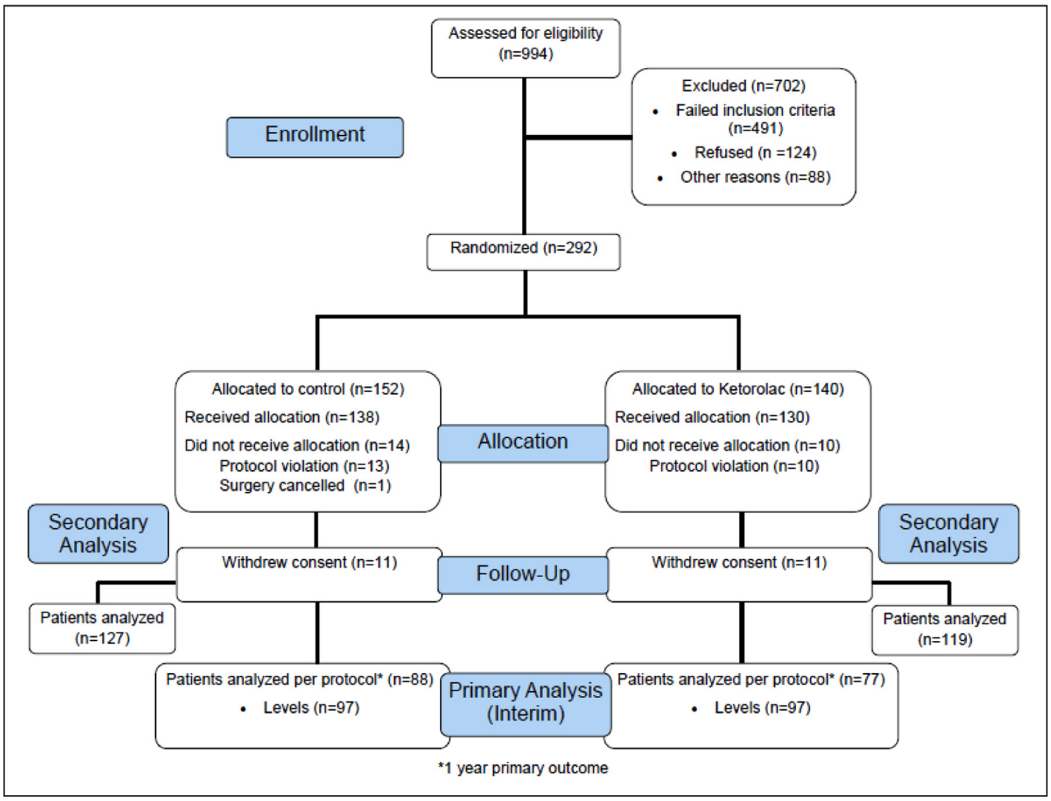


Fig. 1. CONSORT flow diagram of trial profile.

Table 2
Patient operative data

N=246	Ketorolac(n=119)	Control(n=127)	p value
Estimated blood loss (mL)	201.7±167.8	247.1±264.9	.11
Surgery time (min)	139.7±54.3	146.7±52.6	.31
Intraoperative opioids (mcg)	231.5±107.5	247.4±116.3	.27
Durotomy	8 (6.7)	7 (5.5)	.69
Number of operative levels	—	—	.21
One	89 (74.8)	84 (66.1)	—
Two	24 (20.2)	37 (29.1)	—
Three	6 (5.0)	6 (4.7)	—

Continuous data presented as mean±SD. Categorical data presented as n (%). p<.05 considered significant. mL, milliliters; min, minutes; mcg, micrograms of Fentanyl.

Table 3
Fusion outcomes

	Ketorolac	Control	Δ	95% CI	p value
6-Month (N=247)	n=119	n=128			.79
Solid fusion	58 (48.7)	59 (46.1)	2.6	-0.10 to 0.15	—
Probable fusion	49 (41.2)	58 (45.3)	-4.1	-0.17 to 0.08	—
Nonunion	12 (10.1)	11 (8.6)	1.5	-0.06 to 0.09	—
1-Year (N=194)	n=97	n=97			.53
Solid fusion	63 (64.9)	56 (57.7)	7.2	-0.07 to 0.21	—
Probable fusion	25 (25.8)	32 (33.0)	-7.2	-0.20 to 0.06	—
Nonunion	9 (9.3)	9 (9.3)	0	-0.08 to 0.08	—

6-month and 1-year fusion outcomes as evaluated by Suk criteria. Values presented as number of levels (%). p<.05 considered significant.

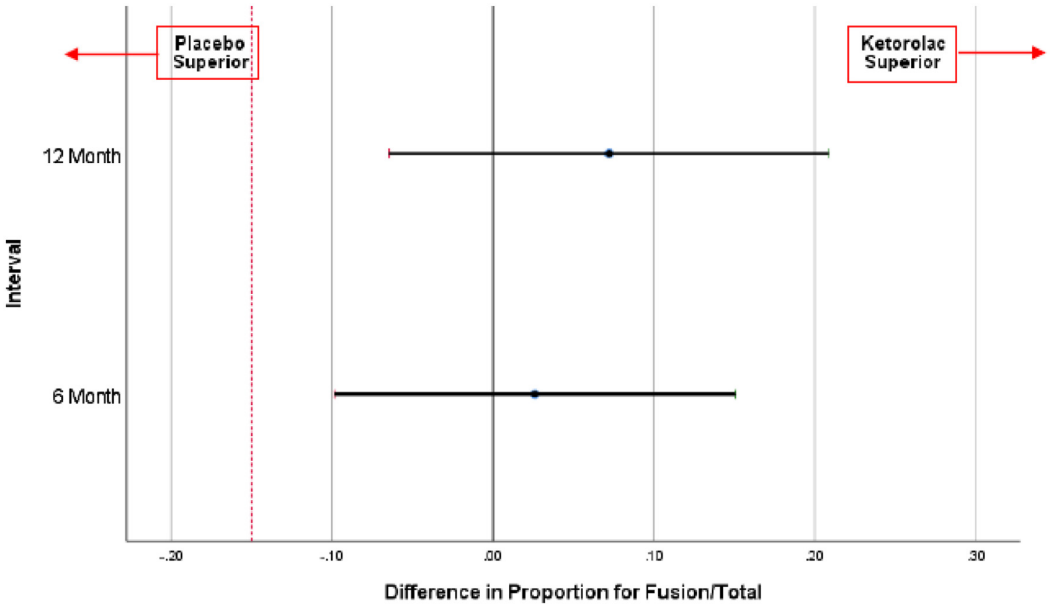


Fig. 2. Comparing solid fusion rates at 6 months and 1 year between the ketorolac and placebo groups. Red dashed line at -0.15 represents the noninferiority margin; the zone left of the noninferiority margin (red dashed line) represents the zone of inferiority. The horizontal black lines represent the confidence intervals (95%) of the difference in fusion rates between the two arms. The black dot in the middle of each horizontal line represents the difference in the fusion rates between the ketorolac vs. placebo group (black vertical line—no difference) for the 6-month and 1-year follow-up intervals.

Table 4
Secondary outcomes

N=246	Ketorolac (n=119)	Control(n=127)	Δ Mean	95% CI	p value
Total MME	52.5±39.5	84.7±55.4	-32.2	-44.3 to -20.2	**<.001**
48-hour MME	46.9±32.1	71.1±42.1	-24.2	-33.6 to -14.9	**<.001**
Postoperative VAS	6.0±1.4	6.2±1.5	-0.2	-0.6 to 0.1	.20
Length of Stay (d)	2.1±1.4	2.7±1.7	-0.7	-1.0 to -0.3	**.001**
Complications	—	—	—	—	—
Epidural hematoma	0	3 (2.4)	—	—	—
Wound hematoma	1 (0.8)	0	—	—	—
AKI	2 (1.7)	2 (1.6)	—	—	.95
Bleeding episode	0	0	—	—	—
Gastrointestinal	0	0	—	—	—
Surgical revisions	—	—	—	—	—
Pseudarthrosis	2 (1.7)	5 (3.9)	—	—	.52
Misplaced hardware	1 (0.8)	2 (1.6)	—	—	.60

Continuous data presented as mean±SD. Categorical data presented as n (%).
Total MME represents the total MME consumption during the entire hospitalization.
48-hour MME represents the total MME consumption within the first postoperative 48 hours.
Postoperative VAS represents the mean of all VAS collected over the first postoperative 48 hours.
p<.05 considered significant. Boldfaced p value indicates significance. MME, milligram morphine equivalence; VAS, visual analog scale; d, days; AKI, acute kidney injury.

demonstrated clinical pseudarthrosis requiring revision surgery (Table 4). Within the placebo arm, five (3.9%) patients demonstrated clinical pseudarthrosis requiring revision surgery.

Opioid consumption

Total milligram intravenous morphine equivalence was recorded during the patients' entire hospitalization and the first 48-hours following surgery. Total mean MME (Δ=32.2, 95% CI, 20.2−44.3, p<.001) and 48-hour mean MME (Δ=24.2, 95% CI, 14.9−33.6, p<.001) was significantly reduced in the ketorolac group when compared with the placebo group (Table 4). Ketorolac patients achieved a significant reduction in mean MME consumption on postoperative day 0, 1, and 2 (Fig. 3).

Pain severity and length of stay

When compared with the controls in the first postoperative 48 hours, patients who received ketorolac did not have a significant reduction in their average pain scores during the first 48 hours postoperatively (Table 4); did not have a significant difference in their mean VAS

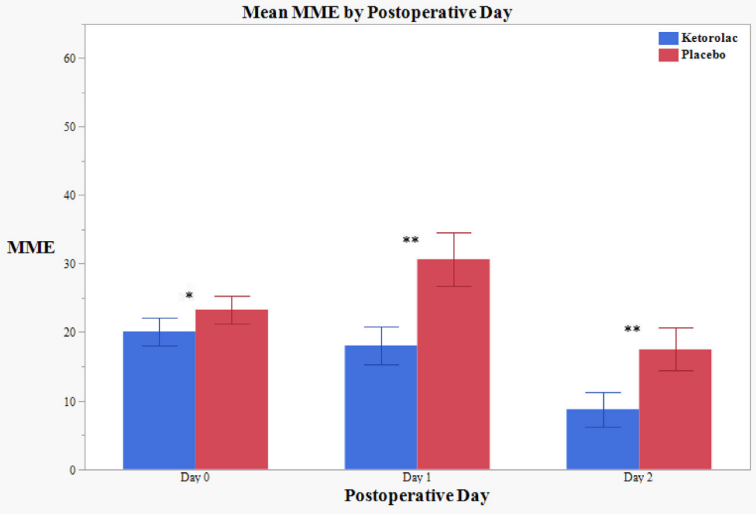


Fig. 3. Mean milligram morphine equivalents (MME) by postoperative day between the ketorolac group (blue) and the placebo group (red). * represents p value <.05. ** represents p value <.001. Error bars represent 95% confidence intervals.

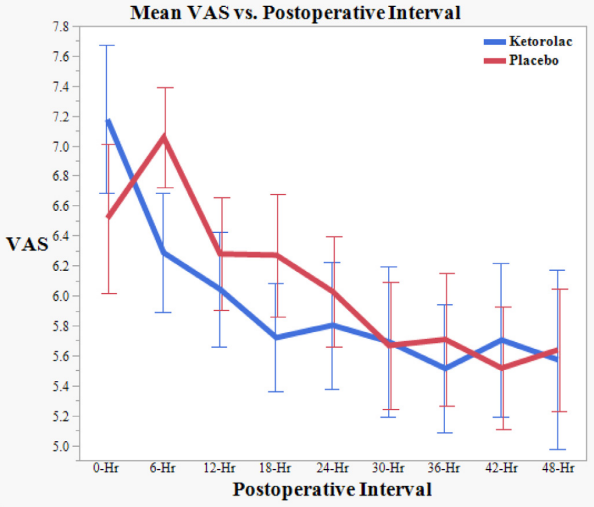


Fig. 4. Mean pain scores using the visual analog scale (VAS) at 6-hour intervals following surgery through 48 hours postoperatively. p value = .11. Error bars represent 95% confidence intervals.

over time as collected every 6 hours (p=.11) (Fig. 4). Patients who received ketorolac had a significant reduction in length of stay (Δ=0.80 days, 95% CI, 0.19−1.17, p=.001)

Adverse events

There was no significant difference in drug-related adverse outcomes between the two groups. Adverse events were rare. Epidural hematoma that required surgical evacuation occurred in three patients (2.3%) in the placebo group and one (0.8%) superficial hematoma which did not extend subfascial was observed in the ketorolac group. AKI was observed in two patients (1.6%) in the placebo group and two patients (1.7%) in the ketorolac group. No patients in the ketorolac group experienced an epidural hematoma, major bleeding episode, or gastrointestinal complication (Table 4).

Patient-reported outcomes

Change in patient-reported outcomes at 6-month and 1-year follow-up demonstrated no significant difference between the ketorolac and control groups (Table 5). Similarly, VAS scores and quality-of-life assessments demonstrated postoperative improvement without significant difference between groups at 6-month and 1-year.

Discussion

This randomized, placebo-controlled trial, analyzing the effect of ketorolac on 246 patients who underwent minimally invasive TLIF with BMP, demonstrated that short-term use of low-dose ketorolac led to a significant reduction in total MME during the hospitalization and the first 48-hour postoperative while maintaining equivalent pain control. We demonstrated comparable fusion rates between the two arms at 6-month and 1-year follow-up. We did not observe significant increased rates of ketorolac-related risks of major bleeding episodes, including epidural hematoma, AKI, or gastrointestinal complications.

NSAIDs remain one the most frequently used medications for the treatment of musculoskeletal pain. By inhibiting prostaglandin synthesis and leukotriene production to achieve anti-inflammatory properties, NSAIDs are highly effective analgesics [29,30]. Thus, the use of NSAIDs, such as ketorolac, has been widely successful in the treatment of postoperative pain following abdominal, gynecologic, and orthopedic surgical procedures [4,9,31]. However, its utilization in patients undergoing spinal fusion remains limited due to the heightened concern for pseudarthrosis [8,11,13,32]. More recently, questions have been raised

Table 5
Patient reported outcomes

	Ketorolac	Control	Δ Mean	95% CI	p value
6-Month (N=217)	n=100	n=117			
Δ ODI	-22.5±20.1	-22.5±22.3	-0.01	-5.7 to 5.7	.99
Δ SF-12 PCS	12.4±11.6	10.6±11.9	-1.76	-4.9 to 1.4	.28
Δ SF-12 MCS	3.0±10.6	2.6±12.0	-0.39	-3.5 to 2.7	.80
Δ SF-12 Sum	15.6±12.4	13.4±15.8	-2.20	-6.0 to 1.6	.25
Δ VAS	-4.4±3.6	-4.4±3.5	-0.01	-1.0 to 1.0	.99
1-Year (N=175)	n=90	n=85			
Δ ODI	-24.3±19.7	-20.3±22.0	3.99	-2.3 to 10.2	.21
Δ SF-12 PCS	12.7±12.0	11.8±12.8	-0.91	-4.7 to 2.8	.63
Δ SF-12 MCS	2.9±10.8	3.5±10.7	0.54	-2.7 to 3.8	.74
Δ SF-12 Sum	15.9±13.8	15.2±15.1	-0.70	-5.0 to 3.6	.75
Δ VAS	-4.8±3.5	-4.3±3.7	0.54	-0.5 to 1.6	.33

Continuous data presented as mean±SD. Categorical data presented as n (%). Δ represents change from baseline score; p<.05 considered significant. ODI, Oswestry Disability Index; SF-12, short form-12; PCS, physical component summary; MCS, mental component summary; VAS, visual analog pain scale.

regarding the effect of timing of NSAID administration and dose on fusion rates [12,13,15,16].

Our study highlighted the opioid-sparing effect of ketorolac as an adjunct to postoperative opioid administration after MIS lumbar fusion surgery. Comparing ketorolac patients with controls, the total cumulative and first 48-hour postoperative opioid consumption were significantly less. Moreover, we demonstrated that the use of ketorolac not only significantly reduced opioid consumption but also maintained equivalent or maybe better postoperative pain scores. Ketorolac significantly reduced the length of stay compared with the placebo cohort which further supported an improved recovery profile in ketorolac patients. Both groups achieved similar improvements without any significant difference in all PRO measures over 6 months and 1 year, demonstrating long-term clinical equipoise.

The significant benefits of ketorolac on opioid consumption following lumber fusion remain overshadowed by the concerns over its potential effect on fusion rates. Many authors have reported significantly lower rates of fusion in those who received ketorolac following spinal fusions [8,10,32–36]. Glassman et al. reported a six times higher relative risk of nonunion in those who received ketorolac [32]. However, variability with regard to ketorolac dose, duration and route of administration, and the predominantly retrospective design of these studies failed to provide a conclusion with rigorous evidence [1,8,10,20,32,34,35,37]. Our interim analysis demonstrated a low radiographic incidence of nonunion in patients who received ketorolac with a rate comparable to the placebo group. Moreover, our rate of clinical pseudarthrosis (clinical presentation in conjunction with imaging findings) in patients who received ketorolac remained exceedingly low, with only 2 of the 119 patients evaluated at 1 year requiring revision surgery.

This study is the first to compare the effects of ketorolac on spinal fusion in combination with the use of BMP. BMP has been well described as a graft enhancer and graft substitute [38]. Its use has even been shown to overcome the inhibitory effects of nicotine and NSAIDs on bone formation in experimental animal models [39,40]. Thus, the use of BMP in combination with ketorolac may confound the true impact of ketorolac on fusion rates. Therefore, future studies are required to confirm similar noninhibitory effects of ketorolac in the absence of BMP use.

As with many other institutions, the COVID-19 pandemic presented unprecedented circumstances that forced unconventional practices in hospitals with diminishing resources. As elective procedures were placed on hold, recruitment and funds allocated to clinical trials were also placed on hold. Additionally, the pandemic created a difficult environment in which patients no longer felt safe to adhere to routine trial protocols such as in-clinic and radiographic follow-up. Such circumstances were discussed with the investigating team, all of which who felt it prudent and necessary to publish our investigation result in the interim, especially in light of the tremendous impact on opioid consumption. Opioid use for acute postoperative pain remains an ongoing challenge following spinal surgery. Thus, opioid-sparing analgesic techniques represent an opportunity to improve treatment protocols aimed at enhancing and optimizing the postoperative recovery process, such as ERAS. Multimodal analgesia strategies for pain control are often a key component of most ERAS programs [41], and the addition of an NSAID may offer superior analgesia [42]. However, major concerns of using NSAIDs in spine surgery regarding nonunion and bleeding remain prevalent [43]. Our interim data demonstrated that in patients who have undergone minimally invasive lumbar fusion, short-term, administration of low-dose ketorolac resulted in fusion rates comparable to the controls and well above the inferiority margin that was determined a priori.

Limitations

Although major sources of bias and confounding were addressed in this study through randomization and allocation concealment, a number of limitations remain that warrant discussion in the interpretation of this randomized controlled trial.

The COVID-19 pandemic has caused considerable barriers in maintaining consistent recruitment and follow-up. With a significant and unavoidable delay in obtaining our long-term fusion outcome, compounded by the ongoing opioid crisis, the authors felt compelled to share our significant results regarding ketorolac's opioid-sparing effect on postoperative analgesia after MIS lumbar fusion. Therefore, an important limitation is the interim nature of our analysis regarding the primary outcome. Even though the entire 95% CI of the fusion rate difference between the two arms was well above the noninferiority margin, the CIs at both 6-month and 1-year follow-up spanned more than 25%. With 50% of our enrollment outstanding, our long-term fusion outcome remains uncertain. Similarly, the lack of significant difference regarding adverse events and long-term patient-reported outcomes could be a function of the inadequate patient numbers at the time of interim analysis. One example is our relatively high observed incidence of epidural hematoma in the placebo group which is likely due to random error given the sample size required to show statistical significance.

Preoperative opioid usage has consistently been demonstrated as one of the strongest predictors of postoperative opioid dependence [44–48] and is also clearly associated with worse postoperative outcomes [49]. We followed our state's online prescription monitoring program (Michigan Automated Prescription System) and defined chronic opioid use as opioid use for ≥14 days in the last 3 months before surgery. However, as a validated definition of opioid

tolerance has not been established, the possibility of selection bias remains. The determination of chronic opioid use before surgery heavily relies on patient self-reporting which introduced reporting bias. Furthermore, granular information regarding the quantity of opioids consumed was not collected and would have ideally provided additional information into establishing the degree of opioid tolerance among participants.

CT has the strongest correlation with the assessment of fusion status [50]. Therefore, the use of CT would have been ideal for the assessment of our primary outcome. However, given the size of the study and the burden of radiation exposure with CT, XR was chosen as our method of evaluation. The 2014 AANS guidelines state a combination of static and lateral flexion/extension images is a valid and useful way of determining fusion in posterior lumbar fusions with instrumentation, as supported by Brodsky et al., who determined the correlation of fusion rates with such images using surgical exploration [51].

Finally, the nature of a randomized controlled trial with its highly selective patient population may lend certain challenges when generalized to the often-complex clinical situation. Examples would be our exclusion of smokers, our use of a standardized MIS TLIF technique and rhBMP-2. As discussed previously, the detrimental effect of ketorolac on spinal fusion may be overcome by the use of BMP. Therefore, our results may not be generalizable to patients undergoing MIS TLIF without BMP. Similarly, our use of a standardized MIS TLIF technique may render our result not generalizable to other fusion techniques. Further studies with different fusion techniques without the use of BMP are warranted. If our final results affirm our interim results, the next step would be to track long-term fusion results associated with the use of ketorolac in a large number of patients in registry studies.

Conclusion

Short-term use of low-dose ketorolac in patients who have undergone MIS TLIF with BMP significantly reduced postoperative opioid use and length of stay while maintaining equivalent postoperative pain control. The use of ketorolac was not associated with an increase in short-term perioperative adverse events. Our interim results suggested noninferior fusion rates with the use of ketorolac. However, confirmation of these results remains ongoing.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Financial support for the conducting of this trial was given by Ascension Providence Hospital, Department of Research and Scholarly Inquiry (#1072359-1). We would like to thank the following ancillary/support staff for their tireless effort and dedication to ensure the quality and performance of this trial: Kenneth Brown, Rebecca Doherty, Amarpal Dosanjh, Joseph Gabrail, Amanda Hagedorn, Connor Hanson, Amanda Murdoch, Nicole Podczervinski, Jessica Townsend, and Carol Wynn.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2021.08.011.

References

[1] Li Q, Zhang Z, Cai Z. High-dose ketorolac affects adult spinal fusion: a meta-analysis of the effect of perioperative nonsteroidal anti-inflammatory drugs on spinal fusion. Spine 2011;36:E461–8. https://doi.org/10.1097/BRS.0b013e3181dfd163.

[2] Mino DE, Munterich JE, Castel LD. Lumbar fusion surgery for degenerative conditions is associated with significant resource and narcotic use 2 years postoperatively in the commercially insured: a medical and pharmacy claims study. J Spine Surg 2017;3:141–8. https://doi.org/10.21037/jss.2017.04.02.

[3] Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of chronic opioids: a survey of chronic pain patients. J Pain 2017;18:360–5. https://doi.org/10.1016/j.jpain.2016.11.001.

[4] Kinsella J, Moffat AC, Patrick JA, Prentice JW, McArdle CS, Kenny GN. Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. Br J Anaesth 1992;69:19–22.

[5] Reuben SS, Connelly NR, Steinberg R. Ketorolac as an adjunct to patient-controlled morphine in postoperative spine surgery patients. Reg Anesth 1997;22:343–6.

[6] Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. Anesth Analg 2001;92:1473–6.

[7] Jahr JS, Montalvo HM, Holton R, Liukkonen J. Does ketorolac tromethamine, a new analgesic, decrease postoperative recovery time, narcotic requirements, nausea and/or vomiting, and unscheduled hospital admissions: a retrospective analysis. Acta Anaesthesiol Belg 1993;44:141–7.

[8] Park S-Y, Moon S-H, Park M-S, Oh K-S, Lee H-M. The effects of ketorolac injected via patient controlled analgesia postoperatively on spinal fusion. Yonsei Med J 2005;46:245–51. https://doi.org/10.3349/ymj.2005.46.2.245.

[9] Litvak KM, McEvoy GK. Ketorolac, an injectable nonnarcotic analgesic. Clin Pharm 1990;9:921–35.

[10] Vitale MG, Choe JC, Hwang MW, Bauer RM, Hyman JE, Lee FY, et al. Use of ketorolac tromethamine in children undergoing scoliosis surgery. An analysis of complications. Spine J 2003;3:55–62.

[11] Urrutia J, Mardones R, Quezada F. The effect of ketoprophen on lumbar spinal fusion healing in a rabbit model. Laboratory investigation. J Neurosurg Spine 2007;7:631–6. https://doi.org/10.3171/SPI-07/12/631.

[12] Simon AM, O'Connor JP. Dose and time-dependent effects of cyclooxygenase-2 inhibition on fracture-healing. J Bone Joint Surg Am 2007;89:500–11. https://doi.org/10.2106/JBJS.F.00127.

[13] Reuben SS, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. Can J Anaesth 2005;52:506–12. https://doi.org/10.1007/BF03016531.

[14] Simon AM, Manigrasso MB, O'Connor JP. Cyclo-oxygenase 2 function is essential for bone fracture healing. J Bone Miner Res 2002;17:963–76. https://doi.org/10.1359/jbmr.2002.17.6.963.

[15] Lumawig JMT, Yamazaki A, Watanabe K. Dose-dependent inhibition of diclofenac sodium on posterior lumbar interbody fusion rates. Spine J 2009;9:343–9. https://doi.org/10.1016/j.spinee.2008.06.455.

[16] Riew KD, Long J, Rhee J, Lewis S, Kuklo T, Kim YJ, et al. Time-dependent inhibitory effects of indomethacin on spinal fusion. J Bone Joint Surg Am 2003;85:632–4. https://doi.org/10.2106/00004623-200304000-00007.

[17] Ho ML, Chang JK, Wang GJ. Effects of ketorolac on bone repair: a radiographic study in modeled demineralized bone matrix grafted rabbits. Pharmacology 1998;57:148–59.

[18] Ho ML, Chang JK, Wang GJ. Antiinflammatory drug effects on bone repair and remodeling in rabbits. Clin Orthop Relat Res 1995:270–8.

[19] Bergenstock M, Min W, Simon AM, Sabatino C, O'Connor JP. A comparison between the effects of acetaminophen and celecoxib on bone fracture healing in rats. J Orthop Trauma 2005;19:717–23.

[20] Li J, Ajiboye RM, Orden MH, Sharma A, Drysch A, Pourtaheri S. The effect of ketorolac on thoracolumbar posterolateral fusion: a systematic review and meta-analysis. Clin Spine Surg 2018;31:65–72. https://doi.org/10.1097/BSD.0000000000000613.

[21] Brusko GD, Kolcun JPG, Heger JA, Levi AD, Manzano GR, Madhavan K, et al. Reductions in length of stay, narcotics use, and pain following implementation of an enhanced recovery after surgery program for 1- to 3-level lumbar fusion surgery. Neurosurg Focus 2019;46:E4. https://doi.org/10.3171/2019.1.FOCUS18692.

[22] Puri KS, Suresh KR, Gogtay NJ, Thatte UM. Declaration of Helsinki, 2008: implications for stakeholders in research. J Postgrad Med 2009;55:131–4. https://doi.org/10.4103/0022-3859.52846.

[23] Abraham J. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. In: Brouder A, Tietje C, editors. Handbook of transnational economic governance regimes. Boston, MA: Brill; 2009. p. 1041–54. https://doi.org/10.1163/ej.9789004163300.i-1081.897.

[24] Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308:2594–604. https://doi.org/10.1001/jama.2012.87802.

[25] Claus CF, Lytle E, Tong D, Sigler D, Lago D, Bahoura M, et al. The effect of ketorolac on posterior thoracolumbar spinal fusions: a prospective double-blinded randomised placebo-controlled trial protocol. BMJ Open 2019;9:e025855. https://doi.org/10.1136/bmjopen-2018-025855.

[26] Lytle EJ, Slavnic D, Tong D, Bahoura M, Govila L, Gonda R, et al. Minimally effective dose of bone morphogenetic protein in minimally invasive lumbar interbody fusions: six hundred ninety patients in a dose-finding longitudinal cohort study. Spine (Phila Pa 1976) 2019;44:989–95. https://doi.org/10.1097/BRS.0000000000002993.

[27] Suk SI, Lee CK, Kim WJ, Lee JH, Cho KJ, Kim HG. Adding posterior lumbar interbody fusion to pedicle screw fixation and posterolateral fusion after decompression in spondylolytic spondylolisthesis. Spine (Phila Pa 1976) 1997;22:210–9 discussion 219-220. https://doi.org/10.1097/00007632-199701150-00016.

[28] Christensen FB, Laursen M, Gelineck J, Eiskjaer SP, Thomsen K, Bünger CE. Interobserver and intraobserver agreement of radiograph interpretation with and without pedicle screw implants: the need for a detailed classification system in posterolateral spinal fusion. Spine 2001;26:538–43. discussion 543-544.

[29] Saag KG, Cowdery JS. Nonsteroidal anti-inflammatory drugs. Balancing benefits and risks. Spine (Phila Pa 1976) 1994;19:1530–4. https://doi.org/10.1097/00007632-199407000-00021.

[30] Coloma M, White PF, Huber PJ, Tongier WK, Dullye KK, Duffy LL. The effect of ketorolac on recovery after anorectal surgery: intravenous versus local administration. Anesth Analg 2000;90:1107–10. https://doi.org/10.1097/00000539-200005000-00019.

[31] Varrassi G, Marinangeli F, Agrò F, Aloe L, De Cillis P, De Nicola A, et al. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine: analgesic efficacy and tolerability after gynecologic surgery. Anesth Analg 1999;88:611–6. https://doi.org/10.1097/00000539-199903000-00028.

[32] Glassman SD, Rose SM, Dimar JR, Puno RM, Campbell MJ, Johnson JR. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine 1998;23:834–8.

[33] Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesth Analg 1998;87:98–102.

[34] Pradhan BB, Tatsumi RL, Gallina J, Kuhns CA, Wang JC, Dawson EG. Ketorolac and spinal fusion: does the perioperative use of ketorolac really inhibit spinal fusion? Spine 2008;33:2079–82. https://doi.org/10.1097/BRS.0b013e31818396f4.

[35] Sucato DJ, Lovejoy JF, Agrawal S, Elerson E, Nelson T, McClung A. Postoperative ketorolac does not predispose to pseudoarthrosis following posterior spinal fusion and instrumentation for adolescent idiopathic scoliosis. Spine (Phila Pa 1976) 2008;33:1119–24. https://doi.org/10.1097/BRS.0b013e31816f6a2a.

[36] Dumont AS, Verma S, Dumont RJ, Hurlbert RJ. Nonsteroidal anti-inflammatory drugs and bone metabolism in spinal fusion surgery: a pharmacological quandary. J Pharmacol Toxicol Methods 2000;43:31–9.

[37] Donohue D, Sanders D, Serrano-Riera R, Jordan C, Gaskins R, Sanders R, et al. Ketorolac administered in the recovery room for acute pain management does not affect healing rates of femoral and tibial fractures. J Orthop Trauma 2016;30:479–82. https://doi.org/10.1097/BOT.0000000000000620.

[38] Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326–37.

[39] Silcox DHI, Boden SD, Schimandle JH, Johnson P, Whitesides TE, Hutton WC. Reversing the inhibitory effect of nicotine on spinal fusion using an osteoinductive protein extract. Spine 1998;23:291–6.

[40] Martin GJJ, Boden SD, Titus L. Recombinant human bone morphogenetic protein-2 overcomes the inhibitory effect of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), on posterolateral lumbar intertransverse process spine fusion. Spine 1999;24:2188.

[41] Tan M, Law LS-C, Gan TJ. Optimizing pain management to facilitate enhanced recovery after surgery pathways. Can J Anaesth 2015;62:203–18. https://doi.org/10.1007/s12630-014-0275-x.

[42] Ong CKS, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010;110:1170–9. https://doi.org/10.1213/ANE.0b013e3181cf9281.

[43] Alboog A, Bae S, Chui J. Anesthetic management of complex spine surgery in adult patients: a review based on outcome evidence. Curr Opin Anaesthesiol 2019;32:600–8. https://doi.org/10.1097/ACO.0000000000000765.

[44] Sharma M, Ugiliweneza B, Aljuboori Z, Nuño MA, Drazin D, Boakye M. Factors predicting opioid dependence in patients undergoing surgery for degenerative spondylolisthesis: analysis from the MarketScan databases. J Neurosurg Spine 2018;29:271–8. https://doi.org/10.3171/2018.1.SPINE171258.

[45] Schoenfeld AJ, Belmont PJ, Blucher JA, Jiang W, Chaudhary MA, Koehlmoos T, et al. Sustained preoperative opioid use is a predictor of continued use following spine surgery. J Bone Joint Surg Am 2018;100:914–21. https://doi.org/10.2106/JBJS.17.00862.

[46] Pugely AJ, Bedard NA, Kalakoti P, Hendrickson NR, Shillingford JN, Laratta JL, et al. Opioid use following cervical spine surgery: trends and factors associated with long-term use. Spine J 2018;18:1974–81. https://doi.org/10.1016/j.spinee.2018.03.018.

[47] Lawrence JTR, London N, Bohlman HH, Chin KR. Preoperative narcotic use as a predictor of clinical outcome: results following anterior cervical arthrodesis. Spine (Phila Pa 1976) 2008;33:2074–8. https://doi.org/10.1097/BRS.0b013e3181809f07.

[48] Qureshi R, Werner B, Puvanesarajah V, Horowitz JA, Jain A, Sciubba D, et al. Factors affecting long-term postoperative narcotic use in discectomy patients. World Neurosurg 2018;112:e640–4. https://doi.org/10.1016/j.wneu.2018.01.113.

[49] Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ 2015;350:g6380. https://doi.org/10.1136/bmj.g6380.

[50] Chun DS, Baker KC, Hsu WK. Lumbar pseudarthrosis: a review of current diagnosis and treatment. Neurosurg Focus 2015;39:E10. https://doi.org/10.3171/2015.7.FOCUS15292.

[51] Brodsky AE, Kovalsky ES, Khalil MA. Correlation of radiologic assessment of lumbar spine fusions with surgical exploration. Spine 1991;16:S261–5.

ELSEVIER

The SPINE JOURNAL

The Spine Journal 22 (2022) 19–38

2021 Outstanding Paper Award Winner

Modic changes are associated with activation of intense inflammatory and host defense response pathways – molecular insights from proteomic analysis of human intervertebral discs

S Rajasekaran, PhD[a,*], Dilip Chand Raja Soundararajan, S FNB (Spine)[a], Sharon Miracle Nayagam, MSc[b], Chitraa Tangavel, PhD[b], M Raveendran, PhD[c], Pushpa Bhari Thippeswamy, FRCR[d], Niek Djuric[e], Sri Vijay Anand, K S MS[a], Ajoy Prasad Shetty, MS[a], Rishi Mugesh Kanna, FNB (Spine)[a]

[a] *Department of Spine Surgery, Ganga Hospital, 313, Mettupalayam road, Coimbatore, India*
[b] *Ganga Research Centre, No 91, Mettupalayam road, Coimbatore 641030, India*
[c] *Department of Plant Biotechnology, Tamil Nadu Agricultural University, Coimbatore 641003 India*
[d] *Department of Radiology, Ganga Hospital, 313, Mettupalayam road, Coimbatore, India*
[e] *Department of Neurosurgery, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, the Netherlands*

Received 25 January 2021; revised 8 May 2021; accepted 2 July 2021

ABSTRACT

BACKGROUND CONTEXT: Patients with modic changes (MC) form a distinct clinical subset with reports of higher intensity of pain, poor clinical and surgical outcomes and higher incidence of recurrence. MC also is an independent risk factor for increased post-operative surgical site infection.

PURPOSE: This study aimed *to investigate the biological changes at molecular level, in discs with MCs*. We also aim to identify biological biomarkers and potential targets for molecular therapy.

STUDY DESIGN: Experimental analysis

MATERIALS AND METHODS: Nucleus pulposus (NP) from 24 patients undergoing microdiscectomy for disc herniation [14 discs with MC and 10 without modic changes (NMC)] were procured. The overall expression of proteins, biological processes, protein-protein and metabolite interactions were analysed and compared. *Host defense response proteins (HDRPs) and immunological pathways activated in patients with MC were documented and analysed.*

RESULTS: Label-free proteomic approach with stringent filters revealed a total of 208 proteins in MC and 193 in NMC groups. 45 proteins were specific to MC; 30 to NMC and 163 common to both. Downregulated proteins in MC belonged to components of extracellular matrix such as collagens (COL- 6A1, 6A2, 6A3, 11A1, 12A1, and 20A1), and proteoglycans (versican (VCAN), and biglycan (BGN)). Inflammatory molecules [plasminogen (PLG), angiogenin (ANG), fibroblast growth factor-binding protein 2 (FGFBP2), tetranectin (CLEC3B), cartilage acidic protein 1 (CRTAC1), kininogen (KNG-1), chitinase-3-like protein 2 (CHI3L2), and ferritin (FTL) were expressed only in the MC group. The significantly altered pathways in MC included Fc Fragment of IgG Receptor IIIa (FCGR3A)-mediated phagocytosis, regulation of Toll-like receptors (TLR) by endogenous ligand, neutrophil and platelet degranulation.

50 HDRPs were identified in the study, 14 of which were specific to MC and included acute phase reactants, antimicrobial peptides, complement cascade proteins, inflammatory molecule and

FDA. Device/drug status: Not applicable

Author disclosure: ***SR:*** Grant, GOREF: (B). ***DCR:*** Nothing to disclose, ***SMN:*** Nothing to disclose, ***CT:*** Nothing to disclose, ***MR:*** Nothing to disclose, ***PBT:*** Nothing to disclose, ***ND:*** Nothing to disclose. (A). ***SVA:*** Nothing to disclose, ***APS:*** Nothing to disclose. ***RMK:*** Nothing to disclose.

*Corresponding author. Department of Orthopaedics and Spine Surgery, Ganga Hospital, 313, Mettupalayam road, Coimbatore, India. Tel.: +(91 98-43022325; fax: +(91) 42-24383863.

E-mail address: rajasekaran.orth@gmail.com (S. Rajasekaran).

https://doi.org/10.1016/j.spinee.2021.07.003

stress response proteins. Metabolite-protein interaction analysis revealed a significant interaction between 19 proteins, specifically involving ubiquitin mediating proteasome degradative pathway and an association with the metabolite-glutamic acid in the MC group. Accumulation of glutamic acid in MC discs was confirmed by quantitative amino acid analysis using High-performance liquid chromatography.

CONCLUSION: *Our study confirms that MC represents an intense inflammatory status and activation of host defense response and immunological pathways*. Downstream effects leading to ubiquitin mediated proteasomal degradation of ECM proteins and the resulting metabolites such as glutamic acid *could cause excessive pain and needs further investigation.*

CLINICAL SIGNIFICANCE: We have documented the expression of inflammatory molecules, immune mechanisms and host defense response proteins which throw molecular insights into the pathological mechanisms of MC. Further, ubiquitin mediated proteasomal degradation and accumulation of glutamate in discs with MC might serve as targets for molecular therapy.

Keywords: Bacterial infection; Host defense response; Intervertebral disc degeneration; Low Back Pain; Modic changes; Proteomics

Introduction

There is mounting evidence that clinical and functional outcomes of patients with chronic low back pain (LBP) are inferior in those with MC compared to patients without MC in both the lumbar and cervical spine [4–6]. MCs have been variably correlated to aging, smoking, mechanical trauma, inflammation, degeneration, genetic single nucleotide polymorphisms (SNPs), and infection [1–3], but the exact pathophysiological mechanisms underlying these changes still remain elusive. To date, no study has investigated why such a difference occurs despite identical treatment modalities but this knowledge is critical to overcome the poor clinical results and surgical outcomes in lumbar disc disease.

We have performed a comparative proteomic analysis of intervertebral discs with and without MC in the current study. Further, we have investigated the underlying molecular mechanisms to identify candidate biomarkers and molecular targets which may improve outcomes in patients with MC.

Materials and methodology

This study was approved by Institutional Review Board and was conducted according to the guidelines and ethical norms laid by Indian Council of Medical Research (ICMR). After obtaining informed consent, nucleus pulposus (NP) from 24 patients undergoing microdiscectomy for disc herniation were procured. The demographic details and grades of degeneration are mentioned in (**Table 1**). Tissue samples were retrieved under aseptic conditions and immediately snap-frozen at -196˚C using liquid nitrogen and stored for further proteomic analysis. Frozen samples were subjected to in-gel based label-free mass spectrometric analysis, as reported earlier. In order to unravel molecular mechanisms in patients with modic changes, a comparative proteomic analysis was performed between 14 discs with MC and 10 without modic changes (NMC).

Cryopreserved tissues were thawed on ice, aliquoted and subjected to in-gel based tryptic digestion as described earlier in our reports [7–9]. Purified tryptic peptides were then subjected to label-free mass spectrometric analysis and the output (.raw/.msf) files were subjected to identification of total proteins using Proteome Discoverer vs 1.4 with in-built SequestHT and Mascot search algorithms. The spectral counts of proteins were relatively quantified by normalized spectral abundance factor (NSAF) method [10]. Stringent filter (≥5 PSM and 30% sample positivity) were applied for further analysis. To understand the biological process involved in pathogenesis, pathway enrichment analysis was performed using Reactome database v.3.7 followed by comparison using Funrich, functional enrichment annotation tool with customized database ‘Reactome’ and their statistical significance was determined by Bonferroni test.

To unveil metabolic regulations, metabolite-protein interaction (MPI) network analysis was made using STITCH (Search Tool for Interactions of Chemicals) vs 5.0 [11]. MPI analysis of specific proteins were done by integrating predictions from active sources ‘expression’ ‘databases’ with confident network edges. The interaction scores were imported into cytoscape vs 3.8.3 with installed ANIMO (Analysis of Networks with Interactive Modeling) plugin for analysis of incoming/ outgoing signals. All the analysis were corrected using Bonferroni test for assessing their significance and further validated using quantitative amino acid analysis, for which around 200mg of intervertebral disc NP tissues were weighed, pulverized using liquid nitrogen and suspended in 1ml of sterile double deionized water. Subsequently, the mixture was subjected to incubation for 1 hour at room temperature with continuous mixing, followed by centrifugation at RT @10,000 x g, for 15 min to remove interfering aggregates. To deproteinize the samples, 2% acetonitrile (v/v) was added prior to quantitative analysis of extracted amino acids using Shimadzu UHPLC N-Series with RF-20A. Following a brief spin, 2μl

Table 1
Demographic and clinical phenotypes of study population considered for this study

Study group	Age	Sex	Levels	MODIC changes	Pfirmann grade	Mean age of the subjects ± SD
MC	21	M	L5S1	2	4	35 ± 11.04
MC	29	F	L5S1	2	3	
MC	31	M	L5S1	2	3	
MC	32	F	L4L5	2	4	
MC	32	M	L4L4	2	4	
MC	34	F	L4L5	1	4	
MC	37	M	L3L4	2	4	
MC	37	M	L4L5	2	4	
MC	38	F	L4L5	2	4	
MC	38	M	L4L5	2	4	
MC	40	F	L4L5	1	4	
MC	43	M	L5S1	2	4	
MC	43	F	L4L5	2	4	
MC	34	M	L4L5	2	4	
NMC	15	M	L4L5		2	36 ± 19.44
NMC	16	F	L5S1		4	
NMC	26	F	L4L5		4	
NMC	26	M	L5S1		4	
NMC	27	M	L4L5		3	
NMC	28	M	L5S1		4	
NMC	40	M	L4L5		3	
NMC	45	M	L4L5		3	
NMC	67	F	L5S1		3	
NMC	70	F	L4L5		5	

++MC- Modic Changes; NMC- Non-Modic Changes.

of deproteinized sample extracts were loaded onto HPLC column (Phenomenex Gemini 5 μm NX-C-18 110 Å (250 mm X 4.6 mm ID) (IICMS/LCC-266). Amino acids were eluted with an increasing gradient of 25mM dipotassium hydrogen phosphate anhydrous in sodium azide (A) and methanol: acetonitrile: water (40:45:15) (B) solvents. A constant flow of 1.0 mL/min was provided to separate amino acids through gradient elution.

To identify specific host defense mechanisms, a comprehensive list of 263 well established host defense response proteins (HDRP) (*Supplementary-Table-1*) was built and their expression were compared between MC and NMC groups. To visualize the concentration of HDRPs between conditions, supervised hierarchical clustering was made by using complete linkage method and distance metrics was calculated by Euclidean distances with the help of R-packages. GOnet (https://tools.dice-database.org/GOnet/) with its human ontology version 2019/07/01 was used to analyze enriched biological processes.

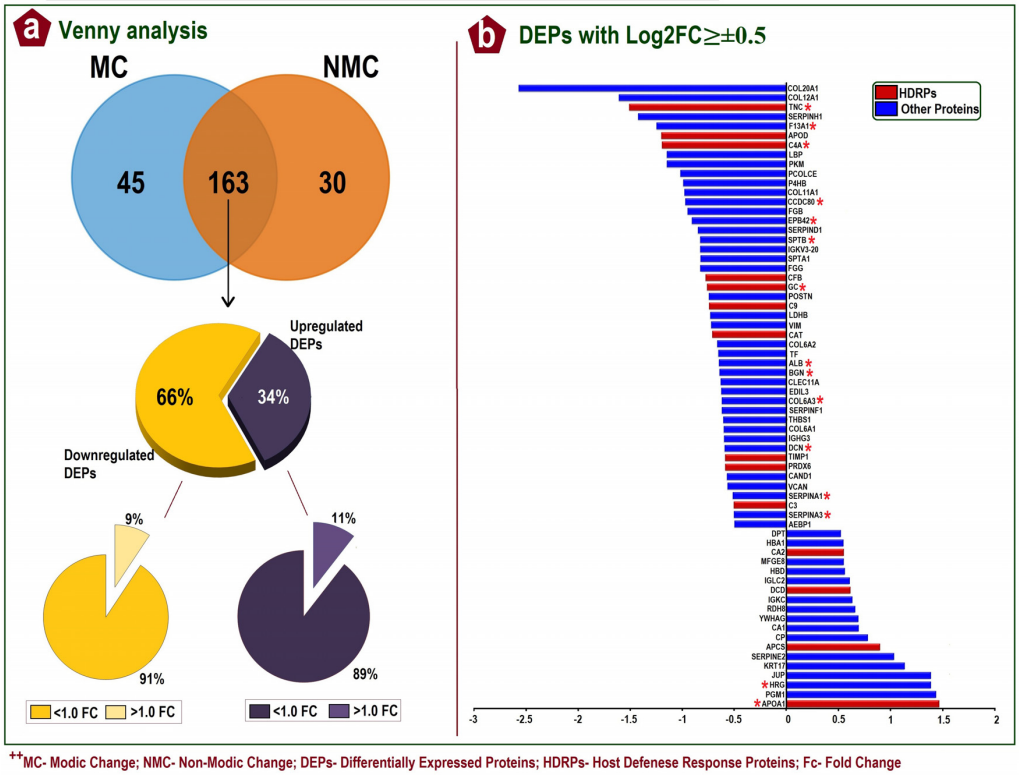
Statistical difference between conditions was analyzed using SPSS software vs.25.0 with the help of t-tests/ Mann-Whitney U tests (in the case of normality violation) and two-tailed alpha was set at 0.05 for all the tests.

Results

Label-free proteomic approach revealed a total of: 585 proteins in MC and 536 proteins in NMC group respectively. By applying a stringent filter on peptide spectral matches (PSMs) (≥5) and sample positivity (≥30%); this list narrowed to 208 proteins in MC and 193 in NMC groups respectively. Draw Venn tool, was used to depict a comparative proteomic analysis (http://bioinformatics.psb.ugent.be/webtools/Venn/) which showed 45 proteins specific to MC; 30 specific to NMC and 163 common to both as shown in Fig. 1A. Among 163 differentially expressed proteins (*Supplementary-Table-2*), 66 proteins were found to have a log2FC±0.5 variation with 14 proteins showing statistically significant differences ($p < .05$) as shown in Fig. 1B.

Differentially expressed proteins

Among the 66 differentially expressed proteins expressed with log2FC ≥±0.5, 19 were upregulated and 47 were downregulated in MC group (Fig. 1B). Acute phase reactants produced in response to trauma, or infection such as apolipoprotein A1 (APOA1), serum amyloid P-component (APCS), and ceruloplasmin (CP) were upregulated in MC. Immune system responses to antigenic exposure viz dermcidin (DCD) representing innate immunity and immunoglobulins [IGKC - immunoglobulin kappa constant (IGKC) and immunoglobulin Lambda Constant 2 (IGLC2)] representing adaptive immunity were upregulated in MC. Cytoprotective proteins in response to inflammation such as carbonic anhydrase (CA2), milk fat globule-epidermal growth factor 8 (MFGE8), serpin peptidase inhibitor clade E member 2 (SERPINE2) were again upregulated in MC.



++MC- Modic Change; NMC- Non-Modic Change; DEPs- Differentially Expressed Proteins; HDRPs- Host Defenese Response Proteins; Fc- Fold Change

Fig. 1. **Comparative Proteomics**- **(A)** Venn diagram representing total number of unique and common proteins between MC and NMC discs. About 163 were present in both the conditions with varying abundances. When compared with NMC, out of 163 proteins, 56 proteins (34%) were upregulated in MC and 107 proteins (66%) were found to be downregulated in MC. Pie chart depicts the contribution of differentially expressed proteins (DEPs) between fold changes (>1.0 and <1.0) in both up and downregulation. **(B)** Bar chart showing 66 differentially expressed proteins (DEPs) with log2FC ≥±0.5 (Up and Downregulation) in MC when compared to NMC considered in this study. *indicates statistical significance ($p<0.05$), using t-test/ MW-U test (in case of normality violation) using SPSS vs 25.0.

Most of the downregulated proteins in MC belonged to components of extracellular matrix such as collagens (COL- 6A1, 6A2, 6A3, 11A1, 12A1, and 20A1), proteoglycans (versican (VCAN), and biglycan (BGN)). Proteins essential to control infection [tenascin C (TNC), lipopolysaccharide binding protein (LBP)] and inflammation [serine protease inhibitors (SERPIN – A1, A3, D1, H1 and F1), vimentin (VIM), and catalase (CAT)] were downregulated in MC. Central component of the complement system (C3) and a protein of the terminal membrane attack complex (C9) were also downregulated.

Proteins specifically expressed in MC

Around 75 proteins were expressed specifically in either of MC/NMC group. Out of these 75 proteins 45 were specific to MC group and 30 proteins to NMC group respectively. Interestingly out of 45 MC specific proteins 14 mapped under host defense response mechanisms (Table 2) in contrast to only two proteins mapped in NMC under this category. The remaining 31 MC specific proteins include mainly immunoglobulins [IGHV3-7, IGLC1, IGKV3-15, IGKV3D-11, IGKV4-1, IGKV2-40, IGHV3OR16-13), metabolic enzymes [adenylate kinase isoenzyme 1 (AK1), glyceraldehyde-3-phosphate dehydrogenase, testis-specific (GAPDHS), ribonuclease 4 (RNASE4), flavin reductase (NADPH) (BLVRB)], nucleosome components [Histone H2A type 1-H (HIST1H2AH), histone H4 (HIST1H4A and purine nucleoside phosphorylase (PNP)], and inflammatory proteins [plasminogen (PLG), angiogenin (ANG), fibroblast growth factor-binding protein 2 (FGFBP2), tetranectin (CLEC3B), cartilage acidic protein 1(CRTAC1), kininogen (KNG-1), chitinase-3-like protein 2 (CHI3L2), ferritin (FTL).

Pathway enrichment analysis to depict its biological role

To understand the significant biological basis underlying MC and NMC, total proteins of MC- 208; NMC- 194 were included as input for the pathway enrichment analysis using Reactome database web browser vs 3.7 and the significantly altered pathways were ranked according to their p-values as shown in (Supplementary-Table-3 and Fig. 2**).** The significantly altered pathways in MC condition include FCGR3A-

Table 2
Clinical Implications of specific proteins of MC and NMC conditions

S. No	Gene Symbol	UNIPROT Protein name	Specific to	HDRP	Clinical implication
1	SOD3	Extracellular superoxide dismutase [Cu-Zn]	MC	Yes	Downregulate MAPK signalling pathway and NF-κB transcription factors thereby controlling inflammatory responses.
2	LGALS8	Galectin	MC	Yes	Potent immune suppressor reported in CSF; one of its isoform GAL-8M is produced in response to bacterial LPS stimulus and returns to normal once LPS is removed.
3	TNFAIP6	Tumor necrosis factor-inducible gene 6 protein	MC	Yes	Known to produce inflammatory effect in animal models of arthritis, cerebral and myocardial infarction.
4	C1S	Complement C1s subcomponent	MC	Yes	Pathogen clearance by classical pathway triggered via binding of pattern recognition molecule C1 complex (consisting of C1Q that has C1R and C1S proteases) to immunoglobin patches on the target pathogen.
5	UBB	Polyubiquitin-B	MC	Yes	Part of UPS complex and involved in degradation and clearance of misfolded proteins
6	CLEC3A	C-type lectin domain family 3 member A	MC	Yes	In vitro studies provide evidence of antimicrobial activity especially with peptides derived from CLEC3A towards septic arthritis.
7	S100A1	Protein S100-A1	MC	Yes	Released when there is inflammation or cellular stress. Regulation of P13/AKT signalling pathway reported in neuronal cells; reported as a pro-inflammatory molecule in Alzheimer disease.
8	CHI3L1	Chitinase-3-like protein 1	MC	Yes	Induced expression observed in inflammatory diseases and certain type of cancers.
9	TIMP3	Metalloproteinase inhibitor 3	MC	Yes	Physiological regulator of inflammation and controls metalloproteases involved in ECM turnover.
10	C1QB	Complement C1q subcomponent subunit B (Fragment)	MC	Yes	Part of C1Q molecule, involved in clearing the apoptotic debris. Upon binding to the apoptotic cells it supresses the dendritic and macrophages that mediate cellular proliferation.
11	APOA2	Apolipoprotein A-II	MC	Yes	Reported to maintain host responses to LPS by suppressing the inhibitory activity of LPS binding protein.
12	C8B	Complement component 8, beta polypeptide, isoform CRA_b	MC	Yes	Part of membrane attack complex (MAC) expressed as a result of pro-inflammatory trigger.
13	PLA2G2A	Synovial phospholipase-A2	MC	Yes	Increased secretion during inflammation and promotes wnt signalling. Present in abundance in biological fluids with inflammatory diseases (arthritis, sepsis and myocardial infarctions).
14	APOH	Beta-2-glycoprotein 1	MC	Yes	Multifunctional glycoprotein involved in transport of lipids into the circulatory system; binds to lipid moiety of bacteria as a host defence protein against bacterial infections; Inflammatory protein in systemic lupus erythematosus.
15	AK1	Adenylate kinase isoenzyme 1	MC	No	Key enzyme functions as immune modulator; assess the risk of pathogenesis due to oxidative stress such as neurodegenerative and metabolic disorders.
16	GAPDHS	Glyceraldehyde-3-phosphate dehydrogenase, testis-specific	MC	No	Malonylation of GAPDH which in turn promotes TNFα transcription leading to inflammation.

Table 2 (***Continued***)

S. No	Gene Symbol	UNIPROT Protein name	Specific to	HDRP	Clinical implication
17	HIST1H2AH	Histone H2A type 1-H	MC	No	Accumulation of histone proteins signals promotion of senescent cells leading to chronic inflammation.
18	PLG	Plasminogen	MC	No	Key molecules involved in regulation of macrophage polarization and phagocytosis of apoptotic cells to resolve inflammation along with its receptor.
19	MYCLP1	Putative myc-like protein MYCL1P1	MC	No	Overexpressed in many type of cancer cells, widely known as activators of tumorigenesis
20	IGHV3OR16-13	Protein IGHV3	MC	No	Involved in positive regulation of B-cell activation
21	ANG	Angiogenin	MC	No	Stress activated protein upregulated in human ocular diseases such as DR, AMD, RP and uveitis.
22	FGFBP2	Fibroblast growth factor-binding protein 2	MC	No	Secreted by cytotoxic lymphocytes and reported as a potential biomarker for Acute Myocardial Infarction.
23	IGHV3-7	Immunoglobulin heavy variable 3-7	MC	No	Involved in positive regulation of B-cell activation
24	IGLC1	Immunoglobulin lambda constant 1	MC	No	Involved in RET signalling helps in axon guidance
25	STOM	Erythrocyte band 7 integral membrane protein	MC	No	Pivotal in stabilisation of mature RBC and as well clear the damaged protein by vesiculation.
26	HIST1H4A	Histone H4	MC	No	Its presence induces neutrophil activation and inflammatory responses; hydrogen peroxide production; cell adhesion; IL-8 generation and degranulation.
27	KRT33B	Keratin, type I cuticular Ha3-II	MC	No	Deamidated protein, being explored for its functionality in hair diseases.
28	PCOLCE2	Procollagen C-endopeptidase enhancer 2	MC	No	Glycoprotein present in ECM; In mice, it's an important component of HDL system involved in reverse cholesterol transport where the cholesterol is returned to liver for excretion and is classified as atheroprotective.
29	IGKV3-15	Immunoglobulin kappa variable 3-15	MC	No	Participates in antigen recognition of humoral immunity
30	POTEE	POTE ankyrin domain family member E	MC	No	Anti-inflammatory molecule negatively regulates the stress response by attenuating NF-KB signals; also suppresses vascular injury in-vivo. In contrary upregulation in CRC cells has been used as novel biomarker for diagnosis.
31	IGKV3D-11	Immunoglobulin kappa variable 3D-11	MC	No	Participates in antigen recognition of humoral immunity
32	IGKV4-1	Ig kappa chain V-IV region Len	MC	No	Participates in adaptive immunity
33	ANK1	Isoform Er16 of Ankyrin-1	MC	No	Highly abundant in the immune microglial cells which are the key regulators in Alzheimer's disease.
34	IGKV2-40	Immunoglobulin kappa variable 2-40	MC	No	Participates in adaptive immunity
35	QSOX1	Sulfhydryl oxidase 1	MC	No	Reported as tissue derived biomarker that promotes lung cancer.
36	CLEC3B	C-type lectin domain family protein 3/ Tetranectin	MC	No	Reportedly, increased expression is positively correlated with the fibrosis in ischemic heart disease which in contrary with the serum concentration levels.
37	CRTAC1	Cartilage acidic protein 1	MC	No	ECM protein capable of forming amyloid-like structures associated in disease milieu.

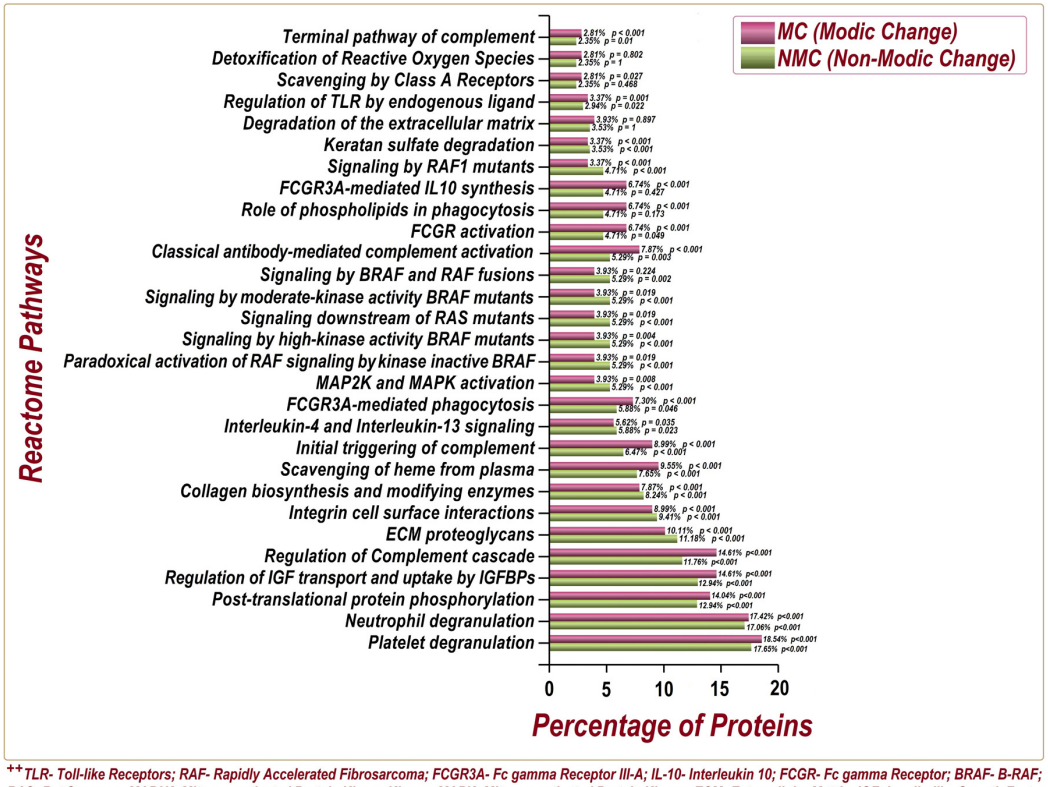
Table 2 (***Continued***)

S. No	Gene Symbol	UNIPROT Protein name	Specific to	HDRP	Clinical implication
38	COL1A1	Collagen alpha-1(I) chain	MC	No	Main structural protein of the ECM in musculoskeletal tissues. Known as protease resistant; associated fibrotic and connective tissue pathology; age-related diseases.
39	RNASE4	Ribonuclease 4	MC	No	Known as immune modulators. Possess antimicrobial activity that is secreted upon injury targeting damaged cells to be cleared from the inflammatory site.
40	BLVRB	Flavin reductase (NADPH)	MC	No	Part of redox cycle, bilirubin converted into biliverdin through ROS which could be a promising therapy for oxidative-stress mediated diseases
41	KNG1	Kininogen-1	MC	No	During *S.pyogenes* infection, KNG1 mediates inflammatory response mechanism
42	PNP	Purine nucleoside phosphorylase	MC	No	Deficient levels causes lymphopenia in humans
43	HBA2	Hemoglobin A2	MC	No	Higher levels lessens the severity of multiple sclerosis
44	CHI3L2	Chitinase-3-like protein 2	MC	No	Stress response protein in IVDD
45	FTL	Ferritin	MC	No	Vital inflammatory marker, as it arises from damaged cells
46	PON1	Serum paraoxonase/ arylesterase 1	NMC	No	Low levels are observed during oxidative stress which are associated with severity of the IVD disease
47	IQGAP1	IQGAP1 protein	NMC	No	Crucial for MAPK-driven microbial invasion
48	COL5A1	Collagen type V, alpha 1	NMC	No	Higher expression levels were observed in tumour cells
49	HSPA5	Endoplasmic reticulum chaperone BiP	NMC	Yes	Part of neuroinflammation and tumour cells produce high levels of HSPA5
50	ACTN1	Alpha-actinin-1	NMC	No	Significantly increased levels were observed in synovial tissues of RA
51	ANXA6	Annexin A6	NMC	No	Acts either as tumour suppressor or promoter based on the malignancy of cancer
52	C1R	Complement C1r subcomponent	NMC	Yes	Absence of C1R resulting in resolving inflammation caused due to clearance of apoptotic cells
53	MYH9	Myosin-9	NMC	No	Mediates TLR in platelets under the influence of Cγ-calpain-myosin 9-Rab7b axis
54	ATP5B	ATP synthase subunit beta, mitochondrial	NMC	No	Involved in electron transport process of respiratory chain
55	FBLN1	Fibulin-1	NMC	No	Simultaneous expression of ADAMTS-1 and FBLN1 induces antitumoral effect in breast cancers
56	MDH2	Malate dehydrogenase	NMC	No	Key protein in central oxidative pathway
57	GPI	Glucose-6-phosphate isomerase	NMC	No	Increased levels were observed in hypoxia-induced angiogenesis in RA
58	COL14A1	Collagen alpha-1(XIV) chain	NMC	No	Found expressed in young intervertebral discs known as regulator of fibrillogenesis.
59	XIRP2	Xin actin-binding repeat-containing protein 2	NMC	No	Xin upregulation is significantly and positively correlated with severity of muscle damage
60	MSN	Moesin	NMC	No	Transduces all LPS-induced signals by blocking monocytes response to LPS
61	ATP5F1B	ATP synthase subunit beta, mitochondrial	NMC	No	Involved in electron transport process of respiratory chain
62	CALR	Calreticulin	NMC	No	Inhibits LPS-induced inflammatory osteoclastogenesis in murine cells

Table 2 (***Continued***)

S. No	Gene Symbol	UNIPROT Protein name	Specific to	HDRP	Clinical implication
63	ACTC1	Actin, alpha cardiac muscle 1	NMC	No	Polymorphisms lead to chronic inflammatory cardiomyopathy
64	VCP	VCP protein	NMC	No	Helps in formation of tER
65	LCP1	Plastin-2	NMC	No	Actin-binding protein. Plastin-deficient PMN lacks killing bacterial pathogens.
66	FLNA	Filamin-A	NMC	No	Increased expression of FLNA in advanced atherosclerotic plaques of human carotid arteries
67	HIST2H2AC	Histone H2A type 2-C	NMC	No	H2A, an important component of NETs possessing antimicrobial activity
68	DYNC1LI1	Cytoplasmic dynein 1 light intermediate chain 1	NMC	No	Adaptor protein that regulate dynein function
69	BMI1	Polycomb complex protein BMI-1	NMC	No	Cell differentiation and proliferation
70	NOA1	Nitric oxide-associated protein 1	NMC	No	Known for disc abnormalities. Causes oxidative stress in age-related diseases
71	MIF4GD	MIF4G domain-containing protein	NMC	No	Potential regulator of p27-dependent cell proliferation in HCC
72	TNRC6B	Trinucleotide repeat-containing gene 6B protein	NMC	No	Involved in RNA-mediated gene silencing
73	YWHAB	14-3-3 protein beta/alpha	NMC	No	Adapter protein involved in many signalling cascades
74	ASPN	Asporin	NMC	No	Binds with TGF-beta and BMP-2 and negatively regulates their activity; potential drug for DDD
75	ATP5F1A	ATP synthase subunit alpha, mitochondrial	NMC	No	Natural drug target for antimicrobial/ antitumor peptides

++MAPK- Map Kinase; NF-κB- Nuclear factor kappa B; CSF- Cerebro Spinal Fluid; LPS- Lipopolysaccharide; UPS- Ubiquitin/ Proteasome system; P13/AKT- Intracellular signalling pathway; ECM- Extracellular Matrix; TNF- Tumour Necrosis Factor; DR- Diabetic Retinopathy; AMD- Age-Related Macular Degeneration; RP- Retinitis Pigmentosa; RET-; RBC-; IL-8- Interleukin 8; HDL- High Density Lipoprotein; CRC- Colorectal Cancer; IVDD- Intervertebral Disc Disease; RA- Rheumatoid Arthritis; tER- transitional endoplasmic reticulum; BMP- Bone Morphogenetic Protein; DDD- Degenerative Disc Disease.



++TLR- Toll-like Receptors; RAF- Rapidly Accelerated Fibrosarcoma; FCGR3A- Fc gamma Receptor III-A; IL-10- Interleukin 10; FCGR- Fc gamma Receptor; BRAF- B-RAF; RAS- Rat Sarcoma; MAP2K- Mitogen-activated Protein Kinase Kinase; MAPK- Mitogen-activated Protein Kinase; ECM- Extracellular Matrix; IGF- Insulin-like Growth Factor 1; IGFBPs- Insulin-like Growth Factor-binding Protein; p- probability value.

Fig. 2. Comparative pathway enrichment analysis of total proteins using Reactome database vs 3.7 of the total proteins across both the conditions- MC and NMC. Significantly enriched pathways with p-value <0.05 are compared between the conditions and the illustrative image was created using FUNRICH, functional enrichment tool vs. 3.1.3 (http://www.funrich.org/). The p-value is calculated by the intersection of input genes against the background sets/ genes found in the database or in the pathways based on predicted molecular evidences using a Fisher's exact test and multiple test correction is applied to all annotated genes used as default. Interestingly, infection-mediated/immune-influenced pathways such as FCGR3A- mediated phagocytosis (role in host-defence mechanisms the uptake and destruction of infectious pathogens); scavenging of heme from plasma (clearing of free heme released by erythrocytes during infection associated with intravascular hemolysis); regulation of TLR by endogenous ligand (active upon tissue damage during infectious and inflammatory mechanisms) and immune responsive pathways- initial triggering of complement; regulation of complement cascade; neutrophil and platelet degranulation were enriched in MC. Whereas, discs with NMC showed pathways that mediate chronic inflammation: Signalling by BRAF and RAF fusions; Signalling by moderate kinase activity BRAF mutants; Signalling downstream of RAS mutants; Signalling by high-kinase activity BRAF mutants; paradoxical activation of RAF-signalling by kinase-inactive BRAF, MAP2K and MAPK.

mediated phagocytosis (role in host-defence mechanisms the uptake and destruction of infectious pathogens) (**Fig. 3**); FCGR3A-mediated IL10 synthesis; scavenging of heme from plasma; regulation of TLR by endogenous ligand; role of phospholipids in phagocytosis and immune responsive pathways - initial triggering of complement; regulation of complement cascade; neutrophil and platelet degranulation. Specific pathways of MC are enlisted under **Table 3**. In contrast discs with NMC showed enrichment of other pathways: transduce extracellular signals mediating inflammation such as signaling by BRAF and RAF fusions; signaling by moderate kinase activity BRAF mutants; signaling downstream of RAS mutants; signaling by high-kinase activity BRAF mutants, paradoxical activation of RAF-signaling by kinase-inactive BRAF, MAP2K and MAPK activation.

Interactive network analysis of specific proteins of MC and NMC

To understand the mechanism of functional modulators, protein-metabolite interactions were studied using Search Tool for Interactions of Chemicals (STITCH) database vs 5.0 for specific proteins in discs with MC and NMC and incoming / outgoing signals were predicted using Cytoscape vs. 3.8.3 with installed ANIMO plugin using UPPAAL running in the background.

In MC, out of 45 specific proteins subjected to interactions, 19 were found to have associations with a clustering coefficient of 0.848 (Fig. 4A). Strong associations were found between POTE ankyrin domain family member E (POTEE), hemoglobin subunit beta (HBB), spectrin beta, erythrocytic (SPTB), histone (HIST1H2AH),

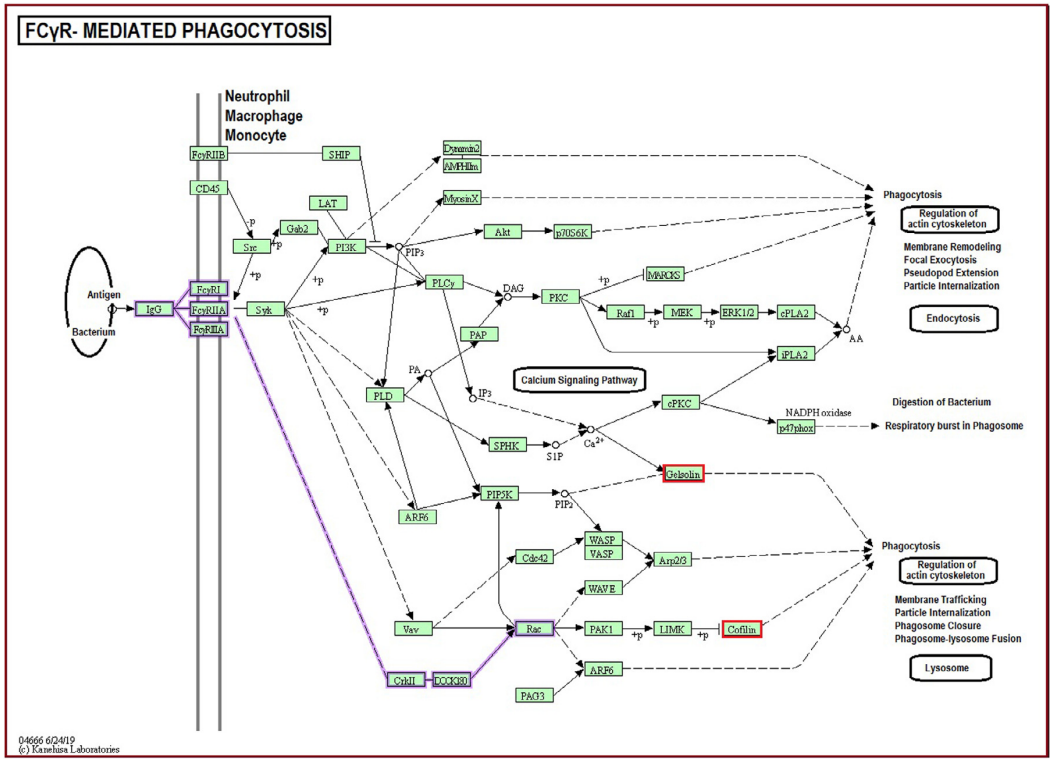


Fig. 3. KEGG pathview representing the significantly enriched pathway FCGR3A-mediated phagocytosis (p-value, 0.001) in Modic discs (MC). Phagocytosis helps in clearance of invading foreign particles where Fc-gamma receptors recognize IgG-coated targets- opsonized pathogens or other circulating invaders with their varying IgG affinity and intracellular trafficking. Recognized particles are processed and later diffused by reactive oxygen species. Highlighted proteins are present in our study (red colour). Violet colour represents cytoskeletal regulation mediated by viruses and bacteria in the host.

galectin (LGALS8), ubiquitin (UBB and UBC), stomatin (STOM), quiescin Q6 sulfhydryl oxidase 1 (QSOX1), and C1 complex. The proteins UBC, UBB, immunoglobulin lambda-like polypeptide 5 precursor (IGLL5), 26S proteasome non-ATPase regulatory subunit (PSMD4), proteasome 26S subunit, non-ATPase (PSMD5) and kininogen-1 (KNG1) were found to be associated with glutamic acid. However, higher number of proteins was found interacting with ubiquitin suggestive of its role in proteasome degradative pathway leading to the degradation of major ECM protein in the disc such as aggrecan and an association with glutamic acid.

In NMC, only 15 proteins had interactions with clustering coefficient 0.801(Fig. 4B). Stronger associations were found between heat shock proteins- (HSP90B1-heat shock protein 90 B1, HSPA5- heat shock protein A5); CALR- calreticulin, actin molecules and ATP transporters- (ATP5A1, ATP5AB, ATP5C1, ATP5D) which all in-turn activating/triggering RAF1 (RAF proto-oncogene serine/threonine-protein kinase, an important member of inflammatory signals).

These results were validated by quantitative amino acid analysis of 18 different proteinogenic and non-proteinogenic amino acids using Shimadzu UHPLC N-Series with RF-20A. Except isoleucine (below detection limit), all other amino acids showed a good separation profiles in representative sample of MC condition (Fig. 5A**).** The results demonstrated that valine was the predominant amino acid in MC condition with leucine in NMC. Majority of amino acids were found elevated in MC condition with the exception of glycine, alanine, phenylalanine, and lysine being higher in NMC condition (Fig. 5B). Glutamic acid, a main excitatory neurotransmitter associated with the sensation of pain was found in higher concentration (4.471 ppm) in MC group, when compared to 2.446 ppm in NMC group.

Profiling of host defence response proteins

Categorization of proteins based on their functions identified 50 host defense response proteins (HDRPs) across discs with MC and NMC. The relative abundance transformed into Z-score for each protein is represented in a heat map as shown in Fig. 6A. Based on supervised hierarchal clustering analysis, the proteins were clustered using complete linkage method and the distances were measured by Euclidean distances. The heat map illustrating an overall enriched presence of HDRPs in MC is indicative of

Table 3.
Biological significance of Reactome pathways specific to MC condition

S. No	Reactome pathway	No. of genes (found/ total) with its ratio	Entities pValue	Participating proteins	Biological significance
1	CD22 mediated BCR regulation	9/72 (0.005)	5.13E-04	IGHM; IGKC; IGKV3-15; IGKV4 1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	Regulator of adaptive and innate TLR-mediated B cell responses
2	Innate Immune System	75/1331 (0.091)	6.80E-04	SERPINA3; SERPINA1; FRMPD3; TNFAIP6; GDI2; HP; HBB; C8B; CLU; HAPLN1; ACTB; IGHG3; C4B; IGHG4; C4A; IGHG1; IGHG2; PNP; IGLC1; QSOX1; LBP; IGLC2; IGHV37; PGM1; FGB; CAP1; FGA; DCD; ANXA2; S100A1; FGG; KRT1; IGKV1D-33; PKM; CAT; IGKV41; SERPING1; CHI3L1; ALDOA; PPIA; VCL; CFB; FTL; C1QB; APCS; C1S; CFH; A1BG; C3; VTN; C5; CAND1; C6; TTR; UBB; IGKC; C9; IGKV3-15; STOM; APOB; HSPA8; GSN; JUP; PLA2G2A; LYZ; PRDX6; TF; IGKV3-20; HSPA1A	Non-specific defense mechanism that evades invading foreign pathogenic cells
3	Role of phospholipids in phagocytosis	12/129 (0.009)	0.002	IGHG3; IGHG4; IGHG1; IGHG2; IGKC; IGKV3-15; IGKV4-1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	Generate essential second messengers and the phospholipases- PLA, PLC, PLD are known to initiate antibody (IgG) mediated phagocytosis
4	FCGR3A-mediated IL10 synthesis	12/141 (0.010)	0.005	IGHG3; IGHG4; IGHG1; IGHG2; IGKC; IGKV3-15; IGKV4-1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	IL10 immunoregulatory cytokine performs dual function either as protective or pathological mediator. During pathology, igG induce IL10 through FcγRs and kills phagocytic cells.
5	FCGR3A-mediated phagocytosis	13/157 (0.011)	0.005	IGKV1D-33; ACTB; IGHG3; IGHG4; IGHG1; IGHG2; IGKC; IGKV4-1; IGKV3-15; IGLC1; IGLC2; IGHV3-7; IGKV3-20	Phagocytosis via fcγRs subsequently activates Rac GTPases and Cdc42 which induces the phagocyte's NADPH oxidase leading to killing mechanism
6	Leishmania phagocytosis	13/157 (0.011)	0.005	IGKV1D-33; ACTB; IGHG3; IGHG4; IGHG1; IGHG2; IGKC; IGKV4-1; IGKV3-15; IGLC1; IGLC2; IGHV3-7; IGKV3-20	Leishmania infects millions of population but resides in macrophages
7	FLT3 signaling by CBL mutants	2/7 (4.76E-04)	0.006	UBB	c-Cbl, a proto-oncogene involved in RTK signaling, acting through its ubiquitin ligase activity and as a

Table 3. (***Continued***)

S. No	Reactome pathway	No. of genes (found/ total) with its ratio	Entities pValue	Participating proteins	Biological significance
					platform for several signaling adaptor molecules
8	Crosslinking of collagen fibrils	3/24 (0.002)	0.008	COL1A1; COL1A2; PCOLCE	In pathological conditions, dietary inhibition of lysl oxidase results in reduced strength of tendons
9	Myoclonic epilepsy of Lafora	2/11 (7.47E-04)	0.015	UBB	Reported in brain disorder and decline in intellectual function
10	Glycogen synthesis	3/26 (0.002)	0.017	UBB; PGM1	Normal cellular functioning pathway
11	Anchoring fibril formation	2/15 (0.001)	0.027	COL1A1; COL1A2	Procollagen dimerization
12	FCERI mediated NF-kB activation	9/175 (0.012)	0.029	UBB; IGKC; IGKV3-15; IGKV4-1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	Highly critical for proinflammatory cytokine production during mast cell activation that lead to allergic inflammatory diseases
13	Regulation of actin dynamics for phagocytic cup formation	13/158 (0.011)	0.031	IGKV1D-33; ACTB; IGHG3; IGHG4; IGHG1; IGHG2; IGKC; IGKV4-1; IGKV3-15; IGLC1; IGLC2; IGHV3-7; IGKV3-20	Involved in actin cytoskeletal organization
14	Role of LAT2 /NTAL/ LAB on calcium mobilization	8/107 (0.007)	0.031	IGKC; IGKV3-15; IGKV4-1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	Regulation of mast cell calcium responses
15	Maturation of protein E	2/8 (5.43E-04)	0.034	UBB	Translation of structural proteins
16	Retinoid metabolism and transport	6/79 (0.005)	0.036	TTR; APOA2; APOA1; APOA4; APOB; HSPG2	Normal cellular functioning pathway
17	FCERI mediated Ca+2 mobilization	8/129 (0.009)	0.039	IGKC; IGKV3-15; IGKV4-1; IGLC1; IGLC2; IGHV3-7; IGKV1D-33; IGKV3-20	Increase in intracellular calcium in mast cells leads to mast cell degranulation
18	Late endosomal microautophagy	5/35 (0.002)	0.043	HSPA8; UBB; HBB; VIM	Non-selective autophagic pathway
19	G2/M Checkpoints	7/154 (0.010)	0.048	YWHAE; HIST1H4A; UBB; YWHAQ; YWHAZ; YWHAG	Normal cellular functioning pathway
20	Chylomicron remodeling	4/17 (0.001)	0.050	APOA2; APOA1; APOA4; APOB	Plasma lipoprotein remodeling

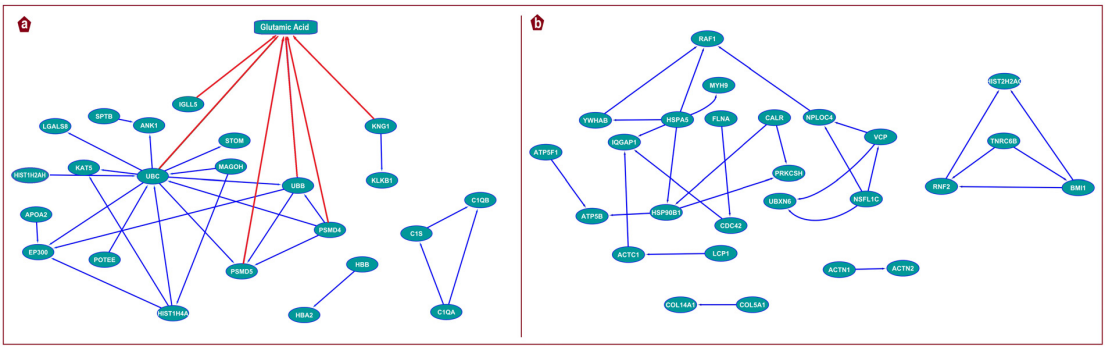


Fig. 4. Metabolite-protein interaction (MPI) network analysis of proteins specific to MC and NMC using STITCH database vs. 5.0. **(A)** With 45 specific proteins in MC given as input, only 19 had interactions with other predicted chemicals/small molecules/ metabolites with a clustering coefficient 0.848. Stronger associations were found between glutamate (metabolite, a neurotransmitter), and other proteins such as ubiquitin, proteasome subunits. **(B)** Non-Modic Change (NMC) had 30 specific proteins, in which only 15 had interactions with other molecules with a clustering coefficient 0.801. Stronger associations are found between RAF1 (oncogene, mediator of inflammatory signals), heat shock proteins and ATP subunits. The predicted incoming/ triggering events were predicted using cytoscape vs. 3.8.3 with installed ANIMO plugin having UPPAAL running in the background. Network nodes are better illustrated as either cylinders (chemicals) or ellipses (proteins, i.e. predicted functional partners). Edges with protein-protein interactions are shown in blue, metabolite/chemical-protein interactions are shown in red. NMC had exhibited no interactions with any other chemicals/ metabolites.

infection-mediated immune response where these HDRPs demonstrate a wide range of utility in bridging between innate and adaptive immunity. Venny analysis was done to know the shared homology of HDRPs between conditions-MC and NMC discs, which showed 34 proteins common to each other with 14 proteins specific to discs with MC and two proteins-[HSPA5 (heat shock protein 5) and C1R (complement C1r)] specific to NMC (Fig. 6B).

Functional analysis of HDRPs common to both conditions

Among the 34 common HDRPs, 4 were found to show significant differential expression between conditions using t-tests/ MW-U tests such as TNC (tenascin-regulates inflammatory axis during TLR signaling); C4A (complement C4A- anaphylatoxin help in degranulation of mast cells); GC (vitamin D binding- modulate host defense); and ApoA1 (apolipoprotein A1- initiate innate host defense) as shown in Fig. 7A. Characterization based on biological process analyzed using GOnet (https://tools.dice-database.org/GOnet/) (Fig. 7B, Supplementary-Table-4) revealed significant enrichment of complement activation-alternate pathway, complement activation-classical pathway, hydrogen peroxide catabolic process, defense response to other organisms, response to stress, immune effector process remains proof for infection and inflammation mediated mechanisms with a p-value threshold of ≤ 3.26e-7. Other significant proteins in lesser order involved in cytolysis: Apolipoprotein A1 (APOA1); Complement proteins C5, C6, C9; lysozyme (LYZ); Inflammatory response- haptoglobin (HP); Complement proteins (C3) and (C5); metalloproteinase inhibitor 1 (TIMP1); serum amyloid P component (APCS); C4A; C4B; peroxiredoxin 2 (PRDX2); LYZ; and perlecan (HSPG2).

HDRPS specific to MC group

The 14 HDRPs found specific to MC included acute phase reactants [Protein S100-A1,and apolipoproteins (APO A2 & H)], antimicrobial peptides [Galectin (LGALS8), C-type lectin domain family 3 member A (CLEC3A), chitinase-3-like protein 1(CHI3L1) and synovial phospholipase-A2 (PLA2G2A)], complement cascade (C1S, C1QB, and C8B), inflammatory molecule [tumour necrosis factor-inducible gene 6 protein (TNFAIP6) and polyubiquitin-B (UBB)] and stress response [extracellular superoxide dismutase (SOD3)].

Discussion

Low back pain associated with Modic changes form a discrete subgroup, as evidenced by the distinct clinical profile and surgical outcome in these patients [4–6,12–15]. Despite many studies documenting an intense inflammatory milieu in discs with MC, the exact pathophysiology leading to recurrent episodes of severe and disabling LBP and poor surgical outcomes have not been clearly documented so far [16]. Recent studies have suggested evidence for bacterial infection in MC using advanced technologies such as fluorescence in situ hybridization (FISH) and confocal laser scanning microscopy [17,18] but this is not universally accepted. In a previous prospective cohort study we followed up patients undergoing microdiscectomy for lumbar disc herniations and demonstrated poorer clinical and functional outcomes in patients with MC at one year following surgery [19]. Unravelling the molecular mechanisms in the etiopathogenesis of MC and their biological basis is important. Our study is the first to investigate the differences at molecular level amongst discs with and

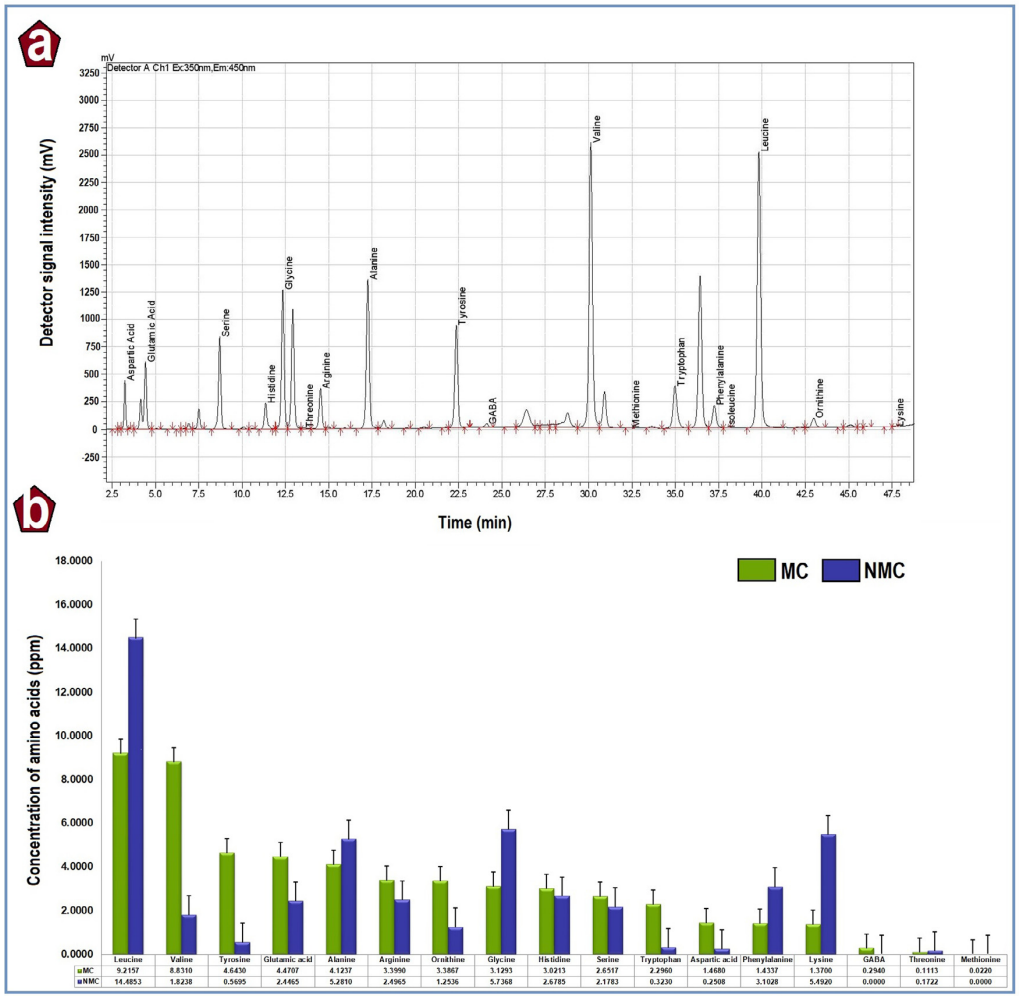


Fig. 5. Profiling of extracted amino acids. (A) Chromatogram of extracted amino acid in a sample representing MC condition. (B) Bar chart representation of mean concentration of amino acids observed across conditions; error bars represent standard errors. Valine and Leucine were found to be the dominant amino acids in MC and NMC conditions respectively. Glutamic acid, a neurotransmitter responsible for sensation of pain, was found elevated in MC.

without modic changes using high throughput proteomic sequencing.

In the current study, we have performed proteomic analysis on the disc samples with and without modic changes and performed a systematic analysis. We first investigated the overall proteomic constitution and documented the differences in discs with MCs. Biological pathway analysis was then performed to identify the metabolic profile. Having identified MC as an independent risk factor for developing SSI in a previous study, we specifically analyzed the role of bacterial etiology by comparing the expression of host-defense response proteins/pathways (HDRPs)[15]. To identify candidate biomarkers and molecular targets for possible therapeutic interventions, we then performed a protein-protein-metabolite interaction analysis which revealed activation of Ubiquitin mediated proteasome degradation pathway and an association with glutamic acid, which was later confirmed by quantitative amino acid analysis using high performance liquid chromatography.

Proteomic phenotype of MC is distinct

We found 45 proteins specific to MC; 30 specific to NMC and 163 common to both. In this study we included herniated discs (which represents a loss in structural integrity of ECM) in both MC and NMC groups. Despite having the same amount of degeneration by Pfirmann grading in MRI, we found the extent of ECM matrix breakdown in nucleus pulposus to be higher in MC as evidenced by the significant downregulation of collagens (COL- 6A1, 6A2, 6A3, 11A1, 12A1, and 20A1), and proteoglycans (versican (VCAN), and

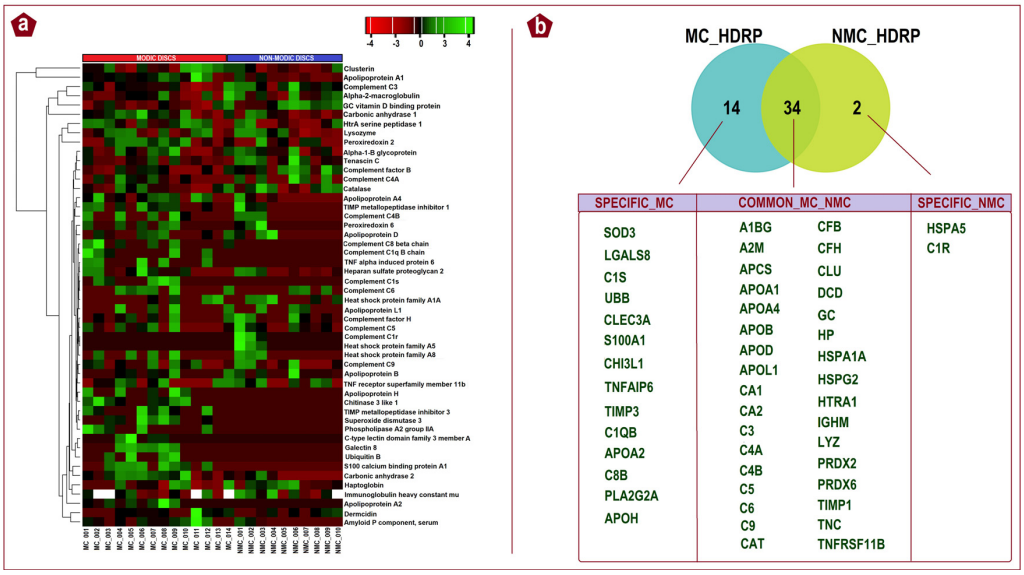
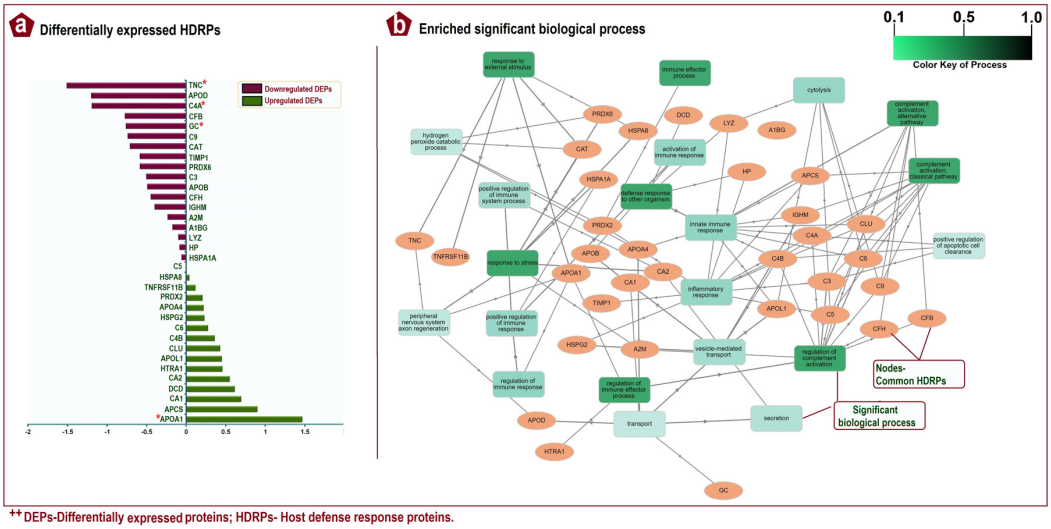


Fig. 6. Profile of HDRP in MC and NMC. (A) Heat map representation of relative abundance of 50 host defense response proteins (HDRPs) across 24 individual samples (MC- 14 samples; NMC- 10 samples) after supervised hierarchical clustering using complete linkage method. Their distance metrics were calculated by Euclidean distance. Left part of heat map shows MC and NMC (right) with the relative abundance based on the spectral count transformed into Z-score. In comparison with NMC, expression of HDRPs was more abundant in MCs which suggests clearance of cellular debris and infection-mediated immune response. (B) Venn diagram showing common and specific HDRPs between conditions- MC and NMC. About 34 (68%) were common, 2 (4%) specific to NMC and 14 (28%) specific to MC.

biglycan (BGN)). Biglycan has been previously documented to have regenerative potential in animal and cell-culture models and needs to be investigated for its ability to reverse or halt degeneration in human intervertebral discs [20]. The excessive ECM breakdown could be secondary to the products of immune and inflammatory pathways which were observed to be upregulated in MC group as discussed below.



++ DEPs-Differentially expressed proteins; HDRPs- Host defense response proteins.

Fig. 7. Functional analysis of differentially expressed HDRPs across MC and NMC conditions – **(A)** Bar diagram represents 34 differentially expressed HDRPs in MC and NMC discs. *indicates statistical significance ($p<0.05$), using t-test/ MW-U test (in case of normality violation) using SPSS vs 25.0. B) Significant biological process of common HDRPs analysed using GOnet with a p-value threshold of ≤3.26e-7. Significant enrichment of complement activation-alternate pathway, complement activation-classical pathway, hydrogen peroxide catabolic process, defense response to other organisms, response to stress, immune effector process remains proof for infection and inflammation mediated mechanisms found indicating in-vitro pathogen associated infection/ inflammatory response.

Inflammatory profile in MC group

On analyzing the 45 proteins expressed only in MC group, 14 of them were host-defense response proteins which are known to initiate inflammatory responses to eliminate pathogens. The remaining 31 proteins mainly consisted of immunoglobulins and inflammatory mediators. The presence of excessive immunoglobulins indicate activation of adaptive immunity in response to chronic pathogenic exposure. On the other hand, we also identified Plasminogen, Angiogenin and Kininogen only in MC group, which have well established roles in inducing vasodilatation, chemotaxis and pain generation through bradykinin production [21,22]. Other strong inflammatory mediators such as Ferritin which has been implicated in systemic inflammations following infections were also present only in MC. The pro-inflammatory status results in accumulation of serine protease (HTRA1) which in turn causes proteolytic degradation of tissues leading to ECM breakdown and more symptoms in MC group.

We also observed the unique expression of TNFAIP6 in MC and upregulation of its receptor (TNFRSF11B) adding evidence to the presence of an intense inflammatory status in MC. Our findings are consistent with that of Ohtori et al. who noticed higher expression of tumor necrosis factor (TNF) and protein gene product 9.5 immunoreactive nerve fibres in MC using immunohistochemistry [23]. TNFA upregulates CRTAC1 expression in primary human articular chondrocytes and synovial fibroblasts causing inflammation and cartilage destruction. Interestingly CRTAC1 was also expressed only in MC group in our study. Deletion of CRTAC1 has provided an anti-inflammatory effect in mice models of inflammation and therefore both TNF and CRTAC1 are potential molecular targets to inhibit inflammatory response in MC group [24].

Stress response proteins

In this study, we also observed an increase in expression of stress response proteins in MC group, which is an inherent compensatory mechanism to tackle accumulated reactive oxygen species (ROS) occurring secondary to tissue oxidative stress following inflammation. Catalase (CAT) and superoxide dismutase (SOD3) expressed only in MC group and the upregulated clusterin (CLU) are crucial antioxidant enzymes that mitigate oxidative stress [25,26]. Peroxiredoxin 2 (PRDX2) is another efficient highly efficient redox protein that neutralizes hydrogen peroxide, rescuing cells from oxidative damage during inflammation. Their upregulation in a disc with MC signifies the amount of inflammatory and oxidative stress in these patients.

Biological process and pathways

To understand and capture the ongoing metabolic activity we analyzed the biological processes amongst both MC and NMC groups. Specific pathways activated amongst MC group mainly involved infection mediated inflammatory and immune responsive pathways. We observed FCERI mediated NF-kB activation which is a well-established antibacterial response resulting in phagocytosis and killing of pathogens in the accumulated macrophages [27]. Other significant immune response pathways observed in MC group included initial triggering of complement; regulation of complement cascade; neutrophil and platelet degranulation. FCGR3A-mediated IL10 synthesis and phagocytosis, Regulation of actin dynamics for phagocytic cup formation, and late endosomal microautophagy found in MC group adds up the evidence towards an active and ongoing antibacterial response.

Host defense response proteins in Modic changes

While the role of bacteria in MC is fiercely debated owing to the contamination theory, we have analyzed the expression of Host defense response proteins in addition to acute phase reactants and complement activation which form the three main pillars of antibacterial response. Out of the 50 HDRPs identified in this study, 29 (**Figs. 6B & 7A**) of them were either expressed only in MC or were upregulated. A heatmap (**Fig. 7A**) generated to compare the HDRPs expression between MC and the non-MC group clearly shows a significantly higher magnitude of expression of bacterial mediated stimulation of HDRPs in MC. While 14 of them were expressed only in MC group, only 2 were specific to NMC group, and 15 out of the 34 commonly expressed HDRPs were found to be upregulated.

Of notable importance was the upregulation of the antimicrobial peptide dermcidin (DCN). DCN is a first line host defense protein which is secreted form neutrophils or macrophages having intense proteolytic activity [7]. Other proteins induced following pathological stimuli such as acute phase reactants (APOA1, APOL1 and APOA4), and mediators of chronic inflammation like serum amyloid P-component (APCS) were also upregulated in MC group. Neutrophilic degranulation, also causes the release of antimicrobial peptides such as synovial-phospholipase-A2 (PLA2G2A)-an anti-bacterial protein to defend the host resulting in opsonisation, phagocytosis, and apoptosis especially in MC [28].Though complement cascade proteins were present in both groups, the presence of these proteins (C1S, C1QB and C8B) in MC alone and upregulation of (C6 and C4B) indicate complement activation.

S100A1, expressed only in MC discs, is a pro-inflammatory molecule that has an immense role in protecting the intra- and extracellular environments during infection. However, its uncontrolled activity has been found to result in many inflammatory and neurodegenerative diseases [29]. Similarly, LGALS8 and C-type lectin domain family three-member A (CLEC3A) are antimicrobial proteins having a well-established role in autophagy of both gram-negative and gram-positive bacteria, which were specifically expressed in the MC group [30].

While the above discussed proteins indicate activation of innate immune system, which represent an acute response, the presence of immunoglobulins (IGHV3-7, IGLC1, IGKV3-15, IGKV3D-11, IGKV4-1, IGKV2-40) and activation of FCGR3A mediated phagocytosis pathway in MC group represent the activation of adaptive immune system. This adds evidence for the existence of a chronic bacterial antigenic stimulus leading to induction and mediation of immune pathways which needs further investigation using multi-disciplinary research co-relating bacterial isolation from discs and proteomic analysis.

Ubiquitin mediated proteasome degradation in Modic changes

In a retrospective case-control study of 1124 patients undergoing lumbar surgeries in a single-center, we found that the preoperative MC (odds ratio 2.725) was an independent risk factor for developing SSI [15]. Further, on comparing patients undergoing lumbar microdiscectomy in a prospectively followed up cohort of 209 patients we found that patients with preoperative MC had less favorable back pain, functional scores, and patient satisfaction [19]. Laustsen et al in a systematic review of literature of 14 articles involving 1652 surgical patients, confirmed a negative association between surgical outcomes and patients with MC [4]. However, to date there is no study which has analyzed the possible pathomechanisms barring association studies.

The overall expression of proteins in the current study revealed strong evidence towards infection mediated host defense response, inflammation and compensatory stress response. To identify potential targets for targeted molecular therapies, we subjected the proteins expressed in MC and non-MC group to a novel data analysis using STITCH database vs 5.0 which provides interactions between proteins, small molecules and chemicals, and found important leads. Many of the above described proteins such as apolipoprotein, kininogens, kallikrein, immunoglobulins and galectins were tightly interacting with ubiquitin (UBB and UBC) which activate formation of chaperones (PSMD4 & PSMD5) and finally proteasome formation. This finding implicates the activation of Ubiquitin mediated proteasome degradation which has immense potential in ECM breakdown if left unchecked.

The Ubiquitination machinery orchestrates a complex inflammasome activation following exposure to pathogenic bacteria [31]. Another interesting observation was the association of all the degradative pathway proteins with glutamic acid. Glutamic acid is an excitatory neurotransmitter, which on excess stimulation is known to cause seizures and many neuropsychic disorders [32]. Multiple studies have demonstrated their excrescence from herniated disc material and ability to have nociceptive effect on dorsal root ganglion of nerves [33]. Excessive glutamic acid production in CSF has been found in patients with bacterial infection. However, it remains unknown as to whether MC have any relation to their excess production, which requires metabolomic studies to compare and quantify glutamic acid production in patients with and without MC.

We performed quantitative estimation of 18 amino acids amongst discs with and without MC using high performance liquid chromatography which confirmed the excessive accumulation of glutamic acid (4.471 ppm) in MC group, when compared to 2.446 ppm in NMC group.

Role of glutamate

Histopathological analysis of damaged end plates show neovascularisation and ingrowth of nerve fibres [34]. While neovascularisation predisposes accumulation of inflammatory molecules, the ingrowth of nerve fibres subjects these patients to excessive nociceptive stimuli. However, it remained unknown as to which metabolite could lead to this phenomenon. The higher expression of glutamate, an excitatory neurotransmitter in MC found in the current study could sensitise these nerve fibres causing excessive pain. It would be interesting to investigate the efficacy of anti-glutaminergic therapy in improving clinical and functional outcomes in patients with MC. Improvement in chronic LBP following high dose of Fasinumab, a monoclonal antibody against nerve growth Factor, is yet another evidence to this phenomenon and needs further focussed research [35].

Molecular targets for improving outcomes

On analyzing the various biological pathways, we found strong evidence for uncontrolled inflammatory response. We found two main downstream targets which could have a positive impact on clinical outcomes. One being the ubiquitin mediated proteasome degradation, antibodies to which have already been developed some of which include Carfilzomib and Bortezomib, which also suppresses inflammatory signals including IL-6 and TNF-A secretion. Another target being anti-glutaminergic therapy due to excess accumulation of glutamic acid in patients with Modic changes documented in the study.

Limitation of the study

In this study, we have performed only molecular analysis of discs with Modic changes and compared it with those without Modic changes. A clinical outcome comparison has not been performed. All the discs harvested were from herniated samples in both the groups and whether non-herniated discs with MC differ have not been analysed. This study involved only 2 Type 1 MC and 12 Type 2 MC. Traditionally, Modic Type 1 changes were considered unstable and Type 2 were considered relatively unstable. However, recent studies have shown that Type 2 are not quiescent lesions and could involve pathological changes. Owing to lower prevalence of MC Type 1, we could not compare their molecular profile with MC Type 2. Further, though our study has clearly documented HDRPs, as one of the main biological changes

in MC, we have not investigated whether bacterial etiology has played a direct role in their activation. Future studies using advanced culture-independent approaches such as Next-generation sequencing (NGS) is necessary to investigate bacterial role in MC. The effect of antiglutaminergic therapy in MC needs further investigation.

Clinical implication

Modic changes have been strongly associated with degenerative disc disease and several aetiologies have been proposed including genetic, mechanical, inflammatory, and infections. Recently, there are increasing number of studies

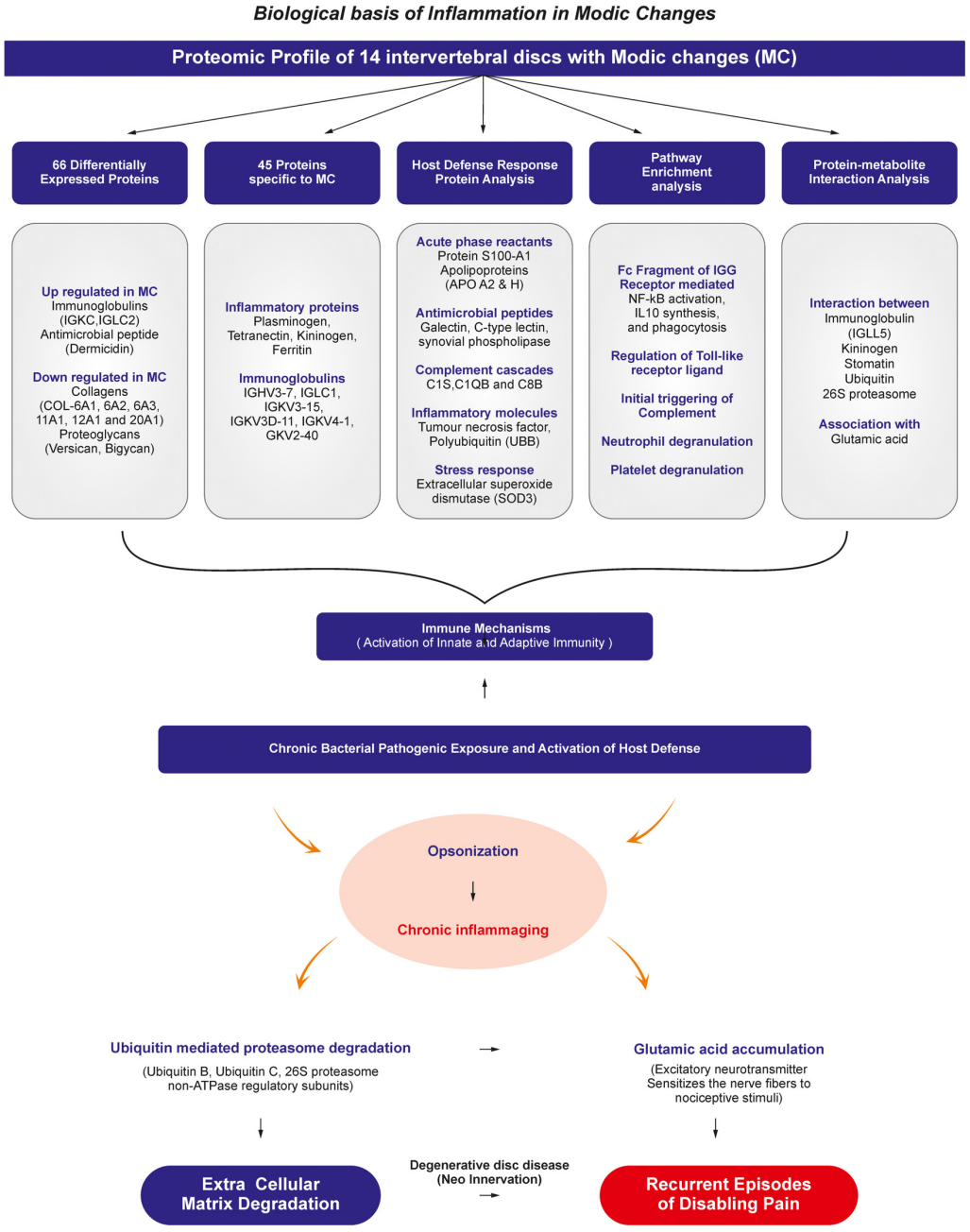


Fig. 8. The proteomic analysis of discs with Modic changes revealed significant bacterial mediated activation of both innate and adaptive immunity evidenced by the host defense response resulting in the accumulation of acute phase reactants, inflammatory proteins, complement proteins, immunoglobulins and related pathways. Ubiquitin mediated proteasome degradation leading to extra cellular matrix degeneration and resultant accumulation of glutamic acid are possible molecular targets for inhibition.

reporting poor clinical and functional outcomes in both conservative and surgical outcomes of patients with Modic changes. However, the exact biological basis causing these difference in outcomes had not been investigated on a molecular level. In this study, the overall proteomic constitution of MC group shows an intense inflammatory status and activation of host defense response proteins, acute phase reactants, complement proteins and Immunoglobins. More importantly, a significant association was found for Ubiquitin mediated proteasome degeneration, which leads to ECM breakdown and accumulation of glutamic acid, an excitatory neurotransmitter and potential pain generator. The findings have been confirmed by amino acid analysis, and the study provides potential targets for molecular therapy, at different levels ranging from TNF-A blockers to inhibit inflammation, monoclonal antibodies targeted against ubiquitin mediated proteasome degradation or downstream targets such as antiglutaminergic therapies for patients with MC.

Conclusion

Our study confirms that MC represents an intense inflammatory status with activation of host defense response and immune reactive pathways. Downstream effects leading to ubiquitin mediated proteasomal degradation of ECM proteins and the resulting metabolites such as glutamic acid were detected and confirmed in MC. Inhibition of Ubiquitin mediated proteasome degradation with specific antibodies or administration of antiglutaminergic therapy were identified as two possible therapeutic interventions in Modic changes Fig. 8.

Funding

The project was funded by Ganga Orthopaedic Research & Education Foundation (GOREF 2019-09)

IRB approval

The study was performed after approval of the IRB committee.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgement

SR, DCR, CT and MR conceived and formulated the project. SMN, CT contributed to the design of the analysis; performed lab experiments and bulk of data analysis; DCR, KSVA, RMK and APS wrote and prepared the manuscript. All authors have read through and given the final approval of the submitted publication. We also acknowledge the efforts of Ms M Sujitha and Ms M Dhanalakshmi for assistance in LC–MS/MS experiments.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2021.07.003.

References

[1] Kanna RM, Shanmuganathan R, Rajagopalan VR, Natesan S, Muthuraja R, Cheung KMC, et al. Prevalence, patterns, and genetic association analysis of modic vertebral endplate changes. Asian Spine J 2017;11:594–600. https://doi.org/10.4184/asj.2017.11.4.594.

[2] Albert HB, Manniche C. Modic changes following lumbar disc herniation. Eur Spine J 2007;16:977–82. https://doi.org/10.1007/s00586-007-0336-8.

[3] Albert HB, Kjaer P, Jensen TS, Sorensen JS, Bendix T, Manniche C. Modic changes, possible causes and relation to low back pain. Med Hypotheses 2008;70:361–8. https://doi.org/10.1016/j.mehy.2007.05.014.

[4] Laustsen AF, Bech-Azeddine R. Do Modic changes have an impact on clinical outcome in lumbar spine surgery? A systematic literature review. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc 2016;25:3735–45. https://doi.org/10.1007/s00586-016-4609-y.

[5] Shahmohammadi MR, Behrouzian S. Effect of preoperative Modic change in the outcome of patients with low back pain following posterior spinal fusion or laminectomy. Asian J Neurosurg 2019;14:432–5. https://doi.org/10.4103/ajns.AJNS_41_18.

[6] Kang KT, Son DW, Kwon O, Lee SH, Hwang JU, Kim DH, et al. Effect of modic changes in cervical degenerative disease. Korean J Spine 2017;14:41–3. https://doi.org/10.14245/kjs.2017.14.2.41.

[7] Rajasekaran S, Tangavel C, Aiyer SN, Nayagam SM, Raveendran M, Demonte NL, et al. ISSLS PRIZE IN CLINICAL SCIENCE 2017: Is infection the possible initiator of disc disease? An insight from proteomic analysis. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc 2017;26:1384–400. https://doi.org/10.1007/s00586-017-4972-3.

[8] Rajasekaran S, Tangavel C, K S SVA, Soundararajan DCR, Nayagam SM, Matchado MS, et al. Inflammaging determines health and disease in lumbar discs-evidence from differing proteomic signatures of healthy, aging, and degenerating discs. Spine J Off J North Am Spine Soc 2020;20:48–59. https://doi.org/10.1016/j.spinee.2019.04.023.

[9] Rajasekaran S, Tangavel C, Soundararajan DCR, Nayagam SM, Matchado MS, Muthurajan R, et al. Proteomic signatures of healthy intervertebral discs from organ donors: a comparison with previous studies on discs from scoliosis, animals, and trauma. Neurospine 2020;17:426–42. https://doi.org/10.14245/ns.2040056.028.

[10] Zybailov B, Mosley AL, Sardiu ME, Coleman MK, Florens L, Washburn MP. Statistical analysis of membrane proteome expression changes in Saccharomyces cerevisiae. J Proteome Res 2006;5:2339–47. https://doi.org/10.1021/pr060161n.

[11] Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M. STITCH 5: augmenting protein-chemical interaction networks with tissue and affinity data. Nucleic Acids Res 2016;44:D380–4. https://doi.org/10.1093/nar/gkv1277.

[12] Chen Y, Yang H, Zhang L, Wang Y, Zou J. Analyzing the influence of modic changes on patients with lower back pain undergoing conservative treatment. Pain Res Manag 2019;2019:8185316. https://doi.org/10.1155/2019/8185316.

[13] Peterson CK, Pfirrmann CWA, Hodler J. Are Modic changes related to outcomes in lumbar disc herniation patients treated with imaging-guided lumbar nerve root blocks? Eur J Radiol 2014;83:1786–92. https://doi.org/10.1016/j.ejrad.2014.06.008.

[14] Djuric N, Yang X, Ostelo RWJG, van Duinen SG, Lycklama à Nijeholt GJ, van der Kallen BFW, et al. Disc inflammation and Modic changes show an interaction effect on recovery after surgery for lumbar disc herniation. Eur Spine J 2019;28:2579–87. https://doi.org/10.1007/s00586-019-06108-9.

[15] Pradip IA, Dilip Chand Raja S, Rajasekaran S, Sri Vijayanand KS, Shetty AP, Kanna RM, et al. Presence of preoperative Modic changes and severity of endplate damage score are independent risk factors for developing postoperative surgical site infection: a retrospective case-control study of 1124 patients. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc 2020. https://doi.org/10.1007/s00586-020-06581-7.

[16] Johnson ZI, Schoepflin ZR, Choi H, Shapiro IM, Risbud MV. Disc in flames: roles of TNF-α and IL-1β in intervertebral disc degeneration. Eur Cell Mater 2015;30:104–17.

[17] Ohrt-Nissen S, Fritz BG, Walbom J, Kragh KN, Bjarnsholt T, Dahl B, et al. Bacterial biofilms: a possible mechanism for chronic infection in patients with lumbar disc herniation - a prospective proof-of-concept study using fluorescence in situ hybridization. APMIS Acta Pathol Microbiol Immunol Scand 2018;126:440–7. https://doi.org/10.1111/apm.12841.

[18] Capoor MN, Ruzicka F, Schmitz JE, James GA, Machackova T, Jancalek R, et al. Propionibacterium acnes biofilm is present in intervertebral discs of patients undergoing microdiscectomy. PloS One 2017;12:e0174518. https://doi.org/10.1371/journal.pone.0174518.

[19] Kumarasamy D, Rajasekaran S, Anand KS SV, Soundararajan DCR, Shetty T AP, Kanna P RM, et al. Lumbar disc herniation and preoperative Modic changes: a prospective analysis of the clinical outcomes after microdiscectomy. Glob Spine J 2021:2192568220976089. https://doi.org/10.1177/2192568220976089.

[20] Rajasekaran S, Soundararajan DCR, Tangavel C, Nayagam SM, S SVK, R S, et al. Uncovering molecular targets for regenerative therapy in degenerative disc disease: do small leucine-rich proteoglycans hold the key? Spine J 2021;21:5–19. https://doi.org/10.1016/j.spinee.2020.04.011.

[21] Rosso M, Fibbi G, Pucci M, Margheri F, Serratì S. The plasminogen activation system in inflammation. Front Biosci J Virtual Libr 2008;13:4667–86. https://doi.org/10.2741/3032.

[22] Lioté F, CHAMPY R, Moenner M, BOVAL-BOIZARD B, Badet J. Elevated angiogenin levels in synovial fluid from patients with inflammatory arthritis and secretion of angiogenin by cultured synovial fibroblasts. Clin Exp Immunol 2003;132:163–8. https://doi.org/10.1046/j.1365-2249.2003.02117.x.

[23] Ohtori S, Inoue G, Ito T, Koshi T, Ozawa T, Doya H, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and Modic type 1 or type 2 changes on MRI. Spine 2006;31:1026–31. https://doi.org/10.1097/01.brs.0000215027.87102.7c.

[24] Ge X, Ritter SY, Tsang K, Shi R, Takei K, Aliprantis AO. Sex-specific protection of osteoarthritis by deleting cartilage acid protein 1. PLoS ONE 2016;11. https://doi.org/10.1371/journal.pone.0159157.

[25] Nandi A, Yan L-J, Jana CK, Das N. Role of catalase in oxidative stress- and age-associated degenerative diseases. Oxid Med Cell Longev 2019;2019:e9613090. https://doi.org/10.1155/2019/9613090.

[26] Ha E-M, Oh C-T, Ryu J-H, Bae Y-S, Kang S-W, Jang I, et al. An antioxidant system required for host protection against gut infection in drosophila. Dev Cell 2005;8:125–32. https://doi.org/10.1016/j.devcel.2004.11.007.

[27] Liu J, Xiang J, Li X, Blankson S, Zhao S, Cai J, et al. NF-κB activation is critical for bacterial lipoprotein tolerance-enhanced bactericidal activity in macrophages during microbial infection. Sci Rep 2017;7:40418. https://doi.org/10.1038/srep40418.

[28] van Hensbergen VP, Wu Y, van Sorge NM, Touqui L. Type IIA secreted phospholipase A2 in host defense against bacterial infections. Trends Immunol 2020;41:313–26. https://doi.org/10.1016/j.it.2020.02.003.

[29] Xia C, Braunstein Z, Toomey AC, Zhong J, Rao X. S100 proteins as an important regulator of macrophage inflammation. Front Immunol 2018;8. https://doi.org/10.3389/fimmu.2017.01908.

[30] Thurston TLM, Wandel MP, von Muhlinen N, Foeglein A, Randow F. Galectin 8 targets damaged vesicles for autophagy to defend cells against bacterial invasion. Nature 2012;482:414–8. https://doi.org/10.1038/nature10744.

[31] Xu T, Guo Y, Qi X. Ubiquitination-mediated inflammasome activation during bacterial infection. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20092110.

[32] Harrington JF, Messier AA, Bereiter D, Barnes B, Epstein MH. Herniated lumbar disc material as a source of free glutamate available to affect pain signals through the dorsal root ganglion. Spine 2000;25:929–36. https://doi.org/10.1097/00007632-200004150-00006.

[33] Osgood DP, Kenney EV, Harrington WF, Harrington JF. Excrescence of neurotransmitter glutamate from disc material has nociceptive qualities: evidence from a rat model. Spine J Off J North Am Spine Soc 2010;10:999–1006. https://doi.org/10.1016/j.spinee.2010.07.390.

[34] Rätsep T, Minajeva A, Asser T. Relationship between neovascularization and degenerative changes in herniated lumbar intervertebral discs. Eur Spine J 2013;22:2474–80. https://doi.org/10.1007/s00586-013-2842-1.

[35] Dakin P, Kivitz AJ, Gimbel JS, Skrepnik N, DiMartino SJ, Emeremni CA, et al. Efficacy and safety of fasinumab in patients with chronic low back pain: a phase II/III randomised clinical trial. Ann Rheum Dis 2020. https://doi.org/10.1136/annrheumdis-2020-217259.

North American Spine Society Journal (NASSJ) 5 (2021) 100052

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Case Studies

Anterior transcorporeal full-endoscopic drainage of a long-span ventral cervical epidural abscess: A novel surgical technique

Vit Kotheeranurak[a,*], Khanathip Jitpakdee[a], Weerasak Singhatanadgige[b], Worawat Limthongkul[b], Wicharn Yingsakmongkol[b], Jin-Sung Kim[c]

[a] Department of Orthopedics, Queen Savang Vadhana Memorial Hospital, Sriracha, Chonburi, Thailand
[b] Department of Orthopaedic, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Department of Neurosurgery, Seoul St. Mary's Hospital, Spine Center, College of medicine, The Catholic University of Korea, Seoul, South Korea

A B S T R A C T

Background: A long-span ventral cervical epidural abscess is a rare and devastating condition. Typically, extensive procedures are chosen to deal with this condition and usually end up with limited cervical motion. Here, we describe a novel minimally invasive anterior full-endoscopic transcorporeal approach for drainage of large ventral cervical epidural abscess.

Case description: A 33-year-old man presented with seizures and acute weakness in all extremities persistent for 2 hours. His motor power of the upper and lower extremities was rapidly declined from grade III to grade 0 within 12 hours. Magnetic resonance imaging (MRI) showed a long-span ventral epidural abscess extending from C2 to T1, cervical spinal cord, and a retropharyngeal abscess. A typical anterior cervical approach to the prevertebral space was performed to evacuate pus from the retropharyngeal abscess, after which anterior transcorporeal full-endoscopic drainage of the large ventral cervical epidural abscess was successfully performed.

Outcome: The patient's motor power recovered to grade IV within 2 weeks post-operation. He had no neck pain or instability following the operation. Postoperative MRI and computed tomography revealed diminished epidural abscess.

Conclusions: For managing cases with a ventral-type cervical epidural abscess, anterior transcorporeal full-endoscopic drainage is an alternative minimally invasive method that yields sufficient debridement and drainage.

Background

Spinal epidural abscess is a bacterial infection characterized by the accumulation of purulent fluid and suppuration in the spinal epidural space [1]. The incidence has been reported as 0.2–2.8 cases per 10,000 hospital admissions per year [2,3]. Hematogenous spread is reported as the most common mechanism of infection (more than half of cases) [4,5]. However, the infectious source was reported to be identified in only up to 50% of cases despite complete investigation [6].

Infected individuals may present with fever, back pain, neck pain and stiffness, muscle weakness, radiculopathy, or bowel and bladder dysfunction with different durations of symptoms. Spinal epidural abscess remains a challenging condition as the various clinical manifestations make early diagnosis and planning of appropriate treatment to prevent further morbidity and mortality difficult.

Abscesses in the cervical spine are less common compared to those in the lumbar and thoracic regions but have a high risk of causing major neurological deficits, morbidity, and death [5,7]. Thus, prompt detection, diagnosis, and management of cervical spinal epidural abscess are the most important prognostic factors that lead to successful resolution and prevention of complications from delayed treatment [8].

When patients present with sepsis, significant or progressive neurological deficits, instability, or failure of medical treatment, surgical intervention is indicated [4,9,10]. The goals of surgical treatment for cervical epidural abscess are infectious source eradication, adequate drainage of abscesses, debridement of necrotic tissue, spinal cord decompression, and stabilization in cases of instability [2,11,12,13].

Cervical epidural abscesses are more common in the dorsal than in the ventral areas, as they are likely to accumulate in larger epidural spaces that contain infection-prone fat [8,14]. Additionally, it is not uncommon for an epidural abscess to extend to multiple levels [15,16,17]. The conventional open surgical drainage for this condition is challenging, often invasive, has high rates of morbidity and mortality, and may lead to spinal instability. Ventrally located abscesses are particularly challenging and may necessitate an extensive multilevel anterior approach for decompression. Therefore, any minimally invasive techniques that are capable of adequately draining the pus and preserving cervical stability are highly beneficial for patients who suffer from this condition.

* Corresponding author.
E-mail address: vitinspine@gmail.com (V. Kotheeranurak).

https://doi.org/10.1016/j.xnsj.2021.100052
Received 5 January 2021; Received in revised form 28 January 2021; Accepted 6 February 2021
Available online 12 February 2021

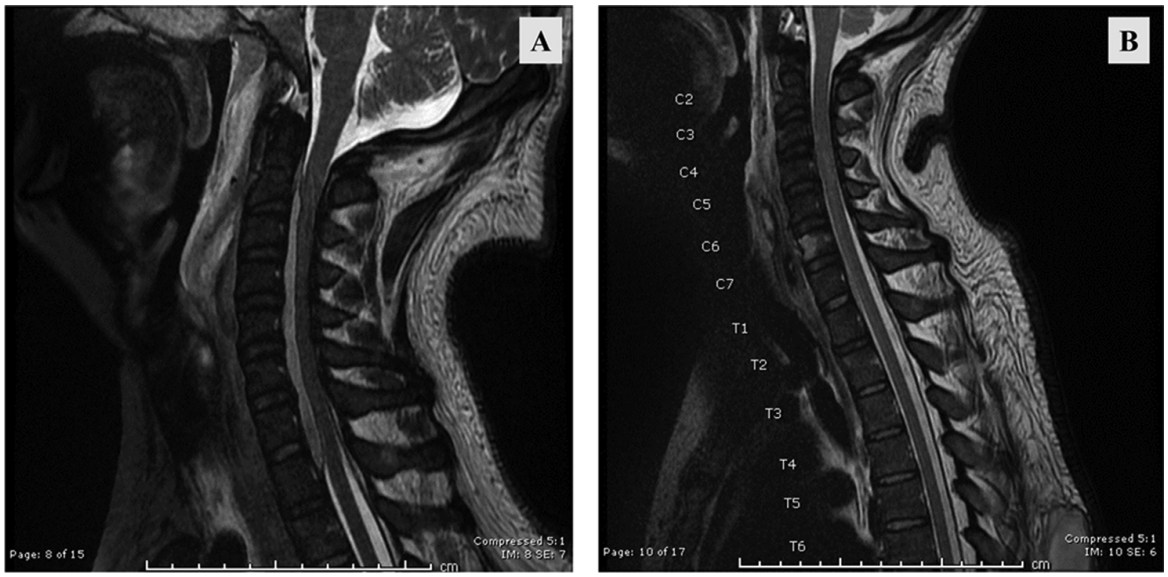


Fig. 1. Preoperative T2W-MRI showing a profound retropharyngeal abscess with long-span ventral cervical epidural abscess from C2-T1 (A). An immediate postoperative T2W-MRI showing significant reduction of pus collection at the anterior epidural space (B)
MRI: magnetic resonance imaging.

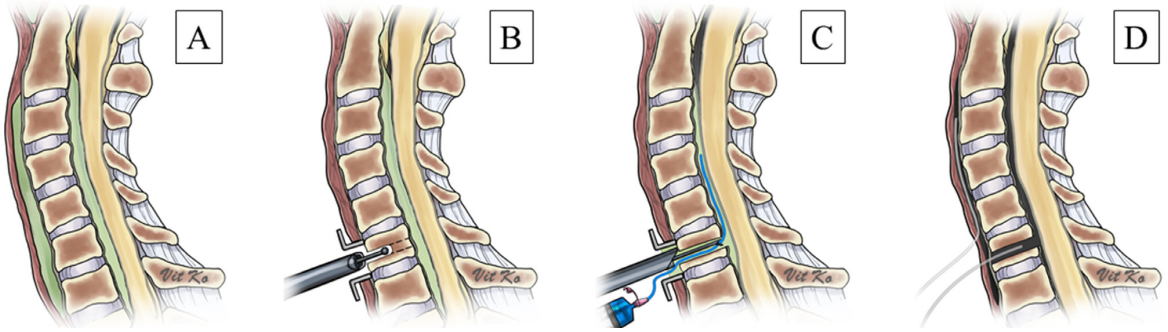


Fig. 2. Depicting the retropharyngeal abscess and long-span ventral cervical epidural abscess (A). Drilling of the C6 vertebral body (transcorporeal approach) after anterior debridement and drainage of the retropharyngeal abscess (B). Inserting the feeding tube in the ventral epidural space and irrigation (C). Placing drains after abscess drainage (D).

We report the case of a long-span ventral cervical epidural abscess that was successfully, safely, and effectively treated with anterior transcorporeal full-endoscopic drainage, a novel minimally invasive alternative method.

Case description

A 33-year-old man was brought to the hospital with acute seizures and weakness in all extremities experienced for 2 hours. He had type 1 diabetes mellitus and hypertension, which were poorly controlled.

Upon admission, neurological examination revealed grade III muscle power of the upper and lower extremities, hyperreflexia of the lower extremities, and the presence of abnormal upper motor neuron reflexes. After intracranial pathology was ruled out, emergent magnetic resonance imaging (MRI) showed a long-span ventral cervical epidural abscess from C2 to T1, compressing the central area of the cervical spinal cord. A retropharyngeal abscess was also noted (Fig 1A., Fig 2A).

The muscle power rapidly declined to grade I and he had sensory loss from C3 downwards within 6 h. At this point, emergent surgical intervention was warranted. After discussion with the patient and the otolaryngologist, drainage via a typical anterior cervical approach to the prevertebral space was performed to evacuate pus from the retropharyngeal abscess. Subsequently, full-endoscopic drainage via the anterior transcorporeal approach was successfully performed.

Written informed consent was obtained from the patient prior to the operation. The procedure performed in study involving human participants was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethical Committee (EC) of the institution approved the study (EC number 33/2020).

Surgical technique

After general anesthesia was administered, the patient was placed in the supine position. A bolster pillow was placed under the cervical spine to achieve a normal lordotic curvature. Skin marking under fluoroscopic guidance was performed to identify the C5-6 intervertebral disc level where the highest amount of prevertebral abscess was noted.

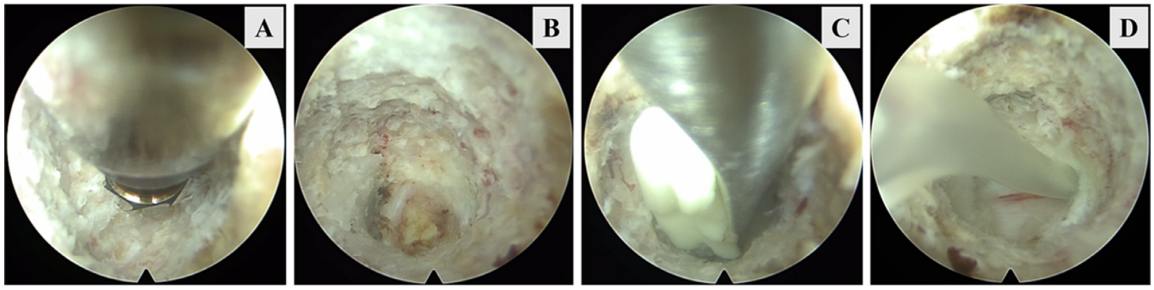


Fig. 3. Endoscopic view. Drilling via cervical vertebral body (A). Reaching the PLL (B). Pus breakout after entering the ventral epidural space (C). Irrigation via the passing NG tube (D)
PLL: posterior longitudinal ligament; NG: nasogastric.

A standard Smith-Robinson approach from the left side was used. In brief, a 4-cm skin incision was made, the platysma muscle was divided vertically, and the deep cervical fascia was incised to locate the plane between the strap muscles and the anterior border of the sternocleidomastoid muscle (SCM). Deep dissection was performed by dividing the pretracheal fascia medial to the carotid sheath. The medial structures (trachea, esophagus, thyroid, and strap muscles) were retracted medially, while the carotid sheath and SCM were retracted laterally using Army-Navy retractors.

The anterior cervical body plane was approached by exposing the swollen and inflamed tissue. A careful blunt dissection was performed, and the pocket of pus (approximately 20 mL) was thoroughly debrided after collected for gram staining, culture and sensitivity test.

The center of the C6 vertebral body was marked. Then, a full endoscopic system was assembled (RIWOspine GmbH, Germany). Under fluoroscopic and endoscopic guidance, anterior drilling was performed using a 2.5 mm cutting tip and a diamond tip burr (Fig. 2B, 3A). During the tunneling process, intraosseous bleeding was managed with bipolar radiofrequency cautery, bone wax, and physical compression. The tunnel was enlarged to allow for endoscope insertion.

The posterior edge of the C6 body was reached before the posterior longitudinal (PLL) ligament was encountered (Fig. 3B). A dissector and hook were used to penetrate the PLL, exposing the stream of flowing exudative fluid in the tunnel (Video 1, Fig. 3C). Further resection of the PLL tissue was performed until adequate space was observed. An 8F nasogastric (NG) tube was inserted outside the endoscope working cannula through the tunnel. Using a pituitary rongeur, the tip of the NG tube was carefully passed between the PLL and the spinal cord (Fig. 2C, Fig. 3D). Normal saline was used as the irrigation fluid, pushing via the NG tube, while endoscopic fluid irrigation was temporally clamped (Video 2).

Advancement of the NG tube was performed gradually (Video 3) until the tip of the NG tube reached the most cranial or caudal part, where the length of the NG tube inserted was in concordance with the extent of pus measured from the preoperative MRI. The endpoint of irrigation was determined by the irrigation fluid characteristics, which showed no turbid appearance. A drain was placed, and the skin was closed in a subcutaneous fashion (Fig 2D).

Outcome

With a multidisciplinary team approach, proper blood glucose control, intravenous antibiotic therapy (adjusted to the culture and sensitivity test), dental and oral hygiene management, rehabilitation, and family counseling and support, the patient's muscle power had recovered to grade IV and sensory returned to near normal within 2 weeks after the operation. The patient had no neck pain or instability following the procedure.

The early postoperative computed tomography (CT) and MRI scans (Fig 1 B) revealed no remaining collection in the epidural space, increasing the space available for the spinal cord, thus correlating with the clinical improvement of the patient.

Discussion

To the best of our knowledge, this is the first published report with a detailed surgical technique description and demonstration of a full endoscopic method to drain a ventral cervical epidural abscess via a transcorporeal approach. However, there are few reports of the endoscopic technique having been used to drain ventral epidural abscess in the cervical, thoracic, and lumbar segments [11,18,19]. Owing to the fact that the patient had a retropharyngeal abscess, which needed to be drained from the anterior approach, and the collection was located at the ventral side of cervical spinal cord, an anterior approach was the preferred surgical option in this instance.

Spinal epidural abscess is a spinal emergency condition due to serious, life-threatening consequences from delayed diagnosis and treatment, such as irreversible neurological damage, sepsis, or death. Infection of the cervical spine is less frequently involved but is more devastating due to major neurological deficits; therefore, prompt early surgical drainage of a cervical epidural abscess followed by antibiotic therapy is generally recommended to avoid serious complications.

However, multilevel cervical epidural abscesses are not uncommon, especially in immunocompromised patients. In these patients, conventional extensive surgical drainage has a high risk of complications such as bleeding, long operative time, development of cervical instability, postoperative neurological deterioration, or other systemic problems [18]. Therefore, a number of various minimally invasive techniques for epidural abscess drainage have been described in the literature.

Percutaneous CT-guided needle aspiration was demonstrated by Lyu et al [20]. A patient with multilevel epidural abscess extending from the lower cervical to lumbar spine was successfully treated with CT-guided posterior needle aspiration. This technique is not suitable for ventrally located epidural abscesses, and intraoperative CT is suggested to avoid dural puncture and subsequent development of meningitis. A limited laminectomy combined with the use of small-diameter silicon epidural catheter irrigation was proposed to limit the need for extensive procedures [6]. However, possible limitations of this strategy include chronic infection with thick pus and adhesions, patients with extensive spinal stenosis, or abscesses located anterior to the spinal cord.

In cases of ventral cervical epidural abscess, anterior debridement is generally preferred to directly access the pathology [19]. Many different approaches have been demonstrated, such as anterior corpectomy, partial corpectomy, discectomy, posterior approach, or other minimally invasive methods [19,21,22,23,24]. The transpedicular approach was proposed [3] to gain access to the ventral epidural space posteriorly. This approach was completed by burring the medial aspect of the pedi-

cle to expose the ventral epidural space without any dural retraction. However, this technique is extensive and inevitably followed by cervical instability, which warrants instrumentation.

Microscopic and endoscopic techniques for cervical epidural abscesses have also been proposed. Recently, Chang et al. [11] demonstrated the full endoscopic removal of a dorsal cervical spinal epidural abscess extending from C4–7. The endoscope was inserted through the posterior cervical muscles to expose the C5–6 interlaminar space. With the advantages of the full endoscopic method, rapid recovery was observed; however, this technique is suitable only for dorsally located cervical epidural abscesses. Muzii et al. [7] performed a single-level anterior microsurgical discectomy to drain a ventral cervical epidural abscess using a silicone catheter. After incising the PLL, a 1.5 mm silicone catheter was inserted through the disc space, caudally and cranially, into the anterior epidural space to continuously lavage and remove the pus. The authors did not perform arthrodesis after abscess drainage. The proposed technique is simple, practical, and effective. However, there may be long-term consequences of cervical discectomy without fusion, such as early cervical disc degeneration or cervical instability.

Typical corpectomy or discectomy may cause postoperative instability requiring fusion and instrumentation, leading to a decrease in cervical motion. However, the presented novel technique resulted in minimal blood loss, less operative time, and early postoperative ambulation, without warranting the need for cervical fusion or instrumentation, thus preserving cervical motion. In addition, the endoscopic transcorporeal approach has proven to result in defect hole remodeling after operations [24]. The adequacy of the drainage should also be considered. Although the long-span abscess was approached by only a small hole via the vertebral body, we were able to pass a small NG tube to flush and debride the pus along its extent, which was monitored and confirmed by the subsidence of the abscess on postoperative CT scan and MRI.

Using the endoscope for surgical drainage of the cervical epidural abscess has other advantages. Infected individuals are typically elderly with multiple comorbidities or are immunocompromised. These patients cannot tolerate extensive procedures, such as corpectomy, multilevel laminectomy, and instrumentation. However, certain limitations are worth mentioned, such as, availability of the endoscopic system, long and steep learning curve, and adequacy of drainage.

Conclusions

The presented novel technique of anterior transcorporeal full-endoscopic drainage of a ventral cervical epidural abscess is feasible and yields satisfactory results and outcomes while sparing cervical motion after surgery.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Declaration Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed patient consent

The authors declare that informed patient consent was taken from the patient or family member.

Acknowledgements

The authors would like to acknowledge Dr.Napaporn Rujipatanamongkol (Department of Radiology, Queen Savang Vadhana Memorial Hospital), and Dr. Sukanya Warathanasin (Department of Otolaryngology, Queen Savang Vadhana Memorial Hospital) for their dedications in taking care of the patient. Also we would like to thank “CU spine conference” line group for friendly and generous open discussion of spine cases including this case.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2021.100052.

References

[1] Schwab JH, Shah AA. Spinal epidural abscess: diagnosis, management, and outcomes. J Am Acad Orthop Surg 2020;28(21):e929–38.
[2] Zimmerer SM, Conen A, Muller AA, et al. Spinal epidural abscess: aetiology, predisponent factors and clinical outcomes in a 4-year prospective study. Eur Spine J 2011;20(12):2228–34.
[3] Lara-Reyna J, Yaeger KA, Margetis K. Transpedicular approach for ventral epidural abscess evacuation in the cervical spine. World Neurosurg 2020;145:127–33.
[4] Sharfman ZT, Gelfand Y, Shah P, et al. Spinal epidural abscess: a review of presentation, management, and medicolegal implications. Asian Spine J 2020;14(5):742–59.
[5] Darouiche RO. Spinal epidural abscess. N Engl J Med 2006;355(19):2012–20.
[6] Panagiotopoulos V, Konstantinou D, Solomou E, Panagiotopoulos E, Marangos M, Maraziotis T. Extended cervicolumbar spinal epidural abscess associated with paraparesis successfully decompressed using a minimally invasive technique. *Spine* (Phila Pa 1976) 2004;29(14):E300–3.
[7] Muzii VF, Mariottini A, Zalaffi A, et al. Cervical spine epidural abscess: experience with microsurgical treatment in eight cases. J Neurosurg Spine 2006;5(5):392–7.
[8] Tetsuka S, Suzuki T, Ogawa T, et al. Spinal epidural abscess: a review highlighting early diagnosis and management. JMA J 2020;3(1):29–40.
[9] Baralo B, Kulkarni M, Ellangovan R, et al. Cervical, thoracic, and lumbar spine epidural abscess: case report and literature review. Case Rep Infect Dis 2020;2020:8834589.
[10] Dai G, Li S, Yin C, et al. Studies on 11 cases of spinal epidural abscess and literature review. Infect Drug Resist 2020;13:3325–34.
[11] Chang KS, Sun LW, Cheng CY, et al. Full endoscopic removal of cervical spinal epidural abscess: case report and technical note. Neurospine 2020;17(1):S160–S1S5 Suppl.
[12] Suppiah S, Meng Y, Fehlings MG, et al. How best to manage the spinal epidural abscess? A current systematic review. World Neurosurg 2016;93:20–8.
[13] Turner A, Zhao L, Gauthier P, et al. Management of cervical spine epidural abscess: a systematic review. Ther Adv Infect Dis 2019;6:2049936119863940.
[14] Stricsek G, Iorio J, Mosley Y, et al. Etiology and surgical management of cervical spinal epidural abscess (SEA): a systematic review. Global Spine J 2018;8(4) Suppl 59S–67S.
[15] Solomou E, Maragkos M, Kotsarini C, et al. Multiple spinal epidural abscesses extending to the whole spinal canal. Magn Reson Imaging 2004;22(5):747–50.
[16] Safavi-Abbasi S, Maurer AJ, Rabb CH. Minimally invasive treatment of multilevel spinal epidural abscess. J Neurosurg Spine 2013;18(1):32–5.
[17] Abel R, von Baum H. Multilevel epidural abscess formation with paraplegia in a healthy 33-year-old man caused by staphylococcus aureus (MSSA). Infection 2003;31(5):359–61.
[18] Akbik OS, Shin PC. Endoscopic transforaminal drainage of a ventrally located thoracic epidural abscess. World Neurosurg Jul 2020;139:268–73.
[19] Iida K, Yoshikane K, Tono O, Tarukado K, Harimaya K. The effectiveness of a percutaneous endoscopic approach in a patient with psoas and epidural abscess accompanied by pyogenic spondylitis: a case report. J Med Case Rep 2019 15;13(1):253.
[20] Lyu RK, Chen CJ, Tang LM, et al. Spinal epidural abscess successfully treated with percutaneous, computed tomography-guided, needle aspiration and parenteral antibiotic therapy: case report and review of the literature. Neurosurgery 2002;51(2):509–12 discussion 12.
[21] Young WF, Weaver M, Snyder B, et al. Reversal of tetraplegia in patients with cervical osteomyelitis–epidural abscess using anterior debridement and fusion. Spinal Cord 2001;39(10):538–40.
[22] Arnautovic KI, Olinger RG. Anterior cervical discectomy, drainage and non-instrumented cortico-cancellous allograft fusion: a treatment option for ventral cervical spinal epidural abscess. Med Arch 2012;66(3):194–7.
[23] Roselli R, Iacoangeli M, Pompucci A, et al. Anterior cervical epidural abscess treated by endoscopy-assisted minimally invasive microsurgery via posterior approach. Minim Invasive Neurosurg 1998;41(3):161–5.
[24] Deshmukh VR. Midline trough corpectomies for the evacuation of an extensive ventral cervical and upper thoracic spinal epidural abscess. J Neurosurg Spine 2010;13(2):229–33.

North American Spine Society Journal (NASSJ) 6 (2021) 100065

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Case Studies

First in man in-situ augmented reality pedicle screw navigation

Mazda Farshad [a,*], Philipp Fürnstahl [b], José Miguel Spirig [a]

[a] Spine Division, Balgrist University Hospital, University of Zurich, Forchstrasse 340, 8008 Zurich, Switzerland
[b] ROCS: Research in Orthopedic Computer Science, Balgrist University Hospital, University of Zurich, Forchstrasse 340, 8008, Zurich, Switzerland

ARTICLE INFO

Keywords:
Spinal navigation
Augmented reality
Pedicle screw navigation
HoloLens
Case report

ABSTRACT

Background: Augmented reality (AR) is a rising technology gaining increasing utility in medicine. By superimposing the surgical site and the operator's visual field with computer-generated information, it has the potential to enhance the cognitive skills of surgeons. This is the report of the first in man case with "direct holographic navigation" as part of a randomized controlled trial.

Case description: A pointing instrument was equipped with a sterile fiducial marker, which was used to obtain a digital representation of the intraoperative bony anatomy of the lumbar spine. Subsequently, a previously validated registration method was applied to superimpose the surgery plan with the intraoperative anatomy. The registration result is shown in situ as a 3D AR hologram of the preoperative 3D vertebra model with the planned screw trajectory and entry point for validation and approval by the surgeon. After achieving alignment with the surgery plan, a borehole is drilled and the pedicle screw placed. Postoperativ computer tomography was used to measure accuracy of this novel method for surgical navigation.

Outcome: Correct screw positions entirely within bone were documented with a postoperative CT, with an accuracy similar to current standard of care methods for surgical navigation. The patient was mobilized uneventfully on the first postoperative day with little pain medication and dismissed on the fourth postoperative day.

Conclusion: This first in man report of direct AR navigation demonstrates feasibility in vivo. The continuation of this randomized controlled study will evaluate the value of this novel technology.

Background

Augmented reality (AR) is a rising technology gaining increasing application in medicine. By superimposing the surgical site and the operator's visual field with computer-generated information, it has the potential to enhance the cognitive skills of surgeons. One crucial task in spine surgery is pedicle screw placement, which bears the risk of neurovascular injury or insufficient screw hold in case of inaccurate screw placement. In order to improve safety and accuracy of screw placement, navigational tools such as optical navigation systems [1], patient-specific instrumentation [2], and even robotic-assisted pedicle screw placement [3] have been developed.

In the last years, substantial efforts have been made to introduce AR as a novel surgical navigation technology into spine surgery [4–14]. Although promising results have been achieved in feasibility studies, only a few methods demonstrated efficiency in patients [6,14]. The aim of our research was to develop a method capable of visualizing the planned screw trajectories by a computer-generated hologram directly on the real surgical situs, which would enable the surgeon to constantly reconcile the surgical task with the navigation information in an intuitive way.

By leveraging surface digitization and inside-out-tracking, we developed a radiation-free approach for the registration of the preoperative plan to the intraoperative anatomy with only an AR head mounted device (HoloLens 2, Microsoft, Redmond, USA) and a marker-equipped pointer [7]. In this manner, expensive navigation systems with external cameras may be replaced by an affordable surgeon-centered navigation approach, which does not suffer from line-of-sight issues.

After completing pre-clinical validation, the first-in-man randomized controlled trial for AR-based holographic surgical navigation of pedicle screw placement in spine surgery could be started. In the following case description, we report on the case of the first patient treated with "direct" holographic spinal navigation.

Case description

Approval by the local ethics committees (NCT04610411) and the national agency for therapeutic products (Swissmedic; EUDAMED reference number: 19-02-027424)) for using the technology as a medical device within a clinical trial was obtained.

* Corresponding author.
E-mail address: mazda.farshad@balgrist.ch (M. Farshad).

https://doi.org/10.1016/j.xnsj.2021.100065
Received 5 February 2021; Received in revised form 17 April 2021; Accepted 20 April 2021
Available online 1 May 2021

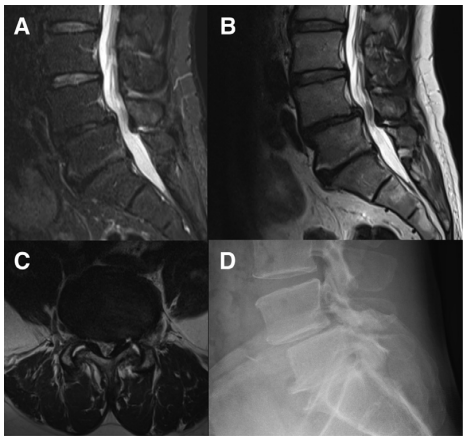


Fig. 1. Preoperative images: (A) sagittal fat suppressed MRI (turbo inversion recovery magnitude (TIRM)) and (B) sagittal MRI (T2 sequence) demonstrating segment degeneration at L4/5 and L5/S1, (C) axial MRI (T2 sequence) at level L4/5 showing spinal stenosis, (D) lateral radiograph showing accentuated spondylolisthesis at L4/5 in standing position.

A standard two-level lumbar fusion case was chosen for the first-in-man application on a 57-year-old patient with severe refractory lumbar back and left leg pain due to L5 nerve root radiculopathy. MR and CT images showed degenerative spondylolisthesis at L4/5 with facet joint effusions, consecutive spinal stenosis, and bilateral foraminal stenosis. Advanced degeneration was also detected at the level L5/S1 with almost completely collapsed disc height, intervertebral osteochondrosis (Modic Type 1), and facet joint osteoarthritis. Indication for fusion from L4 to S1 was given (Fig. 1). The patient gave informed consent to be treated with AR-based holographic surgical navigation.

Surgical planning

Preoperative lumbar CT data with a slice thickness of 1 mm (SOMATOM Edge Plus, Siemens Healthcare GmbH, Erlangen, Germany) were acquired, from which a 3D triangular surface model of each vertebra was generated using commercial segmentation software (Mimics 19.0, Materialise NV, Leuven, Belgium). An in-house developed surgical planning software was used to plan pedicles screw insertion points and trajectories in 3D. The screws were visualized as cylindrical primitives, which were manually placed on the 3D vertebra models by a surgeon. The trajectories were planned along the anatomic pedicle axis, with the entry point at the intersection between the transverse process and superior articular facet (Fig. 2). The insertion points and trajectories were then parameterized as 3D locations and direction vectors, and used as navigation information.

Surgical procedure

The surgical planning data was stored locally on the Hololens device, which was then prepared for surgery following a validated cleaning procedure. A trackable pointer and a clamp for fixation of a marker on a drill sleeve guide were additively manufactured using biocompatible polyamide PA2200 and sterilized in our institution using steam pressure (Fig. 3). The surgical procedure was performed under general anesthesia with the patient in the prone position. The dorsal structures of the spine, such as the spinous process, lamina, and transverse process, were exposed from the midline in a subperiosteal manner as usual.

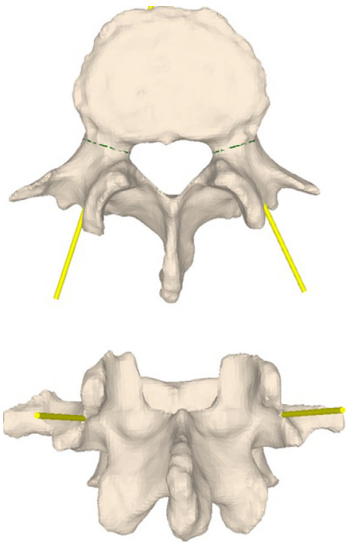


Fig. 2. : Preoperative CT reconstructions with planned screw trajectories (yellow).

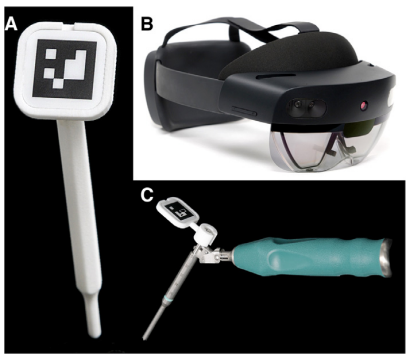


Fig. 3. Navigation equipment: (A) 3D printed pointer with fiducial marker, (B) HoloLens 2, (C) drill sleeve guide with fiducial marker mounted on a 3D printed clamp.

Registration of the bony anatomy

After exposure, the pre-calibrated HoloLens device was placed on the surgeon's head. The surgeon controlled the navigation process with gestures and voice commands (Fig. 4). The pointing instrument was equipped with a sterile fiducial marker (Clear Guide Medical, Baltimore, MD, USA) and used to generate a digital representation of the intraoperative bony anatomy. To this end, the surgeon carefully followed the contours of the spinous process, lamina, and transverse process with the tracked pointer. Marker tracking was implemented using the Aruco library, which was adopted work with Hololens 2. After acquisition of the 3D point cloud of the bony surface, a previously validated and published [7] registration method was applied to superimpose the surgery plan with the intraoperative anatomy. The registration result was presented in-situ as a 3D hologram of the preoperative 3D vertebra model with the planned screw trajectory and entry point for validation and approval (Fig. 5). Registration was done separately for each vertebra.

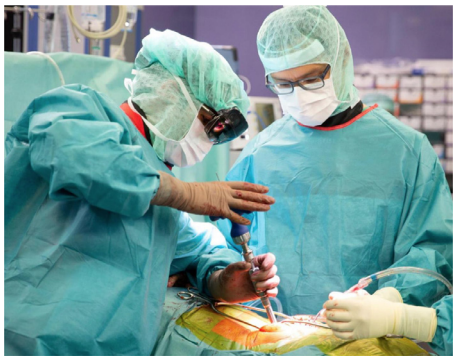


Fig. 4. Surgeon with augmented reality head mounted device during navigation.

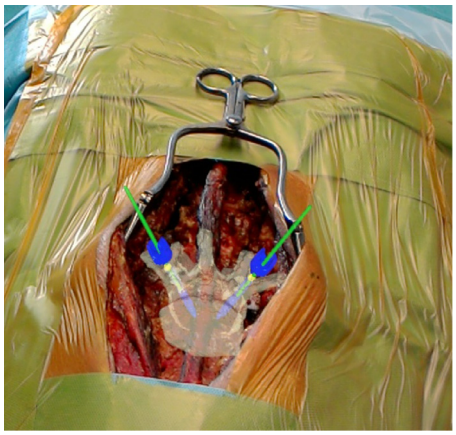


Fig. 5. 3D hologram of the preoperative 3D vertebra model with the planned screw trajectories projected in situ after registration in order to be validated by the surgeon.

Navigation

The L4 and L5 screws were placed using an AR-based holographic surgical navigation without any fluoroscopic control. A conventional drill sleeve guide with a depth limit (Ø 3.2 mm No. 03.614.010, Synapse System, DePuy Synthes, J&J) was turned into an AR-trackable instrument by mounting it to a sterile fiducial marker using a sterile 3D-printed clamp (Fig. 3). The navigation was performed visually based on the drill sleeve's position and orientation, which was acquired in real-time with the HoloLens camera and Aruco marker detection [15]. The current Euclidean distance from the planned entry point and the angular deviation from the planned trajectory was in-situ visualized in millimeters and degrees, respectively.

Furthermore, the direction of trajectory deviation was visualized by three points forming a triangle: the first lying on the entry point, the second on the planned trajectory, and the third on the current trajectory (Fig. 6). After achieving alignment with the surgery plan, a borehole was drilled limited to 40 mm depth. The borehole was checked for pedicle wall perforation with a ball tip probe, before inserting blunt k-wires. Finally, cannulated 7 × 45 mm pedicle screws were inserted under K-wire guidance. S1 screws were inserted in a standard manner under anatomic orientation and lateral fluoroscopic control at the end of the screw insertion procedure to limit the experiment to only four screws, as this was a first-in-man procedure. The final screw position was checked by fluoroscopy, showing a satisfying result. Further steps, like decompressive laminotomy and intervertebral cage insertion, were done in a usual manner.

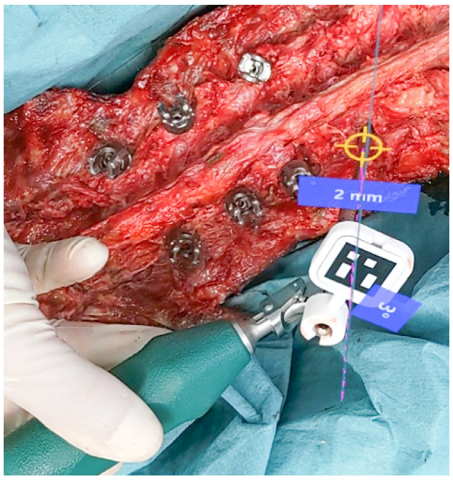


Fig. 6. Surgeon's view during navigation showing current deviation of entry point (3 mm) and trajectory (2°) in real time (for safety reasons shown here only in a cadaver sample).

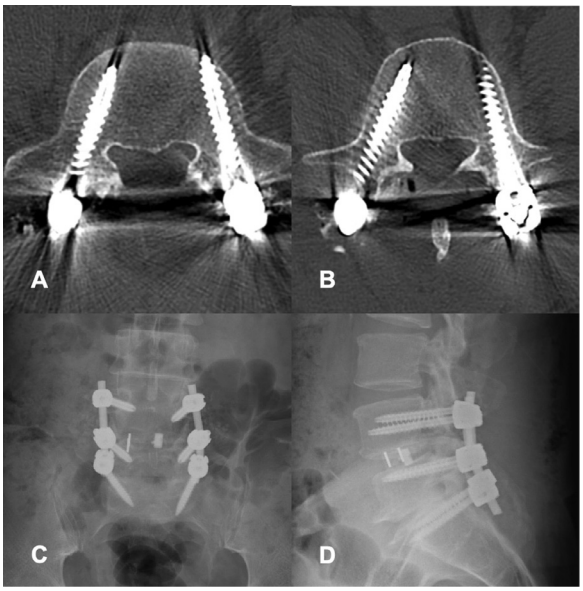


Fig. 7. Postoperative images: (A) axial CT at L5 and (B) axial CT at L4 showing adequate position of navigated screws without pedicle perforation, (C) antero-posterior and (D) lateral radiographs showing final spinal fusion construct.

Outcome

Postoperatively, the patient showed a complete reduction of leg pain and no further signs of radiculopathy. Correct screw positions entirely within bone were documented with a postoperative CT (Fig. 7). The 3D evaluation of the surgical accuracy based on a comparison between preoperative planning and postoperative CT revealed a mean 3D-summed angular deviation of 7.3 ± 3.6° for the trajectories and 3.5 ± 1.9 mm for screw entry points. The patient was mobilized uneventfully on the first postoperative day with little pain medication, and dismissed on the fourth postoperative day.

Discussion

This is the report of the first-in-man application of a new fluoroscopy-free direct holographic surgical navigation technique with in-situ trajec-

tory guidance. This is an essential step for the implementation of AR as the next-generation surgical navigation in surgery. Although surgical accuracy and user-friendliness have to be investigated with more cases, this case report proves the feasibility of direct holographic surgical navigation in an in-vivo setting.

State-of-the-art navigation technologies in spinal surgery have superior accuracy than the free hand technique [2,16–20]. However, the main limitations of such navigation systems are high set-up and maintenance costs, even if these systems might be cost neutral in the long-term in high volume centers [21,22]. This assumption is supported by a survey by Härtl et al., who revealed that surgeons cited high costs as one of the main reasons for not to use navigation systems [23]. Newer robotic assisted navigation systems are associated with even greater costs [24,25]. From technical viewpoint, a considerable limitation of "traditional" optical navigation systems is the dependence to an external camera system, which make it more difficult to have a clear view to the fiducial markers on the anatomy and surgical tools. According to a recent study, line-of-sight problem occurs multiple times in nearly every navigated neurosurgical procedure [26].

Another known limitation is the attention shift, which occurs when the surgeon is obligated to fix the gaze on a remote screen during navigation [27,28]. The approach presented here overcomes such limitations by combining a small, portable, and affordable device with computer vision software (Fig. 3).

However, the here reported novel method of navigation introduces new limitations: First, the operator needs previous training in order to be able to use the system reliably. In our experience, user-dependency seems to be higher at this stage compared to current standard navigations systems. Second, accuracy is dependent on the quality of the registration process and absence of patient motion. Accuracy is high in cadaveric experimental setting with up to 97.5% (unpublished data), comparable to current computer based navigation techniques (96% [16]) or even robotic assisted navigation (95-98% [17,29,30]) and certainly surpassing the conventional free-hand technique (43% to 86% [16,31,32]).

Compared to other navigation techniques, the here presented method seems advantageous, as the surgeon remains the last instance of quality control: He should be able to notice if the projected hologram is not aligned with the anatomy. Eventually, the currently running RCT will provide quantification of accuracy. Third, another potential limitation for broad clinical usage is the potential inconvenience associated with wearing a head mounted device. Further studies evaluating experience and surgeon's acceptance using this navigation are in progress.

So far, we found only a few clinical studies evaluating similar navigation technologies in humans [6,14]. Elmi-Terander and his group uses a sophisticated AR technology based on a video system with four-cameras, permitting fusion of 3D CT information with live video images of the surgical field [6,33–35]. Charles et al. investigated the same system and confirmed applicability in minimal invasive procedures [36]. However, the system of Elmi-Terander et al. is burdened with some degree of attention shift, since the surgeon is still obligated to fix his gaze on a remote screen for navigation. Molina et al. uses a Food and Drug Administration (FDA) approved AR navigation system with a head mounted device which projects navigation information directly into the operator's retina using a transparent near-eyedisplay [14]. In this way, the surgeon sees a 3D segmentation of the spine, overlaying the anatomy, and all navigation information displayed aside. Their approach is promising in reducing attention shift, but their registration method requires to acquire an intraoperative CT [14]. General application of such systems is limited due to the necessity of additional costly equipment. Therefore, we aim to provide an intraoperative image-free method of registration of anatomy. However, our approach without an anchored marker is yet prone to failure in case of position changes of the patient. We believe however that such an error can be noticed by the operator as an obvious offset of the hologram overlay on anatomy.

Conclusion

This case report presents the first in man application of a portable, fluoroscopy free AR based in situ navigation system. While this innovation overcomes some important disadvantages of the current navigation system, it introduces new challenges that need a careful incremental improvement process.

Funding Disclosure Statement: No financial funding sources were acquired for this case report. This work is part of «SURGENT», a flagship project of University Medicine Zurich/Hochschulmedizin Zürich.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2021.100065.

References

[1] Gelalis ID, Paschos NK, Pakos EE, Politis AN, Arnaoutoglou CM, Karageorgos AC, et al. Accuracy of pedicle screw placement: a systematic review of prospective in vivo studies comparing free hand, fluoroscopy guidance and navigation techniques. Eur Spine J 2012;21:247–55. doi:10.1007/s00586-011-2011-3.
[2] Farshad M, Betz M, Farshad-Amacker NA, Moser M. Accuracy of patient-specific template-guided vs. free-hand fluoroscopically controlled pedicle screw placement in the thoracic and lumbar spine: a randomized cadaveric study. Eur Spine J 2016;26:1–12. doi:10.1007/s00586-016-4728-5.
[3] Li HM, Zhang RJ, Shen CL. Accuracy of pedicle screw placement and clinical outcomes of robot-assisted technique versus conventional freehand technique in spine surgery from nine randomized controlled trials: a meta-analysis. Spine (Phila Pa 1976) 2020;45:E111–19. doi:10.1097/BRS.0000000000003193.
[4] Dennler C, Jaberg L, Spirig J, Agten C, Götschi T, Fürnstahl P, et al. Augmented reality-based navigation increases precision of pedicle screw insertion. J Orthop Surg Res 2020;15. doi:10.1186/s13018-020-01690-x.
[5] Müller F, Roner S, Liebmann F, Spirig JM, Fürnstahl P, Farshad M. Augmented reality navigation for spinal pedicle screw instrumentation using intraoperative 3D imaging. Spine J 2020;20. doi:10.1016/j.spinee.2019.10.012.
[6] Elmi-Terander A, Burström G, Nachabe R, Skulason H, Pedersen K, Fagerlund M, et al. Pedicle screw placement using augmented reality surgical navigation with intraoperative 3D imaging: a first in-human prospective cohort study. Spine (Phila Pa 1976) 2019;44:517–25. doi:10.1097/BRS.0000000000002876.
[7] Liebmann F, Roner S, von Atzigen M, Scaramuzza D, Sutter R, Snedeker J, et al. Pedicle screw navigation using surface digitization on the Microsoft HoloLens. Int J Comput Assist Radiol Surg 2019. doi:10.1007/s11548-019-01973-7.
[8] Molina CA, Theodore N, Ahmed AK, Westbroek EM, Mirovsky Y, Harel R, et al. Augmented reality–assisted pedicle screw insertion: a cadaveric proof-of-concept study. J Neurosurg Spine 2019;31:139–46. doi:10.3171/2018.12.SPINE181142.
[9] Burström G, Nachabe R, Persson O, Edström E, Elmi Terander A. Augmented and virtual reality instrument tracking for minimally invasive spine surgery. Spine (Phila Pa 1976) 2019;44:1097–104. doi:10.1097/BRS.0000000000003006.
[10] Ma L, Zhao Z, Chen F, Zhang B, Fu L, Liao H. Augmented reality surgical navigation with ultrasound-assisted registration for pedicle screw placement: a pilot study. Int J Comput Assist Radiol Surg 2017;12:2205–15. doi:10.1007/s11548-017-1652-z.
[11] Elmi-Terander A, Burström G, Nachabe R, Skulason H, Pedersen K, Fagerlund M, et al. Pedicle screw placement using augmented reality surgical navigation with intraoperative 3D imaging. Spine (Phila Pa 1976) 2019;44:517–25. doi:10.1097/BRS.0000000000002876.
[12] Edström E, Burström G, Nachabe R, Gerdhem P, Elmi Terander A. A novel augmented-reality-based surgical navigation system for spine surgery in a hybrid operating room: design, workflow, and clinical applications. Oper Neurosurg 2019. doi:10.1093/ons/opz236.
[13] Wu JR, Wang ML, Liu KC, Hu MH, Lee PY. Real-time advanced spinal surgery via visible patient model and augmented reality system. Comput Methods Programs Biomed 2014;113:869–81. doi:10.1016/j.cmpb.2013.12.021.
[14] Molina CA, Sciubba DM, Greenberg JK, Khan M, Witham T. Clinical accuracy, technical precision, and workflow of the first in human use of an augmented-reality head-mounted display stereotactic navigation system for spine surgery. Oper Neurosurg 2020;20. doi:10.1093/ons/opaa398.
[15] Garrido-Jurado S, Muñoz-Salinas R, Madrid-Cuevas FJ, MJ Marín-Jiménez. Automatic generation and detection of highly reliable fiducial markers under occlusion. Pattern Recognit 2014;47:2280–92. doi:10.1016/j.patcog.2014.01.005.
[16] Mason A, Paulsen R, Babuska JM, Rajpal S, Burneikiene S, Nelson EL, et al. The accuracy of pedicle screw placement using intraoperative image guidance systems. J Neurosurg Spine 2014;20:196–203. doi:10.3171/2013.11.SPINE13413.

[17] Van Dijk JD, Van Den Ende RPJ, Stramigioli S, Köchling M, Höss N. Clinical pedicle screw accuracy and deviation from planning in robot-guided spine surgery: Robot-guided pedicle screw accuracy. Spine (Phila Pa 1976) 2015;40:E986–91. doi:10.1097/BRS.0000000000000960.
[18] Meng X, Guan X, Zhang H, He S. Computer navigation versus fluoroscopy-guided navigation for thoracic pedicle screw placement: a meta-analysis. Neurosurg Rev 2016;39:385–91. doi:10.1007/s10143-015-0679-2.
[19] Du JP, Wang DH, Zhang J, Fan Y, Wu QN, Hao DJ. Accuracy of pedicle screw insertion among 3 image-guided navigation systems: systematic review and meta-analysis. World Neurosurg 2018;109:24–30. doi:10.1016/j.wneu.2017.07.154.
[20] Benech CA, Perez R, Benech F, Greeley SL, Crawford N, Ledonio C. Navigated robotic assistance results in improved screw accuracy and positive clinical outcomes: an evaluation of the first 54 cases. J Robot Surg 2019:1–7. doi:10.1007/s11701-019-01007-z.
[21] Lee YC, Lee R. Image-guided pedicle screws using intraoperative cone-beam CT and navigation. A cost-effectiveness study. J Clin Neurosci 2020;72:68–71. doi:10.1016/j.jocn.2020.01.025.
[22] Dea N, Fisher CG, Batke J, Strelzow J, Mendelsohn D, Paquette SJ, et al. Economic evaluation comparing intraoperative cone beam CT-based navigation and conventional fluoroscopy for the placement of spinal pedicle screws: a patient-level data cost-effectiveness analysis. Spine J 2016;16:23–31. doi:10.1016/j.spinee.2015.09.062.
[23] Härtl R, Lam KS, Wang J, Korge A, Kandziora F, Audigé L. Worldwide survey on the use of navigation in spine surgery. World Neurosurg 2013;79:162–72. doi:10.1016/j.wneu.2012.03.011.
[24] Fiani B, Quadri SA, Farooqui M, Cathel A, Berman B, Noel J, et al. Impact of robot-assisted spine surgery on health care quality and neurosurgical economics: a systemic review. Neurosurg Rev 2020;43:17–25. doi:10.1007/s10143-018-0971-z.
[25] Malham GM, Wells-Quinn T. What should my hospital buy next?—Guidelines for the acquisition and application of imaging, navigation, and robotics for spine surgery. J Spine Surg 2019;5:155–65. doi:10.21037/jss.2019.02.04.
[26] Mehbodniya AH, Moghavvemi M, Narayanan V, Waran V. Frequency and causes of line of sight issues during neurosurgical procedures using optical image-guided systems. World Neurosurg 2019;122:e449–54. doi:10.1016/j.wneu.2018.10.069.
[27] Rahmathulla G, Nottmeier EW, Pirris SM, Deen HG, Pichelmann MA. Intraoperative image-guided spinal navigation: technical pitfalls and their avoidance. Neurosurg Focus 2014;36:E3. doi:10.3171/2014.1.FOCUS13516.
[28] Léger É, Drouin S, Collins DL, Popa T, Kersten-Oertel M. Quantifying attention shifts in augmented reality image-guided neurosurgery. Healthc Technol Lett 2017;4:188–92. doi:10.1049/htl.2017.0062.
[29] Laudato PA, Pierzchala K, Schizas C. Pedicle screw insertion accuracy using O-arm, robotic guidance, or freehand technique. Spine (Phila Pa 1976) 2018;43:E373–8. doi:10.1097/BRS.0000000000002449.
[30] Zhang JN, Fan Y, Hao DJ. Risk factors for robot-assisted spinal pedicle screw malposition. Sci Rep 2019;9. doi:10.1038/s41598-019-40057-z.
[31] Chan A, Parent E, Narvacan K, San C, Lou E. Intraoperative image guidance compared with free-hand methods in adolescent idiopathic scoliosis posterior spinal surgery: a systematic review on screw-related complications and breach rates. Spine J 2017;17:1215–29. doi:10.1016/j.spinee.2017.04.001.
[32] Nevzati E, Marbacher S, Soleman J, Perrig WN, Diepers M, Khamis A, et al. Accuracy of pedicle screw placement in the thoracic and lumbosacral spine using a conventional intraoperative fluoroscopy-guided technique: a national neurosurgical education and training center analysis of 1236 consecutive screws. World Neurosurg 2014;82. doi:10.1016/j.wneu.2014.06.023.
[33] Elmi-Terander A, Burström G, Nachabé R, Fagerlund M, Ståhl F, Charalampidis A, et al. Augmented reality navigation with intraoperative 3D imaging vs fluoroscopy-assisted free-hand surgery for spine fixation surgery: a matched-control study comparing accuracy. Sci Rep 2020;10. doi:10.1038/s41598-020-57693-5.
[34] Edström E, Burström G, Persson O, Charalampidis A, Nachabe R, Gerdhem P, et al. Does augmented reality navigation increase pedicle screw density compared to free-hand technique in deformity surgery? single surgeon case series of 44 patients. Spine (Phila Pa 1976) 2020;45:E1085–90. doi:10.1097/BRS.0000000000003518.
[35] Edström E, Burström G, Nachabe R, Gerdhem P, Terander AE. A novel augmented-reality-based surgical navigation system for spine surgery in a hybrid operating room: Design, workflow, and clinical applications. Oper Neurosurg 2020;18:496–502. doi:10.1093/ons/opz236.
[36] Charles YP, Cazzato RL, Nachabe R, Chatterjea A, Steib J-P, Gangi A. Minimally Invasive transforaminal lumbar interbody fusion using augmented reality surgical navigation for percutaneous pedicle screw placement. Clin Spine Surg 2021. doi:10.1097/BSD.0000000000001132.

North American Spine Society Journal (NASSJ) 8 (2021) 100089

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Studies

Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 24-Month treatment arm results

Theodore Koreckij[a,*], Scott Kreiner[b], Jad G. Khalil[c], M. Smuck[d], J. Markman[e], Steven Garfin[f], on behalf of the INTRACEPT Trial Investigators

[a] Department of Orthopedic Surgery, Kansas City Othropedic Alliance, Kansas City, MO, USA
[b] Department of Interventional Spine and Sports, Barrow Brain and Spine, Phoenix, AZ, USA
[c] Department of Orthopaedic Surgery, William Beaumont Hospital, Royal Oak, MI, USA
[d] Physical Medicine & Rehabilitation Division, Stanford University, Redwood City, CA, USA
[e] Department of Neurosurgery, Translational Pain Research Program, University of Rochester School of Medicine, Rochester, NY, USA
[f] Department of Orthopaedic Surgery, University of California-San Diego, La Jolla, CA, USA

ARTICLE INFO

Keywords:
Chronic low back pain
Basivertebral nerve
Basivertebral nerve ablation
Radiofrequency ablation
Modic
Vertebrogenic pain

ABSTRACT

Background: Vertebral endplates, innervated by the basivertebral nerve, can be a source of vertebrogenic low back pain when damaged with inflammation, visible as types 1 or 2 Modic changes. A randomized controlled trial (RCT) compared basivertebral nerve ablation (BVNA) to standard care (SC) showed significant differences between arms at 3 and 6-months. At 12-months, significant improvements were sustained for BVNA. We report results of the BVNA arm at 24-months.

Methods: Prospective, open label, single-arm follow-up of the BVNA treatment arm of a RCT in 20 US sites with visits at 6-weeks, and 3, 6, 9, 12 and 24-months. Paired comparisons to baseline were made for the BVNA arm at each timepoint for Oswestry Disability Index (ODI), Visual Analog Scale (VAS), Short Form Health Survey (SF-36), EQ-5D-5L, and responder rates.

Results: 140 patients were randomized, 66 to BVNA. In the 58 BVNA patients completing a 24-month visit, 67% had back pain for >5 years, 36% were actively taking opioids at baseline, 50% had prior epidural steroid injections, and 12% had prior low back surgery. Improvements in ODI, VAS, SF-36 PCS, and EQ-5D-5L were statistically significant at all timepoints through 2 years. At 24 months, ODI and VAS improved 28.5±16.2 points (from baseline 44.5; $p < 0.001$) and 4.1±2.7 cm (from baseline 6.6; $p < 0.001$), respectively. A combined responder rate of ODI≥15 and VAS≥2 was 73.7%. A ≥50% reduction in pain was reported in 72.4% of patients and 31.0% were pain-free at 2 years. At 24 months, only 3(5%) of patients had BVNA-level steroid injections, and 62% fewer patients were actively taking opioids. There were no serious device or device-procedure related adverse events reported through 24 months.

Conclusion: Intraosseous BVNA demonstrates an excellent safety profile and significant improvements in pain, function, and quality of life that are sustained through 24 months in patients with chronic vertebrogenic low back pain.

Background

Clinicians treating axial chronic low back pain (CLBP) have historically been challenged with limited objective differentiators for pain sources, as well as poor effect sizes and a lack of high-quality evidence for existing treatments [1]. This in turn has resulted in large variations in treatment, including overtreatment, with therapeutic decisions often based on non-specific imaging findings, or diagnoses made by exclusion [2,3]. Advancing science surrounding physiologic and immunohistochemical changes of degenerative disc disease suggests pain result-

Abbreviations: BVN, Basivertebral Nerve; BVNA, Basivertebral Nerve Ablation; CLBP, Chronic Low Back Pain; SC, Standard Care; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; RCT, Randomized Controlled Trial; DMC, Data Management Committee; MCID, Minimal Clinically Important Difference; QOL, Quality of Life; AE, Adverse Events; ANCOVA, Analysis of Covariance; LS, Least Squares; ESI, Epidural Steroid Injection; RDQ, Roland-Morris Disability Questionnaire.

* Corresponding author at: Medical Plaza Bldg 1, Ste. 610, 4320 Wornall Road, Kansas City, MO 64111.
E-mail address: tkoreckij@gmail.com (T. Koreckij).

https://doi.org/10.1016/j.xnsj.2021.100089
Received 7 August 2021; Received in revised form 18 October 2021; Accepted 20 October 2021
Available online 26 October 2021

ing from vertebral endplate changes as a clinically distinct subgroup of CLBP. Vertebral endplates are innervated by the basivertebral nerve (BVN), a branch of the sinuvertebral nerve, which becomes thinly or non-myelinated after entering the bone marrow through the posterior basivertebral foramen (BVF) [4,5]. Biomechanically, the endplates are subjected to significant loads during activities of daily living and are susceptible to damage. With physiological aging, endplates gradually thin and calcification occurs. High tensile strains associated with disc degeneration further increase the endplate vulnerability [6]. Endplate damage has been shown to result in cellular communication between the inflammatogenic disc nucleus and vertebral bone marrow triggering chronic inflammation and densification of endplate nociceptors [7], a process that is visible as Modic changes on magnetic resonance imaging (MRI) [8]. An association has been reported between the presence of Type 1 or Type 2 Modic changes and CLBP [9,10].

Two randomized controlled trials (RCTs) have evaluated the BVN as a target for radiofrequency ablation in treating this subgroup of vertebrogenic CLBP patients. In the pivotal SMART trial, a significant difference between arms for reduction in mean Oswestry Disability Index (ODI) was demonstrated for BVNA over a sham-control at the 3-month primary endpoint and clinically relevant improvements in visual analog pain scores (VAS) and function were sustained through 2 and 5 years [11–13]. A second RCT was conducted to compare BVNA to non-surgical standard care (SC). A pre-specified intent-to-treat interim analysis conducted when $N = 104$ patients ($n = 51$ BVN ablation, $n = 53$ SC) completed their 3-month primary endpoint visit, demonstrated clear statistical superiority ($p < 0.001$) of BVNA over SC for all primary and secondary endpoints (change in ODI, VAS, SF-36, EQ-5D-5L) and resulted in a recommendation by the independent Data Management Committee (DMC) to halt study enrollment and offer the SC arm an early cross to active treatment [14].

At the point of crossover (median of 5.8 months), the between arm results for the full randomized cohort ($N = 140$) showed a significant difference in mean ODI reduction (26.1 points for BVNA vs 1.6 points for SC; $p < 0.001$) and in mean VAS reduction (3.6 cm for BVNA vs 0.3 cm for SC; $p < 0.001$). Likewise, in the 91% of SC arm patients that opted to cross to BVNA, similar results were observed, with reductions of 25.9 points in mean ODI and 3.8 cm in mean VAS from re-baseline at 6 months post ablation. Treatment outcomes for the BVNA remained durable through 12 months [15]. We report 24-month outcomes of the treatment arm for this second RCT and explore the applicability of these results in practice today.

Methods

Design

The INTRACEPT trial is a prospective, parallel, open-label RCT of 140 patients randomized in 20 U.S. sites from September 2017 to January 2019. The trial was registered on ClinicalTrials.gov as NCT03246061 (https://clinicaltrials.gov/ct2/show/NCT03246061) and sponsored by Relievant Medsystems, Inc. (Minneapolis, MN). The study was conducted under Institutional Review Board approval and participant informed consent. Data was source-verified by independent study monitors (M Squared Associates Inc., New York, NY). Independent statisticians (Abond CRO Inc., Grand Rapids, MI) prepared the computer-generated randomization schemes and conducted the statistical analyses. Full design details were previously published [14].

Participants

Study participants were recruited from current pain populations at study sites and through web-based self-referral. Consecutively consented patients were screened for further eligibility prior to MRI review for endplate changes and radiographic exclusion criteria. The primary requirements for inclusion were CLBP of vertebrogenic origin with a duration of greater than 6-months with conservative treatment and associated Modic Type 1 or Type 2 changes in vertebral levels L3 to S1. See Table 1 for a full listing of the inclusion and exclusion criteria. Eligibility for randomization was confirmed by an independent orthopedic surgeon medical monitor and included a review of pain characteristics and radiographic presentation to rule out other primary sources of CLBP. Consecutive eligible patients were randomized 1:1 to either BVNA or SC using permuted blocks of four or six stratified by study site.

Interventions

Patients randomized to BVNA received treatment at all levels (L3-S1) that exhibited qualifying Modic changes using the Intracept ® System (Relievant Medsystems, Minneapolis, MN USA) which was performed under image guidance, under moderate conscious sedation or general anesthesia, and in an outpatient setting, using a unilateral transpedicular approach to access the BVN. Targeted location for electrode placement was approximately 30–50% across vertebral body width from the posterior wall, and in the same horizontal plane as the BVF (channel that houses the BVN) on sagittal imaging. After confirmation of placement, thermal ablation was delivered for 15 min at 85°C to create an approximately 1-cm spherical lesion within each vertebral body [14]. All patients continued nonsurgical therapies as per the investigator's medical judgment and patient symptoms.

Standard care for both arms was determined by the investigator based on patient treatment history and clinical need. Standard care treatments included (but was not limited to) the following: physical therapy, exercise, chiropractic treatment, acupuncture, oral pain medications and spinal injections.

Follow-up

Per the original protocol design, BVNA arm patients were followed at 6 weeks, and 3, 6, 9, 12, and 24-months. SC patients were to be followed at 3, 6, 9, and 12-months, and then offered active treatment with BVN ablation. A pre-specified interim analysis was performed when approximately 60% of randomized patients completed their 3-month primary endpoint visit. Statistical superiority was demonstrated in the primary and all secondary endpoints. Per informed consent regulations that require disclosure of new information during a clinical trial that may affect a participant's decision to continue participation, the reviewing DMC recommended stopping randomization and offering the SC arm early cross to active treatment after collecting a re-baseline at their next scheduled study visit. Re-baseline occurred at a median of 175 (range 24 to 372) days post randomization. SC arm patients who elected to cross to active treatment with BVN ablation were followed at 6-weeks, 3-months, and 6-months post BVNA treatment per the original protocol. SC patients that declined BVN ablation were exited from the study. The BVNA treatment arm continued systematic, prospective follow-up per the protocol through 24 months and are reported here.

Target success

MR imaging (T1, T2, and STIR time constants) was performed at 6-weeks post BVN ablation for all treated patients. Target success was confirmed by an independent neuroradiologist based on a pre-defined threshold of overlap between the terminus of the BVN and the ablation lesion. All levels with either Type 1 or Type 2 Modic changes between L3 and S1 were required to be treated. Untreated levels with Modic changes were deemed a target failure.

Outcome measures

The validated patient-reported outcomes completed by subjects at each study visit included: functional impact using the Oswestry Disability Index (ODI) [16] with a minimal clinically important difference (MCID) of 15-points [17], low back pain using a Visual Analog

Table 1
Inclusion and exclusion criteria. A listing of the inclusion and exclusion criteria for the study is noted.

Inclusion criteria	Exclusion criteria
• Skeletally mature patients with chronic (≥6 months) isolated lumbar back pain, who had not responded to at least 6 months of non-operative management • Type 1 or Type 2 Modic changes at one or more vertebral body for levels L3-S1 • Minimum Oswestry Disability Index (ODI) of 30 points (100-point scale) • Minimum Visual Analog Scale (VAS) of 4 centimeters (cm) on a 10 cm scale • Ability to provide informed consent, read and complete questionnaires	• Magnetic Resonance Imaging (MRI) evidence of Modic at levels other than lumbar level 3 to sacral level 1 (L3-S1) • Radicular pain (defined as nerve pain following a dermatomal distribution and that correlates with nerve compression in imaging) • Previous lumbar spine surgery (discectomy / laminectomy allowed if > 6 months prior to baseline and radicular pain resolved) • Symptomatic spinal stenosis (defined as the presence of neurogenic claudication and confirmed by imaging) • Metabolic bone disease, spine fragility fracture history, or trauma / compression fracture, or spinal cancer • Spine infection, active systemic infection, bleeding diathesis • Radiographic evidence of other pain etiology • Disc extrusion or protrusion > 5 millimeters (mm) • Spondylolisthesis > 2 mm at any level • Spondylolysis at any level • Facet arthrosis / effusion correlated with clinically suspected facet-mediated low back pain • Beck Depression Inventory (BDI) > 24 or 3 or > Waddell's signs • Compensated injury or litigation • Currently taking extended-release narcotics with addiction behaviors • Body Mass Index (BMI) > 40 • Bedbound or neurological condition that prevents early mobility or any medical condition that impairs follow up • Contraindication to MRI, allergies to components of the device, or active implantable devices, pregnant or lactating

Abbreviations: MRI, magnetic resonance imaging; ODI, Oswestry Disability Index; VAS, visual analogue scale; cm, centimeters; mm, millimeters; Beck Depression Index, BDI; BMI, body mass index.

Scale (VAS) [18] from 0 (no pain) to 10 (worst pain imaginable) with a MCID of 2.0 cm [17], and health status and quality of life (QOL) using the Short Form (SF-36) [19] with a physical component MCID of 4.9 [17] and EuroQual Group 5 Dimension 5-Level Quality of Life (EQ-5D-5L) [20] with a MCID of 0.03 points [17]. Data entries by research coordinators for patient-completed questionnaires were verified by the independent study monitors. Spinal and neurological adverse events (AEs) were collected at each study visit and were adjudicated by an independent clinical event committee (CEC) that determined relatedness to the device therapy. All pain interventions and surgeries that were performed in patients post randomization were adjudicated by the CEC for a determination of BVNA treatment failure based on location and reason for treatment from submitted medical records and images.

Sample calculations

The primary endpoint for this study was the difference between arms in the change in mean ODI at 3-months. The study had one planned interim analysis for primary end-point superiority testing. Statistical significance of the primary endpoint was defined as $p < 0.025$ for the group sequential design for an overall alpha of $p < 0.05$. Initial sample size was 150 patients (75 in each group) with an estimated 15% attrition rate to detect a 10-point difference in mean ODI reduction between arms.

Statistical analysis

Statistical analysis was performed with SAS version 9.3 software (SAS Institute Inc, Cary, NC), using an analysis of covariance (ANCOVA) with a factor of treatment group and a covariate of baseline scores for statistical comparisons between arms for the primary endpoint ODI and secondary endpoints of VAS, SF-36 and EQ-5D-5L. The 3-month ODI was analyzed as intent to treat with multiple imputations for missing data for both arms. Six-month between arm results are reported using last observation prior to the blinded re-baseline in the standard care control arm. Comparisons between post BVNA and the baseline values at 12 and 24 months are performed using a paired t-test without imputation for missing values. Responder rates, using MCID thresholds described above, were analyzed using Fischer's Exact test.

Study revisions

Protocol revisions allowed for treatment of up to four vertebrae and non-consecutive levels from L3-S1 with FDA clearance, as described previously [14], and the addition of an optional five-year follow-up sub study for BVNA arm patients. An evaluation of the impact of protocol revisions to the 3-month primary endpoint detected no significant differences, and therefore no adjustment was required. A final study revision stopped randomization and allowed for re-baseline and the early option of active treatment to the SC control arm patients per the DMC recommendation.

Results

Patient disposition, baseline characteristics, and treatment success

At the time of the DMC recommendation to stop enrollment, 140 patients were randomized (66 BVNA, 74 SC) at 20 study sites. In the BVNA treatment arm 58 of the 66 randomized patients had a 24-month follow-up visit (a retention rate of 88%). See Fig. 1 for a detailed participant disposition at each follow-up timepoint. In this population of BVNA randomized patients with a 24-month visit, the percentage of patients with LBP symptoms ≥ 5 years was 67% and patients reported moderate to severe pain and disability levels at baseline with mean VAS of 6.6

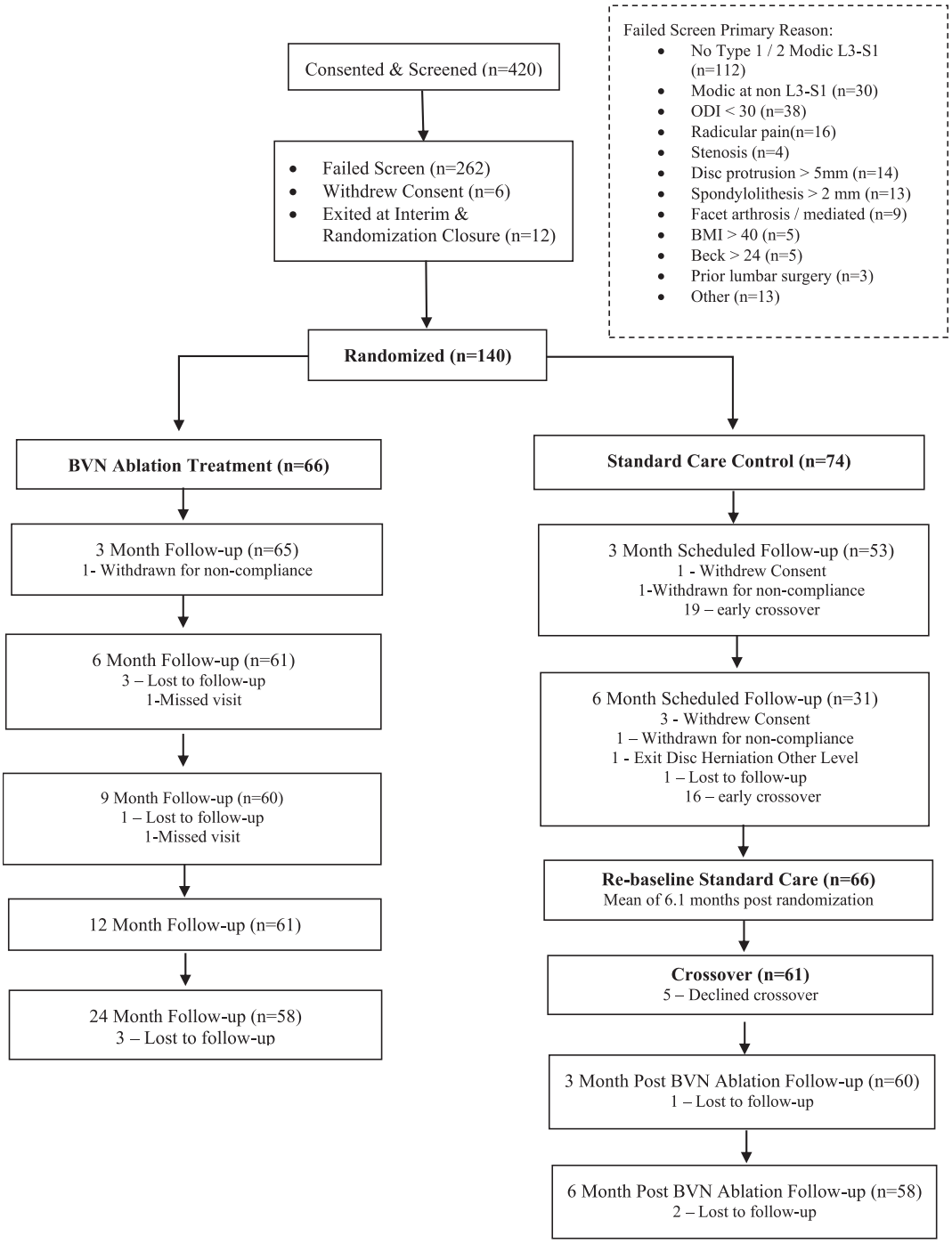


Fig. 1. Patient disposition flow diagram. At the point of enrollment halt due to statistical superiority at an interim analysis, 140 participants were randomized (66-BVN Ablation, 74-SC) in the study. After a blinded re-baseline, the remaining SC arm patients (n = 66) were offered BVN ablation, with 61(92%) electing to cross to active treatment (N = 61); of whom 3 were lost to follow-up. In the BVN ablation treatment arm 58 of the 66 randomized had a 24-month follow-up visit (a retention rate of 88%). Details on reasons for study exit are reported for each follow-up time point. Abbreviations: ODI, Oswestry Disability Index; VAS, visual analogue scale; BMI, body mass index; BVN, basivertebral nerve.

Table 2
Baseline characteristics. Demographic and baseline characteristics for BVN ablation randomized patients showed no statistically significant differences between those with a 24-month follow-up and the full treatment arm.

	Basivertebral nerve ablation arm full cohort(N = 66)	Basivertebral nerve ablation arm with 24 month visit(N = 58)
Mean Age in years (range)	49.4 (30 to 68)	50.4 (30 to 68)
Male, *n* (%)	34 (51.5%)	30 (51.7%)
Duration LBP symptoms ≥ 5 years *n*(%)	42 (63.6%)	39 (67.2%)
Mean Days per week with LBP	6.8 (4 to 7)	6.8 (4 to 7)
Pain Location (per patient-completed body diagram)		
Midline only *n* (%)	17 (25.8%)	17 (29.3%)
Paraspinal only *n* (%)	8 (12.1%)	7 (12.1%)
Midline and Paraspinal *n* (%)	25 (37.9%)	20 (34.5%)
Lateral only *n* (%)	12 (18.2)	10 (17.2%)
Below mid-gluteal line *n* (%)	4 (6.1%)	4 (6.9%)
Mean ODI (Range)	44.7 (30 to 76)	44.2 (30 to 76)
Mean VAS (Range)	6.7 (4.0 to 10.0)	6.6 (4.0 to 9.0)
Mean SF-36 PCS[2] (Range)	32.06 (18.43 to 46.93)	32.33 (18.43 to 46.07)
Mean SF-36 MCS[3] (Range)	53.42 (22.24 to 69.80)	53.85 (33.18 to 69.80)
Mean EQ-5D-5L[4] (Range)	.613 (.270 to .832)	0.624 (0.378 to 0.832)
Mean BDI[5] (Range)	6.2 (0 to 20)	6.2 (0 to 20)
Grade 1 Spondylolisthesis *n* (%)	9 (13.6%)	7 (12.1%)
Disc Protrusion (< 4 mm) *n* (%)	37 (56.1%)	33 (56.9%)
Pfirrmann Grades in Patients *n* (%)	Patients (N = 66)	Patients (N = 58)
Grade I *n* (%)	0 (0.0%)	0 (0.0%)
Grade II *n* (%)	1 (1.5%)	1 (1.7%)
Grade III *n* (%)	15 (22.7%)	12 (20.7%)
Grade IV *n* (%)	32 (48.5%)	29 (50.0%)
Grade V *n* (%)	25 (37.9%)	23 (39.7%)
Pfirrmann Grades for Treated Motion Segment *n* (%)	Motion Segments(n = 82)	Motion Segments(n = 73)
Grade I *n* (%)	0 (0.0%)	0 (0.0%)
Grade II *n* (%)	1 (01.2%)	1 (01.4%)
Grade III *n* (%)	18 (22.0%)	14 (19.2%)
Grade IV *n* (%)	37 (45.1%)	34 (46.6%)
Grade V *n* (%)	26 (31.7%)	24 (32.8%)
Treatment History *n* (%)		
Opioid Use at Baseline *n* (%)	22 (33.3%)	21 (36.2%)
Epidural Steroid Injections *n* (%)	36 (54.5%)	29 (50.0%)
Past Lower Pack Surgeries *n* (%)	7 (10.6%)	7 (12.1%)
Type of Modic by Subject, *n* (%)		
Type 1	23 (34.8%)	19 (32.8%)
Type 2	34 (51.5%)	32 (55.2%)
Mixed (Type 1 & Type 2)	9 (13.6%)	7 (12.1%)

Abbreviations: LBP, low back pain; ODI, Oswestry Disability Index; VAS, Visual Analog Scale; SF-36, Short Form 36, PCS, physical component summary; MCS, mental component summary; EQ-5D-5L, EuroQual Group 5 Dimension 5-Level Quality of Life; BDI, Beck Depression Index; BVN, basivertebral nerve; BVNA, basivertebral nerve ablation.

and mean ODI of 44.2. The majority (81%) of patients in this BVNA 24-month population presented with midline and /or paraspinal axial back pain that was exacerbated with sitting, standing, and flexion. Twenty-two percent of the patients in this follow-up had one or more BVNA treated motion segments with associated Modic changes that were categorized as Pfirrmann grade III (on the 5-point Pfirrmann grading scale) per independent radiologic review.

Fifty percent of the patients had epidural steroid injections in the 24-months prior to baseline, 36% were actively taking opioids, and 12% had previous low back surgery (microdiscectomy or laminectomy) of the same level as planned treatment (with a minimum of 6-months healing period prior to enrollment). Baseline characteristics of the full cohort of BVN ablation treatment arm patients (N = 66) and patients with a 24-month visit (N = 58) are similar. See Table 2. Targeting success in this group of patients with a 24-month visit was 98% (130/132) of vertebral bodies treated per independent radiologic review.

BVN ablation arm: 24-month results

In the BVNA treatment arm patients with a 24-month visit, statistically significant improvements in pain and function compared to baseline were observed for all timepoints through 24 months. BVN ablation arm patients with a 24-month follow-up visit reported a mean improvement in ODI of 28.5 ± 16.2 points (from a paired baseline of 44.5 to 16.0; $p < 0.001$) and mean improvement in VAS of 4.1 ± 2.7 cm (from 6.6 to 2.5; $p < 0.001$) at 2 years post ablation. See Table 3 and Figs. 2 and 3.

Seventy-two percent (72%) of the BVN ablation arm patients reported a ≥ 50% reduction in VAS, 47% achieved a >75% reduction, and 31% reported 100% pain relief at their 24-month visit. See Fig. 4. An ODI improvement of ≥ 15-points was reported in 77.2% ($p < 0.001$), and ≥ 20-points in 68.4% of these patients ($p < 0.005$). Seventy-nine percent reported a reduction in VAS pain score by ≥ 2 cm at 24-months. The combined MCID function and pain responder rate (ODI ≥ 15 and VAS ≥ 2 reduction) for BVN ablation arm patients with a 24-month visit was 73.7% ($p < 0.001$). See Table 4. Quality of life outcomes measured via SF-36 (physical component) and EQ-5D-5L were also significant for all timepoints through 24 months. See Table 3.

Healthcare utilization and treatment success rate

In the 24 months prior to enrollment 29/58 (50%) of BVN ablation arm patients with a 24-month follow-up visit received an epidural steroid injection (ESI). In the 24-months following BVNA 7/58 (12%) of BVN ablation arm patients received an ESI (a 76% reduction); with only three of the post ablation ESIs involving the same treatment level as BVNA. In BVNA arm patients 11/58(19%) were taking opioid medications at 24 months compared to 21/58 (36%) at baseline with 10/21(48%) stopping opioid medications entirely. In the BVNA arm patients who continued opioid medications, only 8 (14%) were actively

Table 3
BVNA arm patients with a 24 month visit outcomes. Paired comparisons to baseline demonstrated significant reductions for both pain and function at all follow-up timepoints through 24-months for the BVNA arm patients who had a 24-month follow-up. Quality of life outcomes (SF-36 PCS and EQ-5D-5L) were also significant compared to baseline at all timepoints of follow-up through 24-months while SF-36 MCS did not achieve significance.

Visit	Baseline	Month 3	Month 6	Month 9	Month 12	Month 24
Oswestry Disability Index (ODI)						
N	66	66[a]	61	60	61	57
Baseline Mean ODI± SD	44.7 ± 11.3	44.6 ± 11.3	44.3 ± 11.1	44.4 ± 11.2	44.3 ± 11.1	44.5 ± 11.2
Follow-up Mean ODI±SD		21.0 ± 16.0	19.1 ± 15.4	18.8 ± 16.4	18.6 ± 15.7	16.0 ± 15.6
Δ from Baseline ± SD		-23.6[b] ± 18.0	-25.1 ± 17.4	-25.6 ± 17.1	-25.7 ± 18.5	-28.5 ± 16.2
p-value[b]		<0.001	<0.001	<0.001	<0.001	<0.001
Visual Analog Scale (VAS)						
N	66	66	60	60	61	58
Baseline Mean VAS± SD	6.7 ± 1.3	6.7 ± 1.3	6.7 ± 1.2	6.7 ± 1.3	6.7 ± 1.3	6.6 ± 1.2
Follow-up Mean VAS±SD		3.2 ± 2.7	3.1 ± 2.4	2.6 ± 2.5	2.9 ± 2.6	2.5 ± 2.5
Δ from Baseline ± SD		-3.5 ± 2.6	-3.5 ± 2.5	-4.0 ± 2.6	-3.8 ± 2.6	-4.1 ± 2.7
p-value[b]		<0.001	<0.001	<0.001	<0.001	<0.001
SF-36 Physical Component Score (PCS)						
N	66	64	61	60	61	57
Baseline Mean SF-36 PCS	32.06 ± 6.76	32.12 ± 6.84	32.48 ± 6.75	32.21 ± 6.55	32.11 ± 6.53	32.26 ± 6.66
Follow-up Mean SF-36 PCS ± SD		45.63 ± 9.67	45.80 ± 9.67	46.75 ± 9.52	47.03 ± 9.87	48.56 ± 9.76
Δ from Baseline ± SD		13.51 ± 9.05	13.32 ± 9.82	14.55 ± 9.54	14.92 ± 10.16	16.30 ± 10.32
p-value[b]		<0.001	<0.001	<0.0001	<0.0001	<0.0001
SF-36 Mental Component Score (MCS)						
N	66	64	61	60	61	57
Baseline Mean SF-36 MCS	53.42 ± 9.49	53.84 ± 8.77	53.77 ± 8.47	53.38 ± 8.80	53.53 ± 8.81	53.95 ± 8.59
Follow-up Mean SF-36 MCS ± SD		56.17 ± 7.33	55.12 ± 8.42	54.06 ± 8.58	54.36 ± 7.60	53.62 ± 9.97
Δ from Baseline ± SD		2.32 ± 6.80	1.36 ± 9.47	0.685 ± 7.54	0.830 ± 8.01	-0.328 ± 9.38
p-value[b]		0.0081	0.2678	0.4846	0.4212	0.7931
EQ-5D-5L						
N	66	65	61	60	61	57
Baseline Mean EQ-5D-5L	0.613 ± 0.132	0.614 ± 0.133	0.623 ± 0.126	0.616 ± 0.130	0.616 ± 0.129	0.622 ± 0.124
Follow-up Mean EQ-5D-5L ± SD		0.793 ± 0.130	0.809 ± 0.138	0.805 ± 0.157	0.806 ± 0.159	0.822 ± 0.144
Δ from Baseline ± SD		0.179 ± 0.150	0.186 ± 0.157	0.189 ± 0.181	0.189 ± 0.187	0.200 ± 0.164
p-value[b]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[a] Multiple imputation for missing values for 3 Month ODI primary endpoint, all other measurements as observed.
[bPbp] -value from a paired t-test.

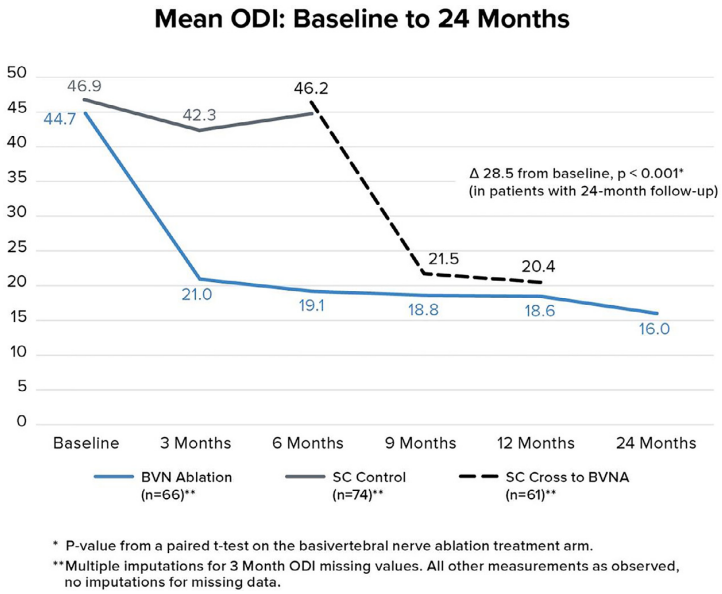


Fig. 2. Mean oswestry disability index (ODI) over time. This graph depicts the mean ODI at each study follow-up for each arm of the RCT through the longer-term follow-up of the BVNA arm. A statistically significant and clinically meaningful difference in mean ODI was observed from baseline/re-baseline for each timepoint in patients treated with BVN ablation, including in control patients that crossed to active treatment. Abbreviations: ODI, Oswestry Disability Index; BVNA, basivertebral nerve ablation.

taking opioids greater than one time per week, for an overall 62% reduction in active opioid use from baseline at 24 months.

Five of the 66 BVNA arm patients (8%) had an additional pain procedure or surgery performed at the same treatment level through 24-months (1- fusion at 24 months for disc collapse and radiating pain, 1- fusion at 24 months reason unknown, 1- disc replacement at 6 months reason unknown, 2 - radiofrequency neurotomy for ongoing low back pain). Seventy-two percent of BVNA patients met the composite treatment success definition that included the following criteria: 1.) an ODI improvement of ≥15-points from paired baseline, 2.) a VAS

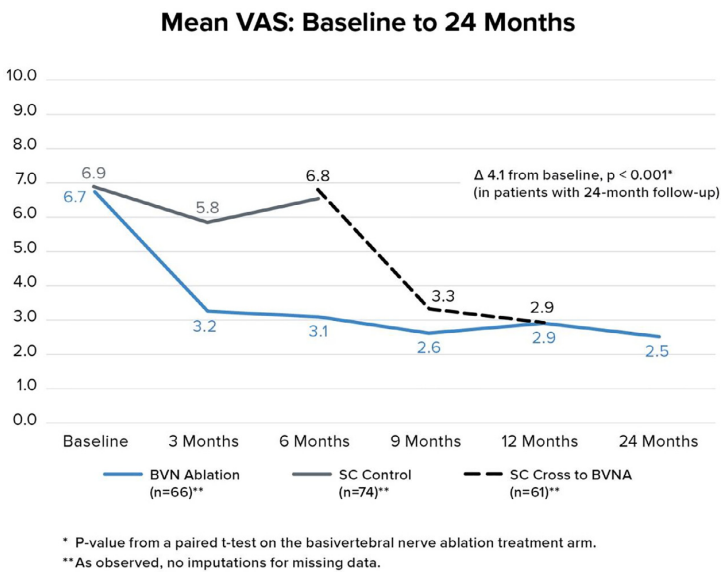


Fig. 3. Mean visual analog scale (VAS) over time. This graph depicts the mean VAS at each study follow-up for each arm of the RCT through the longer-term follow-up of the BVNA arm. A statistically significant and clinically meaningful difference in mean VAS was observed from baseline/re-baseline for each timepoint in patients treated with BVN ablation, including in control patients that crossed to active treatment. Abbreviations: VAS, visual analogue scale; BVNA, basivertebral nerve ablation.

Table 4
Responder rates. Responder rates were defined as ≥15-point reduction in Oswestry Disability Index (ODI) and ≥2 cm reduction in Visual Analog Scale (VAS). Individual measurement responder rates and combined responder rates were significant at all timepoints for BVNA arm patients.

Responder rates (≥ 15-point ODI and ≥ 2 cm VAS reduction)	Basivertebral nerve ablation arm ($N = 66$)	*p*-Value
3 Month	$N = 65$[a]	<0.001[b]
ODI ≥ 15-point reduction – *n* (%)	45 (69.2%)	
VAS ≥ 2 cm reduction – *n* (%)	48 (72.7%)	
Combined (reductions in ODI ≥ 15 and VAS ≥ 2) – *n* (%)	41 (63.1%)	
6 Month	$N = 60$[a]	<0.001[b]
ODI ≥ 15-point reduction – *n* (%)	41 (67.2%)	
VAS ≥ 2 cm reduction – *n* (%)	45 (75.0%)	
Combined (reductions in ODI ≥ 15 and VAS ≥ 2) – *n* (%)	35 (58.3%)	
9 Month	$N = 60$[a]	<0.001[b]
ODI ≥ 15-point reduction – *n* (%)	40 (66.7%)	
VAS ≥ 2 cm reduction – *n* (%)	45 (75.0%)	
Combined (reductions in ODI ≥ 15 and VAS ≥ 2) – *n* (%)	37 (61.7%)	
12 Month	$N = 61$[a]	<0.001[b]
ODI ≥ 15-point reduction – *n* (%)	42 (68.9%)	
VAS ≥ 2 cm reduction – *n* (%)	48 (78.7%)	
Combined (reductions in ODI ≥ 15 and VAS ≥ 2) – *n* (%)	40 (65.6%)	
24 Month	$N = 57$[a,c]	<0.001[b]
ODI ≥ 15-point reduction – *n* (%)	44 (77.2%)	
VAS ≥ 2 cm reduction – *n* (%)	46 (79.3%)	
Combined (reductions in ODI ≥ 15 and VAS ≥ 2) – *n* (%)	42 (73.7%)	

Abbreviations: ODI, Oswestry Disability Index; VAS, visual analogue scale; cm, centimeters
[a] As observed, with no imputation for missing data.
[bPbp] -value from a Binomial test.
[c] 57 patients with ODI and 58 patients with VAS at 24 months.

improvement of ≥2 cm from paired baseline, 3.) no spinal injections post ablation, and 4.)no additional low back pain procedures/surgeries of the same etiology and treatment level as BVNA at 24 months of follow-up.

Patient satisfaction

Seventy-nine percent (79%) of BVN ablation arm patients reported improvement of their condition (with 50% of those indicating "vastly improved") and 21% reported no change in their condition at 24-months post procedure. Seventy-one percent (71%) of the patients reported they had returned to the level of activity that they enjoyed prior to having low back pain and 84% indicated they would have the procedure again.

Adverse events

No serious device-related adverse events were reported through 24 months. Eleven percent (14/127) of the patients with BVN ablation treatments (66 BVNA and 61 patients SC crossing to BVNA) in this study reported non-serious device-procedure related leg pain events. All except one event (which was unable to be evaluated due to technical limitations of the MRI) were deemed a pedicle breach (with access being too medial per independent evaluation of the tract using the 6-week MRI). Thirteen of the breaches were at levels L5 or S1. Reported leg pain events were transient, with resolution in a median of 48.5 days, and mild in severity (primarily treated with a single course of oral medications). The events occurred at nine different study sites with no ob-

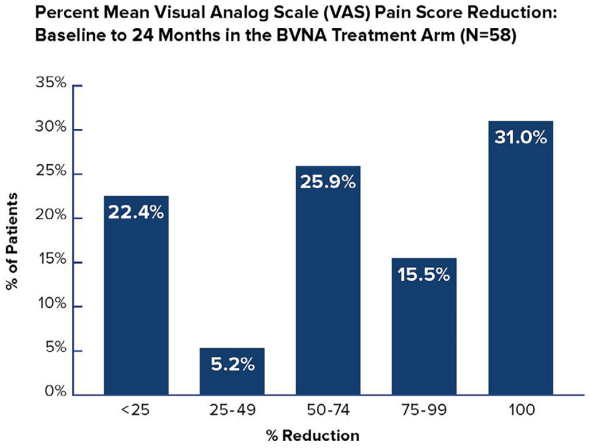


Fig. 4. Visual analog scale (VAS) pain reduction by quadrant of improvement. At 2 years post BVN ablation, 72.4% of patients in the BVNA treatment arm with a 24 month visit, reported a greater than 50% reduction in pain from baseline and 31.0% had complete pain relief. Abbreviations: VAS, visual analogue scale; BVNA, basivertebral nerve ablation.

served correlations to specialty or procedure experience of the treating physician.

Discussion

This report outlines the 24-month results of the treatment arm of the INTRACEPT RCT. Significant differences between BVNA and SC in pain reduction and functional improvement that were reported at 3 and 6 months were sustained through 12-months for BVNA patients [14,15]. We report statistically significant and clinically meaningful improvements in paired analyses from baseline values for all timepoints post ablation through 24 months for the BVNA arm in this trial.

Improvements in pain and function in this single arm follow-up of BVNA arm patients compared favorably to the SMART RCT treatment arm results at 24 months with a mean ODI reduction of 28.5 points compared to 23.4 and a mean VAS reduction of 4.1 cm compared to 3.6 cm) [12]. Outcomes are also similar to treatment arm outcomes at 5 years in the SMART trial where patients reported mean reductions from baseline in ODI of 25.9 points and VAS of 4.4 cm at a mean of 6.4 years, supporting the durability of treatment effect.

Improvements noted in this study for BVNA treated patients were consistent with a single arm multi-center study conducted in typical spine practices where significant reductions from baseline in mean ODI and VAS were reported to be 32.31 and 4.31, respectively, at 12 months post ablation [21]. Lastly, pain and functional improvements in the BVNA patients in this study are similar to an independent single arm cohort study of 56 intraosseous BVN ablated patients, were a mean ODI reduction of 32.1 and a mean VAS reduction of 4.3 at 12 months post ablation was reported; further demonstrating the reproducibility of outcomes for BVNA [22].

In the three studies conducted on this therapy to date, 297 BVNA procedures have been performed at 41 different global study sites, by proceduralists from multiple specialties who were previously trained in transpedicular access [12,14,21]. Similar response rates and a low event rates have been demonstrated across these studies, supporting the generalizability of these outcomes with standard procedure training and transpedicular access experience.

Conservative treatments for axial CLBP are often limited by low effect sizes [1], with low patient satisfaction [23]. In comparing these longer term BVNA treatment results to non-surgical pain interventions, patients in this study demonstrated nearly twice the degree of functional improvement compared to lumbar interlaminar steroid injections for CLBP (reduction of 28.5 in mean ODI compared to 14.6) with an average of 6 injections over a 24-month period required to maintain results [24].

In comparing to other pain procedures, improvements in function for the BVNA arm of this study at 24 months are nearly 4 times those reported for biacuplasty (use of cooled radiofrequency to lesion the nociceptive fibers of the annulus fibrosus for discogenic low back pain) with reported mean ODI reduction of 7.43 at 6 months [25]. Likewise, the mean low back pain VAS reduction of 4.1 from a baseline of 6.6 observed in this study at 24 months is similar to lumbar radiofrequency neurotomy where an average VAS reduction of 4.1 from a baseline of 5.1 is reported at 12 months in a well-selected study population [26]. Finally, while long term data are not available for cooled radiofrequency ablation of the medial branch nerves, responder rates at 24 months in this trial were much higher at 72.4% of patients reporting ≥50% reduction in VAS than a response rate of 52% at 6 months in a recently reported RCT [27].

In comparing BVNA results to surgical treatment, functional improvements found in this study are approximately twice those of lumbar fusion for degenerative low back pain where a systematic review of RCTs reported 12-month ODI reductions of 11 to 15 points compared to 28.5 points at 24 months in this study [28,29].

While this RCT had a rigorous review process of medical history, clinical assessment, and imaging confirming a primary diagnosis of vertebrogenic pain (damaged vertebral endplates as the source of low back pain), the patients included in this study are reflective of typical axial low back pain patients seen in clinical practice with patients having low grade spondylolisthesis (12%), prior low back surgeries (12%), and disc protrusions (57%). A clinical picture of the vertebrogenic pain patient is emerging with analysis of clinical presentation and pain location body diagrams and associated response rates from aggregated characteristics from the three published studies on intraosseous BVN ablation. Responders to BVNA present with midline and /or paraspinal anterior column low back pain that infrequently radiates below the mid gluteal line. Pain is often exacerbated upon sitting and standing, and with flexion.

Surprising to the authors is the proportion of the patients in this study of vertebrogenic pain that had one or more vertebral bodies that displayed Modic changes where the associated motion segments were classified as Pfirrmann grades IIII or below per independent radiologic evaluation (22% of patients in this 24-month BVNA population). This suggests that endplate changes may occur alongside less degenerated discs yet contribute to disabling chronic vertebrogenic pain (study required a minimum VAS level of 4 and minimum ODI of 30). Responder rates did not significantly differ based on Pfirrmann grade of the treated motion segments in this study, further suggesting that treatment with BVNA is appropriate when clinical assessment and imaging findings are consistent with vertebrogenic pain.

Patients treated with BVN ablation in this study utilized fewer healthcare resources post procedure. A substantial decrease in opioid use was observed in this study with 62% of the patients who were taking opioids at baseline either stopping or reducing their use of opioids to less than one time per week by 24 months: a meaningful reduction in a population at increased risk for developing opioid use disorder.

In patients who had received epidural steroid injections in the 24 months prior to treatment, only 3(5%) had an injection performed at the same level as the BVN ablation in the 24 months post ablation. Decreasing the reliance on short-term steroid injections is clinically important as it has been reported that patients who have > 3 epidural steroid injections within a two-year period have a statistically greater likelihood of undergoing subsequent lumbar surgery [29].

Consistent with long-term data from the previous RCT on BVN ablation [12], in 24-months of follow-up in this study only 2/66 (3.0%) of BVNA treatment arm patients had additional pain interventions and 3/66 (4.5%) had surgery for unresolved low back pain or increasing radiculopathy. The composite treatment success rate of 72% observed

in this study at 24 months post ablation is impressive in a patient population where 2/3 of the patients had been experiencing CLBP for ≥ 5 years despite active treatment including injections and prior low back surgeries.

Patients in this study indicate a high degree of satisfaction with 79% reporting improvement in their low back pain and 71% of patients reporting they had returned to a level of activity that they enjoyed prior to experiencing low back pain. This degree of patients' enhanced quality of life and satisfaction along with the clinical treatment success rates and reductions in healthcare utilization following BVN ablation in this study further supports the value of this therapy.

Safety data in this study is consistent with the 5-year safety data reported in the SMART trial which reported one serious device-procedure related event [13]. In this study there were no serious device or procedure related adverse events reported in BVNA randomized patients through 24 months in this study. The risk of this minimally invasive procedure remains low, with only one serious device-procedure related event reported in the literature for the 493 clinical study cases (including sham and crossover procedures) for an overall serious device-procedure related event rate of 0.2% [12,14,15,21].

The primary non-serious device-procedure related event reported in this study were transient leg and back pain events. Leg pain events were mild in nature, primarily treated with oral medications, and had a median resolution of 48.5 days. It is noteworthy that the days to resolution may be inflated as the date of resolution was often clustered around a study visit. The possibility that the actual resolution timeframe is shorter is further supported by treatment with a single dose pack in most instances of leg pain.

Leg pain events were all considered to be related to a pedicle breach in independent MRI evaluation and the majority were at the L5/S1 levels where a more medialized approach for targeting the BVN is needed. While most of the investigators in the clinical studies did have transpedicular access experience, all but four of the treating physicians were new to the BVNA procedure. There were no observed learning curve patterns for anesthesia type, proceduralist specialty, or experience with the procedure for the leg pain events. Pedicle breaches were not isolated to initial cases and were spread across nine different study sites.

A review of the 473 clinical studies procedures performed to date (involving the unilateral transpedicular access of 868 vertebral bodies) showed 24 non-serious reports of post-ablation radiculitis and radiculopathy for an overall leg pain rate of 5%. Therefore, it is reasonable to counsel patients (particularly those with L5/S1 anatomy that requires a more medialized approach), that they may have approximately a 5% risk of experiencing temporary leg pain after the procedure which typically resolves with a single course of oral medication in an average of 4 to 6 weeks.

Strengths and limitations

Strengths of this study are the robust design, the independent oversight of the study and results, the low attrition rate, and the consistency of outcomes for patients with active treatment to other RCT results. While enrollment was halted in this study at the interim analysis, limiting the between arm results to 6 months, the treatment arm patients continued with systematic, prospective follow-up per protocol through 24 months with a high retention rate. Pain and functional outcomes observed in this study are consistent with long-term results of other RCTs on vertebrogenic pain patients treated with BVN ablation including one non-sponsored single arm study [22]. The generalizability of treatment outcomes for a well-defined subgroup of vertebrogenic CLBP patients was further demonstrated by this study with similar results reported by the 20 different study sites performing BVNA in this study compared to previously published RCTs and single arm studies involving 21 different study sites and multiple specialties.

Limitations of this study include potential sources of bias, such as an open-label design, industry-funding, and a non-structured standard care control. Multiple processes were implemented in this RCT to limit any potential selection or results bias in this industry-funded study including an independent medical monitor confirming inclusion of a primary vertebrogenic population, third-party monitoring of source data, the independent adjudication of events and interventions by the CEC, and data analysis by a third-party statistical firm and reporting overseen the independent DMC. Results of this study are consistent with 12-month results for a non-industry funded single arm study of intraosseous BVN ablation compared to standard care [22].

Although this study population was derived from a randomized control trial, there may have been a nocebo effect in this study where it was impossible to blind patients to their treatment, and closer observation and management of patients when participating in a research study may have led to an enhanced treatment effect. However, an open-label study design is acceptable in a post-market environment where the treatment effect has previously been demonstrated in comparison to a sham procedure, and treatment outcomes have remained consistent across studies and through long-term follow-up; further suggesting that improvements are largely due to the intervention. Additionally, the standard care performance in this study was in line with non-surgical care control arm results in a meta-analysis of RCTs for lumbar fusion [30].

While regression to the mean is a possibility given the non-controlled nature of the study follow-up, in a population where 67% of patients experienced LBP for > 5 years, such regression to the mean phenomenon would likely already have occurred. Additionally, prior analyses of ODI reduction from baseline to 12 months estimated as a function of the baseline ODI using a regression analysis, demonstrated that improvements were due to the intervention rather than a regression to the mean [21].

These results demonstrate the benefits of BVN ablation relative to currently available alternatives. Standard care treatments in this study were based on the clinical assessment by the treating investigator and are reflective of the variability in conservative treatment that exists in actual practice today with multiple specialties involved in the care of low back pain, a lack of clarity on the effectiveness of therapies, and limited treatment consensus. This study design provides a more clinically meaningful understanding of real-world outcomes than comparing to a prescribed control.

Conclusions

This study further demonstrates the long-term clinical effectiveness and safety of BVN ablation in a well-defined primary vertebrogenic CLBP population. Patients treated with BVN ablation exhibited statistically significant and clinically meaningful improvements from baseline in measurements of pain, function, and quality of life at all follow-up timepoints through 24 months. Responder rates remained high at 24 months while opioid use and injections were significantly reduced, further demonstrating the utility and clinical impact of BVN ablation for patients with vertebrogenic CLBP over existing treatments with published poor effect sizes.

Informed Patient Consent

The authors declare that informed patient consent was taken from all the patients.

Declarations of Competing Interests

The following authors declare conflicts of interest related to consulting, teaching/proctoring roles, and/or scientific board roles for Relievant Medsystems – Dr. J. Khalil and Dr. S. Garfin.

The following authors declare conflicts of interest for research funding paid to their institution from Relievant Medsystems during the con-

duct of the study – Dr. T. Koreckij, Dr. J. Khalil, Dr. M. Smuck, Dr. S. Kreiner, and Dr. Markman.

The following authors declare no conflicts of interest for the submitted work: Dr. S. Kreiner, Dr. T. Koreckij, Dr. M. Smuck, and Dr. Markman.

Funding

This study was funded by Relievant Medsystems, Inc.
Study Type: Clinical Study

Summary sentence

INTRACEPT RCT 24-month treatment arm results demonstrate the safety, durability, reproducibility, and effectiveness of basivertebral nerve ablation for the treatment of vertebrogenic CLBP.

Acknowledgements

On behalf of the INTRACEPT Trial Investigators:
Douglas Beall, M.D., Clinical Investigations, LLC
Scott Bainbridge, M.D., Denver Back Pain Specialists
Jad G. Khalil, M.D., William Beaumont Hospital
Theodore Koreckij, M.D., Saint Luke's Hospital
Paul Kalapos, M.D., Penn State Hershey Medical Center
Frank Phillips, M.D., Rush University Medical Center
John Keel, M.D., Emory University
Jeffrey Wang, M.D., Keck Hospital of USC
Matthew Smuck, M.D., Stanford Hospital
Charles Munyon, M.D., Temple University
John Markman, M.D., University of Rochester
Bruce Vrooman, M.D., Dartmouth Hitchock Medical Center
Neel Anand, M.D., Cedars Sinai Spine Center
Daniel Lieberman, M.D., Phoenix Spine
Larry Shannon II, M.D., Bassett Medical Center
Scott Kreiner, M.D., Barrow Brain and Spine
Aaron Calodney, M.D., Precision Spine Care
Ken Yonemura, M.D., Salt Lake Center for Spine and Peripheral Nerve Surgery
Bradly Goodman, M.D., Alabama Clinical Therapeutics, LLC
Gregory Moore, M.D., NeuroSpine Institute
Michael Schaufele, M.D., Drug Studies America
Al Rhyne, M.D., OrthoCarolina
Dan Nguyen, M.D., Oklahoma Spine Hospital

References

[1] Keller A, Hayden J, Bombardier C, van Tulder M. Effect sizes of non-surgical treatments of non-specific low-back pain. Eur Spine J 2007;16(11):1776–88. doi:10.1007/s00586-007-0379-x.
[2] Mafi JN, McCarthy EP, Davis RB, Landon BE. Worsening trends in the management and treatment of back pain. JAMA Intern Med 2013;173(17):1573–81. doi:10.1001/jamainternmed.2013.8992.
[3] Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: time to back off? J Am Board Fam Med 2009;22(1):62–8. doi:10.3122/jabfm.2009.01.080102.
[4] Antonacci MD, Mody DR, Heggeness MH. Innervation of the human vertebral body: a histologic study. J Spinal Disord 2008;11(6):526–31.
[5] Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral end plate in low back pain. Global Spine J 2013;3(3):153–64. doi:10.1055/s-0033-1347298.
[6] Fields AJ, Lee GL, Keaveny TM. Mechanisms of initial endplate failure in the human vertebral body. J Biomech 2010;43(16):3126–31. doi:10.1016/j.jbiomech.2010.08.002.
[7] Fields AJ, Liebenberg EC, Lotz JC. Innervation of pathologies in the lumbar vertebral endplate and intervertebral disc. Spine J 2014;14(3):513–21. doi:10.1016/j.spinee.2013.06.075.
[8] Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. Eur Spine J 2016;25(11):3723–34. doi:10.1007/s00586-016-4459-7.
[9] Kjaer P, Korsholm L, Bendix T, Sorensen JS, Leboeuf-Yde C. Modic changes and their associations with clinical findings. Eur Spine J 2006;15:1312–19. doi:10.1007/s00586-006-0185-x.
[10] Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA. Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. Eur Spine J 1998;7(5):363–8. doi:10.1007/s005860050091.
[11] Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J 2018;27(5):1146–56. doi:10.1007/s00586-018-5496-1.
[12] Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 2-year results from a prospective randomized double-blind sham-controlled multicenter study. Int J Spine Surg 2019;13(2):110–19. doi:10.14444/6015.
[13] Fischgrund J, Rhyne A, Macadaeg K, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. Eur Spine J 2020;29(8):1925–34. doi.org/10.1007/s00586-020-06448-x.
[14] Khalil JG, Smuck M, Koreckij T, et al. A prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain. Spine J 2019;19(10):1620–32. doi:10.1016/j.spinee.2019.05.598.
[15] Smuck M, Khalil JG, Barrett K, Hirsch JA, Kreiner S, Koreckij T, et al. Prospective, randomized, multicenter study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results. Reg Anesth Pain Med 2021 rapm-2020-102259. doi:10.1136/rapm-2020-102259.
[16] Roland M, Fairbank J. The Roland-Morris disability questionnaire and the Oswestry disability questionnaire. Spine 2000;25(24):3115–24. doi:10.1097/00007632-200012150-00006.
[17] Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study Questionnaire Short Form 36, and pain scales. Spine J 2008;8(6):968–74. doi:10.1016/j.spinee.2007.11.006.
[18] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17(1):45–56. doi:10.1016/0304-3959(83)90126-4.
[19] Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992;305(6846):160–4. doi:10.1136/bmj.305.6846.160.
[20] Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–36. doi:10.1007/s11136-011-9903-x.
[21] Macadaeg K, Truumees E, Boody B, Pena E, Arbuckle A, Gentile J, et al. A prospective, open-label, single-arm, multi-center study of intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 12-month results. NASSJ 2020;3(100030) E-pub 18 Sept 2020. doi:10.1016/j.xnsj.2020.100030.
[22] DeVivo AE, D'Agostino GD, Anna G, Al Qatami H, Gil I, Ventura F, et al. Intra-osseous basivertebral nerve radiofrequency ablation (BVA) for the treatment of vertebrogenic chronic low back pain. Neuroradiology 2020;63:809–15. doi:10.1007/s00234-020-02577-8.
[23] Silvis WL, Lakke SE, Stegeman P, et al. Can patients with low back pain be satisfied with less than expected? Spine 2016;41(20):1606–12. doi:10.1097/BRS.0000000000001592.
[24] Manchikanti L, Cash K, McManus C, Pampati V. A randomized, double-blind, active–controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: results of 2- year follow-up. Pain Physician 2013;16:E491–504.
[25] Kapural L, Vrooman B, Sarwar S, et al. A randomized, placebo-controlled trial of transdiscal radiofrequency, biacuplasty for treatment of discogenic lower back pain. Pain Med 2013;14(3):362–73.
[26] Dreyfuss P, Halbrook B, Pauza K, Joshi A, McLarty J, Bogduk N. Efficacy and validity of radiofrequency neurotomy for chronic lumbar zygapophysial joint pain. Spine 2000;25(10):1270–7. doi:10.1097/00007632-200005150-00012.
[27] Fritzell P, Hagg O, Wessberg P, Nordwall ASwedish Lumbar Spine Study Group. 2001 Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 2001;26(23):2521–32 discussion 2532-2524.
[28] Brox JI, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine 2003;28(17):1913–21.
[29] Friedly J, Nisho I, Bishop M, Maynard C. The relationship between repeated epidural steroid injections and subsequent opioid use and lumbar surgery. Arch Phys Med Rehabil 2008;89:1011–15.
[30] Yavin D, Casha S, Wiebe S, et al. Lumbar fusion for degenerative disease: a systematic review and meta-analysis. Neurosurgery 2017;80:701–15. doi:10.1093/neuros/nyw162.

NASS COVERAGE POLICY RECOMMENDATIONS

Lumbar Fusion

NASS® ADVANCING GLOBAL SPINE CARE

DEFINING APPROPRIATE COVERAGE POSITIONS

North American Spine Society 7075 Veterans Blvd. Burr Ridge, IL 60527
spine.org

COVERAGE COMMITTEE

NASS Coverage Policy Recommendations

NASS Coverage Committee

North American Spine Society
Coverage Policy Recommendations

7075 Veterans Boulevard
Burr Ridge, IL 60527 USA
(630) 230-3600
www.spine.org

ISBN 1-929988-68-0

Introduction

North American Spine Society (NASS) coverage policy recommendations are intended to assist payers and members by proactively defining appropriate coverage positions. Historically, NASS has provided comment on payer coverage policy upon request. However, in considering coverage policies received by the organization, NASS believes proactively examining medical evidence and recommending credible and reasonable positions may benefit both payers and members in helping achieve consensus on coverage, avoiding unnecessary controversies. This coverage recommendation reflects the best available data as of 6/6/2019; information. Data published after 6/6/2019 is thus not reflected in this recommendation and could warrant deviations from this recommendation, if appropriate.

Methodology

The coverage recommendations put forth by NASS use an evidence-based approach to spinal care. When the available data does not meet strict evidence-based criteria, the recommendations reflect the multidisciplinary expertise of the authors in order to reflect reasonable, standard practice indications in the United States.

NASS Coverage Policy Methodology

Scope and Clinical Indications

Lumbar fusion (regardless of the technique, which includes noninstrumented fusion) may be indicated for the following diagnoses with qualifying criteria, when appropriate.

1. **Infection** (including tuberculosis) involving the spine in the form of discitis, osteomyelitis or epidural abscess in EITHER of the following cases:
    a. Instability is present
    b. Debridement and/or decompression is anticipated to result in instability
2. **Tumor** involving the spine or spinal canal in EITHER of the following cases:
    a. Instability is present
    b. Resection and/or decompression is anticipated to result in instability
3. **Traumatic injuries,** including fractures, fracture-dislocations, dislocations, or traumatic ligamentous disruption in EITHER of the following cases:
    a. Instability is present
    b. Decompression of the spinal canal is anticipated to result in instability
    c. Bracing even though an option, not feasible secondary to medical status, additional injuries or comorbidities
4. **Deformity** that includes the lumbar spine (eg, scoliosis that is restricted to the lumbar spine or a thoracolumbar deformity that ends in the lumbar spine) that meets ALL of the following criteria:
    a. Sagittal or coronal imbalance of at least 5 cm is present, as measured on long-plate, standing radiographs of the entire spine OR documented progression of deformity by at least 10° as measured on consecutive radiographs over a one year period OR a fixed curve greater than 30° in the coronal plane OR lateral listhesis of at least 10%[1] OR proximal junctional kyphosis defined as a segmental Cobb angle of at least 10° or 10° of progression from the immediate postoperative images[2]
    b. Substantial functional limitation including severe back pain, difficulty ambulating and decreased ability to perform activities of daily living
    c. Failure of nonoperative treatment
5. **Stenosis** in the lumbar spine (either central or foraminal), as an adjunct to decompression (either direct or indirect, the latter of which can be affected via a lateral interbody fusion or anterior interbody fusion with disc space distraction and realignment), that meet ANY of the following criteria: (note: assumption is that the patient fulfills criteria for stenosis decompression as per *Lumbar Laminectomy Coverage Recommendation*)[3]
    a. Dynamic instability is present, as documented by flexion-extension radiographs or comparison of a supine and upright image, defined as a difference in translational alignment between vertebrae greater than 3 mm between views
    b. Spondylolisthesis (defined as at least 3 mm of anterolisthesis of the upper vertebra in relation to the lower vertebra) is present, either isthmic (ie, secondary to a posterior arch fracture) or degenerative type
    c. Cases in which decompression will likely result in iatrogenic instability, such as foraminal stenosis, during which greater than 50 percent of the facet joint will be removed to adequately decompress the exiting nerve root, or in which disc

space distraction is intended (eg, interbody fusion) to achieve indirect central or foraminal decompression in lieu of direct decompression via aggressive resection of the facet joints and lamina
   d. Adjacent level stenosis, eg, stenosis that has developed above or below a previous fusion
   e. Recurrent stenosis, eg, that which developed at a level that has been previously operated
6. **Disc herniations** in the lumbar spine, as an adjunct to disc excision, that meet ANY of the following criteria: (note: assumption is that the patient fulfills criteria for discectomy as per *Discectomy Coverage Recommendation*)[4]
   a. Primary extraforaminal disc herniation is present at L5-S1, in which a far lateral approach is not feasible because of the presence of the iliac wings for which facet resection is necessary to retrieve the disc, which will result in iatrogenic instability
   b. Primary foraminal disc herniation for which facet resection is necessary to retrieve the disc, which will result in iatrogenic instability
   c. Recurrent disc herniation — a second time recurrent disc herniation or recurrent disc herniation associated with lumbar instability, deformity or chronic axial low-back pain
   d. Primary disc herniation in the lumbar spine that is at the level of the spinal cord (ie, low lying conus medullaris) in which the surgeon determines that the surgical approach necessary to safely address the disc herniation while avoiding manipulation of the spinal cord will result in iatrogenic instability
7. **Synovial facet cysts** in the lumbar spine, as an adjunct to cyst excision
8. **Discogenic low back pain** secondary to a degenerated disc that meet ALL of the following criteria:
   a. Advanced single-level disease noted on an MRI and plain radiographs of the lumbar spine, characterized by moderate to severe degeneration of the disc with Modic changes (defined as peridiscal bone signal above and below disc space in question) as compared to other normal or mildly degenerative levels (characterized by normal plain radiographic appearance and no or mild degeneration on MRI)
   b. Presence of symptoms for at least 6 months AND that are not responsive to multimodal nonoperative treatment over that period that should at least include physical therapy/rehabilitation program but may also include (but not limited to) pain management, injections, cognitive behavioral therapy, and active exercise programs
   c. Absence of unmanaged psychiatric disorders that can lead to symptom magnification, such as anxiety disorder, that have not been controlled
   d. Absence of smoking for at least 6 weeks prior to surgery date
   e. Primary complaint of axial pain, with a possible secondary complaint of lower extremity pain
9. **Pseudarthrosis** in the lumbar spine that meet ALL the following criteria (a through d) OR demonstrate presence of a gross failure of the instrumentation (eg, pedicle screw breakage, screw loosening, curve/correction decompensation)
   a. Mechanical low back pain that is approximately at the level of the pseudarthrosis, qualified as pain that can be somewhat positionally abated
   b. A period of time following the index surgery during which the patient had symptomatic relief
   c. Presence of symptoms for at least 6 months
   d. Failure of nonoperative treatment
   e. CT or plain films that are highly suggestive of nonunion at a lumbar segment at which a fusion had been previously attempted. These criteria can include either:
      i. Lack of bridging bone
      ii. Dynamic motion noted on flexion-extension radiographs

Lumbar fusion is **NOT** indicated in cases that do not fulfill the above criteria. Of note, lumbar fusion is not indicated in the following scenarios:

1. **Disc herniations:**
   a. As an adjunct to primary excision of a central or posterolateral disc herniation at any level in the absence of instability or spondylolisthesis
2. **Stenosis:**
   a. As an adjunct to primary decompression of central and/or lateral recess stenosis in the absence of instability, foraminal stenosis, or spondylolisthesis and when greater than 50% bilateral facet resection is not required to achieve neurologic decompression
3. **Discogenic low back pain:**
   a. Any case that does not fulfill ALL of the above criteria

b. Presence of advanced multilevel degeneration (3 or more levels) on a preoperative MRI and plain radiographs. The presence of 2 levels of degenerative disc disease should be viewed as a relative contraindication to lumbar fusion as there may be carefully selected patients with 2 levels of degenerative disease that will benefit from lumbar fusion surgery.
c. Presence of unmanaged psychiatric disorders that can lead to symptom magnification, such as anxiety disorder, that have not been controlled
d. Patient is actively smoking

Rationale for Coverage Recommendation

Lumbar fusion remains one of the most commonly performed procedures in spinal surgery. Pervasive negative attention has been placed on lumbar fusion in the lay media and many scientific publications (http://www.nytimes.com/2010/04/13/health/research/13proc.html, http://www.nytimes.com/2003/12/31/business/an-operation-to-ease-back-pain-bolsters-the-bottom-line-too.html). It is interesting that even in cases of highly publicized success, such as Tiger Woods' lumbar fusion, the lay media continue to highlight the unpredictability of results (https://www.nytimes.com/2019/05/15/sports/how-tiger-woods-pga-back-surgery.html). Despite this, lumbar fusion continues to have a critical and important role in the treatment of a variety of spinal conditions in well-selected, appropriate patients for a variety of conditions. This updated Coverage Recommendation put forth by NASS utilizes an evidence-based approach to spinal care when possible. In the absence of strict evidence-based criteria, this coverage recommendation utilizes the multidisciplinary and nonconflicted experience and expertise of the Committee in order to reflect reasonable standard practice indications in the United States.

In **item 1,** the rationale for coverage of lumbar fusion for the treatment of spinal infections is based on what most practitioners would consider to be accepted practice patterns. The primary focus of treatment of a spinal infection is to either treat impending neurological deficit from a progressive deformity or expanding focus of infection. The latter can manifest from an epidural abscess or an invasion of infected, necrotic, or pathologically fractured bone into the spinal canal or neural foramina. Instability remains judged on an individual case-by-case basis and can be evidenced by progressive deformity, bone loss, or involvement of a stabilizing structure such as a facet joint. Instability is a frequent by-product of surgical debridement or decompression, such as in cases in which an anterior corpectomy is performed in order to remove infected bone and disc material or access an epidural abscess. This can also be the case in which a posterior approach is used to access an abscess or infected disc or vertebral body (eg, posterolateral approach). During this approach, extensive removal of the posterior elements, including bilateral facet joints, pedicles, and transverse processes, are performed in order to access the anterior elements. This would substantially destabilize the spine, thus necessitating instrumentation and fusion of the operated segments. Of note, there are no randomized controlled trials comparing operative to nonoperative intervention for spinal infections or comparing decompression versus decompression and fusion. The most likely reason for this is that most would consider such trials to be unethical in nature because of the established benefit of fusion in this patient population.

Literature Update

Recent works have highlighted the utility of lumbar fusion for the treatment of infections. Ackshota et al documented reasonable outcomes with multilevel corpectomy and fusion for a group of 56 patients with vertebral osteomyelitis.[6] Of note, there was a higher complication rate compared to historical controls with 1- and 2-level corpectomy, which is intuitive in that more extensive infection was present and surgery was performed.

With the popularity of less invasive fusion techniques, lateral interbody fusion has been successfully used to treat lumbar osteomyelitis and abscess as well.[6-9] Other various studies have reported reasonably successful outcomes with lumbar fusion procedures with instrumentation for the treatment of pyogenic bone infections of the spine.[2,10-11] These works all continue to support the critical role of lumbar fusion in the treatment of spinal infections.

In **item 2,** the rationale for coverage of lumbar fusion for spinal tumors is again based on what most practitioners would consider to be accepted practice patterns. Of note, in distinction to some other policies that the Coverage Committee has reviewed, this should not be limited to primary bone tumors. In fact, the most common indication for spine tumor surgery is in the treatment of metastatic disease. This field has grown owing to the improved survival of many forms of cancer with improved medical treatment. The removal of extradual soft-tissue tumors, such as those that might occur with metastatic disease or lymphoma that do not necessarily cause bone destruction will often require destabilizing approaches to the spine in order to safely access and remove the lesion. Thus, for a similar rationale as detailed above for item 1, the spine necessitates instrumentation and fusion to restore stability. Of note, there is a randomized controlled

trial comparing operative to nonoperative treatment for the treatment of metastatic spinal cord compression, which has clearly shown an advantage for surgery in maintaining and restoring neurological function.[12]

Literature Update

There has been continued work on the role of surgery for metastatic spine disease. Recently published, in a propensity matched retrospective study, Schoenfeld et al reported a higher likelihood that patients with metastatic disease of the spine who underwent surgery were ambulatory than those who had nonoperative treatment at 6 months.[13] As in the Patchell et al[12] study referenced above, these data support the role for fusion surgery for the maintenance or restoration of neurological function and ambulatory status in this group of patients.

In **item 3**, the rationale for coverage for fusion for traumatic injuries of the lumbar spine is based on both high-level evidence for injuries such as burst fractures of the thoracolumbar junction as well lower level evidence and accepted practice patterns. The main indications for surgery after a traumatic injury to the lumbar spine are instability, which can be evidenced in a number of different manners, and neurological compression with or without a neurological deficit. A randomized controlled trial published by Wood et al[14] found equivalent treatment outcomes between surgery and bracing in patients with stable thoracolumbar burst fractures without neurological deficits. Excluding this precise injury, which represents only one of many types of injuries that can occur in the thoracolumbar spine, there are no prospective, randomized comparisons between operative and nonoperative treatment. The role of fusion and instrumentation for the treatment of unstable fractures, dislocations, fracture-dislocations, or purely ligamentous injuries is well-established among spine practitioners and will not likely be studied in the future by a randomized trial of operative and nonoperative treatment modalities.

Literature Update

Wood et al published a very long-term follow-up of a prior randomized controlled trial comparing operative to nonoperative treatment of stable thoracolumbar burst fractures without neurological deficit. In all cases, the posterior ligamentous complex was felt to be stable preoperatively.[15] At 16 to 22 years follow-up, patients in the nonoperative group had less pain and better function than those in the operative group. These are consistent with the current coverage recommendations in that these were mechanically stable injuries in patients without neurological deficit. Fusion continues to be supported in mechanically unstable injuries in those with deficits.

In **item 4**, the rationale for coverage for lumbar fusion for the treatment of adult spinal deformities is based on an evolving and increasing body of peer-reviewed evidence. In 2006, Schwab et al studied the disability in 947 patients with adult spinal deformity (ASD).[16] This group of highly experienced deformity surgeons utilized the following inclusion criteria that are relevant to the lumbar spine: sagittal or coronal imbalance of at least 5 cm, scoliotic curve of at least 30°, lumbar kyphosis in more than 3 levels, and documented curve progression of 10°. Among their study cohort, they found significant associations between various curve parameters and Oswestry Disability Index (ODI) scores as well as SRS-22 questionnaire scores. In 2005, Glassman et al, in a review of 298 patients, found that the coronal imbalance of greater than 4 cm and positive sagittal imbalance were the most reliable predictors of clinical symptoms.[17] The results of corrective surgery of deformity have similarly been most predicted by the degree of sagittal balance correction achieved.[18,19] With restoration of sagittal balance, health-related quality of life outcome measures are improved. Of most importance, this coverage recommendation includes the failure of nonoperative treatment prior to surgery. That being stated, a study by Glassman et al published in 2010 found no significant improvements in HRQOL measures in a cohort of 123 patients who were treated with nonoperative care for spinal deformities.[20] More recently, a prospective randomized and observational study by Kelly et al showed no significant change in outcomes scores over time with nonoperative treatment for adult scoliosis patients, compared to substantial improvement with surgical management.[21]

Literature Update

A plethora of works investigating the outcomes of fusion for ASD continue to be published including studies with newer data comparing operative and nonoperative treatment of this patient population. Choi et al performed a systematic review and meta-analysis of the literature regarding ASD including studies published as of May 2018.[22] Of 246 articles identified, only 4 were ultimately eligible for full review that compared operative to nonoperative care. Of these, only one was published in the past 5 years, with the other 3 published in 2009. A meta-analysis revealed that numerical back and leg pain scores were significantly lower with operative treatment, as ODI and SRS-22 scores were significantly improved with operative compared to nonoperative care. Of note, none of the studies were randomized, and thus the authors found high selection bias.

Teles et al also performed a systematic review of literature comparing operative and nonoperative treatment of ASD.[23] This group was more liberal with their search and included 26 articles, not all of which were direct comparisons of operative and nonoperative care. While they found that surgery resulted in significant reduction in disability, pain and HRQOL, they considered the literature regarding nonoperative treatment to be biased, though it did not indicate significant improvements at 2-year follow-up.

In a recent trial, Kelly et al compared operative and nonoperative treatment of ASD, specifically adult lumbar scoliosis. In the randomized arm, the results of 30 operative patients with ASD were compared to 33 nonoperative patients.[21] Of note, there was high crossover from nonoperative to operative treatment (64%). Ultimately, the intent-to-treat analysis demonstrated no differences at 2 years in outcomes as measured by ODI and SRS scores while an as-treated analysis showed significantly better ODI and SRS scores in the operative compared to nonoperative groups. In the observational arm, 112 operative patients were compared to 111 nonoperative patients. Operative care was similarly found to result in significantly better SRS and ODI scores. There was an overall 14% rate of revision surgery in the operative group.

Liu et al compared the likelihood of achieving minimal clinically important difference (MCID) in patients who underwent operative vs nonoperative treatment for ASD in a multicenter, prospective investigation.[24] They found operative patients were more likely to achieve MCID for ODI, SF-36 and SRS activity scores. Though patients undergoing nonoperative care also improved, achieving MCID was less likely at 1-year follow-up. Importantly, the authors did note that there was a subset of patients who underwent surgery who exhibited no or minimal improvement.

Scheer et al performed a retrospective review of 479 patients with ASD, 258 of whom had surgery and 221 of whom did not.[25] After matching the patients for baseline characteristics, they found that the mean QALYs at 1, 2 and 3 years after surgery were significantly greater than those for nonoperatively treated patients. In a similar study from this group, operative treatment resulted in significant improvement of HRQOL at 2-years follow-up while nonoperative treatment resulted in no change.[26]

It is worthwhile substantiating the coverage recommendation's definition of lateral listhesis considered to be at risk for progression after decompression alone. Kelleher et al found a significantly higher rate of revision surgery required (ie, revision decompression and fusion) in patients with lateral listhesis more than 10% following a decompression alone.[1] This was in fact a best scenario situation as the surgery performed was minimally invasive, presumably the least destabilizing type of decompression techniques.

The definition of proximal junctional kyphosis also deserves attention. This is derived from the work of Kim and Iyer in which a sagittal Cobb angle of at least 10°, or 10° of progression from the immediate postoperative imaging, at the segment above the fusion had been delineated.[2] These are well-accepted criteria and based on a comprehensive review of the available literature.

In **item 5,** the rationale for fusion in select patients who are to be operated on for lumbar stenosis is rooted in the current evidence base. Historically, classic studies that supported fusion following decompressive surgery in patients who have an underlying degenerative or isthmic spondylolisthesis have been well-accepted. Herkowitz and Kurz found significantly better clinical (and radiographic) results when fusion was performed following laminectomy for spinal stenosis with degenerative spondylolisthesis.[27] The NASS *Evidence-Based Guidelines on Degenerative Spondylolisthesis*, in an extensive review of the literature, recommended fusion in the scenario as well.[28] In an analysis of the SPORT data, Weinstein et al found substantially better outcomes in those patients treated with laminectomy and fusion

compared to nonoperatively managed patients.[29] There has been, however, more recent, very high-level data that has been published, discussed below in the literature update. These data have contested older literature and questioned the universal indication of lumbar fusion for degenerative spondylolisthesis.

Literature Update

In a 2016 *New England Journal of Medicine* article, Forsth et al found no difference in clinical outcomes between those who underwent decompression vs decompression and fusion among 247 patients with lumbar spinal stenosis.[30] A large group had degenerative spondylolisthesis as well, which were randomized in a separate block. No difference was found between the fusion and nonfusion groups. Importantly, the radiographic criterion for spondylolisthesis was at least 3 mm of forward slippage.

Published in the same issue, Ghogawala et al reported the results of an RCT of 66 patients with stenosis and spondylolisthesis.[31] At 4-years follow-up, the differences included slightly (but statistically significant) better SF-36 physical component summary scores in the fusion group, while other clinical outcomes were not different, and a much higher reoperation with decompression alone (14% vs 34%). The definition of spondylolisthesis was a slip of 3 to 14 mm. However, patients with more than 3 mm difference on flexion-extension views were considered to be unstable and excluded. Also, patients who were felt to have mechanical low back pain were also excluded.

In an editorial regarding these 2 RCTs, Ghogawala et al concluded that fusion was strongly supported by the Ghogawala et al study (also known as the SLIP study)[31] as it was a homogenous population powered to detect a difference in the primary outcome measure.[32]

Burgstaller et al performed a systematic review of RCTs regarding surgical treatment for lumbar stenosis.[33] While definitive conclusions were not made, the group highlighted the disagreement on how to define instability, as instability is widely held as indication for adding fusion to a decompression. Of note, the study period antedated the 2 *NEJM* RCTs.

Yavin et al performed a systematic review and meta-analysis of studies regarding a variety of degenerative lumbar disorders. They found support for fusion for patients with spondylolisthesis but not for those with only stenosis.[34] Inose et al published the results of an RCT comparing decompression, decompression and fusion, and decompression and stabilization with an artificial ligament (ie, dynamic stabilization).[35] Among the 85 patients with degenerative spondylolisthesis enrolled, there was no significant difference with the 3 treatments at 1- to 5-year follow-up. The definition of spondylolisthesis was more than 3 mm slippage.

Indirect decompression of lumbar stenosis with spondylolisthesis has become more popular, particularly with minimally invasive approaches. Isaacs et al reported comparable outcomes with a minimally invasive transforaminal lumbar interbody fusion (TLIF) compared to lateral interbody fusion (LIF) for this condition.[36] Some direct decompression was performed in the TLIF group but not in the LIF group.

Other indications for fusion with stenosis

High-level evidence also exists regarding the role of fusion for adult isthmic spondylolisthesis, which usually presents with concomitant foraminal stenosis at the slipped level. In a prospective randomized controlled trial, Moller and Hedlund found significantly better clinical outcomes in patients who underwent surgery (that included fusion) than nonoperative care.[37]

Concerning dynamic instability, there are currently no randomized controlled trials comparing operative to nonoperative treatment for dynamic instability of the lumbar spine. Patients who have dynamic instability, with or without the presence of spinal stenosis on a static MRI (which, in the supine position, usually demonstrates the spine in a reduced position that will underestimate the degree of stenosis), if symptomatic, have a clear indication of an unstable spinal segment. To the Coverage Committee's knowledge, there is not an accepted nonfusion method of surgically treating such a patient. Of note, there are currently no accepted radiographic criteria by which the change in alignment on flexion-extension views can be considered "instability." White and Panjabi have established criteria for clinical instability, with varying degrees of translational and angular deformity noted between two adjacent vertebrae.[38] However, these criteria were developed in order to aid physicians in recognizing occult traumatic instability using plain radiographs, and were not intended to be

used to determine clinical instability in the degenerative setting. As the measurement error of measurements made on flexion-extension views has been found to be between 0.7° and 1.6°,[39] the Coverage Committee thought it would be reasonable to conclude that 3 mm of translational difference would reflect a real difference and be beyond the measurement error.

There are cases of lumbar stenosis that pose particular challenges. For cases in which there is severe foraminal stenosis, adequate decompression often can require aggressive resection of one or both facet joints at a particular level. Removal of an entire facet joint, even unilaterally, is generally thought to be a destabilizing event in the lumbar spine.[40] While most cases of unilateral foraminal stenosis can be adequately decompressed with a nondestabilizing procedure, such as a foraminotomy, there are some cases in which the compression can be so severe and the orientation of the joint is such that achieving adequate decompression without producing iatrogenic instability can be difficult, if not dangerous to the underlying nerve root. This is a particular clinical scenario that would be exceedingly difficult to study that will likely not be addressed by a prospective, randomized trial (or other comparative trial for that matter). Recognizing this limitation in the evidence, that will likely persist, evidence-based medicine surgeons have made it clear that this should be reserved as a potential indication for fusion in the setting of stenosis without obvious signs of preoperative spondylolisthesis or instability.[41]

Stenosis that redevelops at a level that has been previously operated on is a particular challenge to spinal practitioners. Patients who have failed nonoperative measures and are deemed operative candidates usually require a revision laminectomy/decompression. Almost implicitly, portions of the facet joint had been removed during the index procedure. Thus, a revision decompression often relies on resection of additional facet joint (or other posterior arch structures) in order to safely mobilize the dural or neural elements from the bony borders and adequately achieve decompression. In these cases, iatrogenic destabilization is a frequent occurrence and many times a planned portion of the surgery to enable safe execution. Thus, the rationale that fusion should be indicated in cases of revision decompression, even in the absence of clear signs of dynamic or static instability, is made based on technical considerations derived from surgical experience. As discussed above, this will likely not be studied in a prospective, randomized manner in the future. In an extensive review of the literature performed by one of the Coverage Committee members, such a study could not be found.[42]

The unique case of adjacent level stenosis is also worth discussing. The proposed mechanism by which adjacent level degeneration develops is rooted in the abnormal mobility and increased range of motion demands on the supra- or infrajacent level to a fusion. Thus, it would be difficult to rationalize performing a revision decompression at an adjacent level without extending the fusion to include the decompressed level. Again, there are no available randomized controlled trials comparing decompression at an adjacent level with or without fusion. However, in line with what most spine surgeons and the members of this Committee believe to be reasonable and appropriate practice, such a study is unlikely to be performed. Evident of this fact, the literature concerning surgical treatment of adjacent level stenosis is replete with series of patients treated with revision decompression and extension of fusion.[43]

As evidenced by **item 6,** there are limited circumstances in which a fusion would be indicated in the setting of performing a primary discectomy. In fact, there is literature to substantiate that routine inclusion of fusion in this setting does not improve outcomes.[44,45] However, this does not account for a few particular situations. First, it is technically very difficult, if not impossible, to perform a far lateral approach at the L5-S1 level. Thus, for a primary surgery to remove an extraforaminal/far-lateral disc herniation at L5-S1, a fusion is often needed because the facet joint at L5-S1 must be completely removed in order to gain access to the disc herniation.[46]

Similarly, a foraminal disc herniation, which accounts for a very small percentage of all lumbar disc herniations, is often difficult to access through a standard laminotomy with medial facetectomy OR a far-lateral approach. In this unusual circumstance, performing a full facectomy to allow direct access to the disc herniation and visualization of the nerve root can afford the safest and most effective surgical treatment. While we are aware of case series that show that unilateral destabilization in the form of pars resection does not always result in instability requiring fusion,[47] this technique for removal of intraforaminal disc herniations is not widely used or accepted. Very rarely, a lumbar disc herniation at an upper level, such as L1-2 or L2-3, can occur in a patient with a low-lying spinal cord (ie, conus medullaris). In effect, this is a case of spinal cord compression and should be treated more like a thoracic disc herniation. As the spinal cord cannot be retracted, removing the offending disc material can necessitate extensive resection of the posterior elements, such as is performed in a lateral extracavitary approach in the thoracic spine. In this rare case, fusion is a reasonable indication.

Finally, cases of recurrent disc herniation pose similar challenges as outlined above for recurrent stenosis. The presence of scar and previous facet joint resection, which is nearly omnipresent following an index discectomy, can risk iatrogenic destabilization of the facet joint with further resection for safe and adequate exposure. While there are no clear-cut guidelines, many practitioners feel that a fusion is reasonably indicated following a second recurrence. However, the technical considerations discussed above are often present at the

time of a revision discectomy for a first recurrence. Notwithstanding the presence of dynamic or static instability, fusion in the setting of a revision discectomy for a recurrent lumbar disc herniation is a reasonable practice. Recent comparative data has shed additional light on this topic, reviewed below.

Literature update

Drazin et al performed a systematic review of the treatment of recurrent lumbar disc herniations.[48] This included studies in which fusion was performed in conjunction with a revision discectomy. While they found no significant difference in the outcomes between discectomy alone and discectomy with fusion, they stated that selected articles did show that including fusion may result in greater pain improvement. Specifically, a study by Fu et al found better outcomes with posterolateral fusion and revision discectomy versus discectomy alone.[49] This group acknowledged adding fusion to a first-time revision discectomy continues to be debated.

El Shazly et al performed a prospective, randomized trial comparing revision discectomy alone, revision discectomy and TLIF and revision discectomy and posterolateral fusion (PLF) in patients with first time recurrent disc herniations.[50] There were some methodological biases in that the procedure was pseudo-randomized in a rotating order, not by computer generated assignments or sealed envelopes. The authors noted the technical benefit of a full facetectomy afforded with fusion in that it avoided excessive retraction of the neural tissues, which would be limited by postoperative epidural scar. Statistically, a power analysis was not performed a priori, nor was a power calculation made post hoc. The only difference found in the fusion groups was less postoperative back pain compared to the discectomy alone group and a lower rate of dural tear, recurrent herniation, and so-called neural damage. There was no additive benefit of TLIF compared to PLF.

In another systematic review, Kerezoudis et al analyzed 15 studies, 2 of which were RCTs.[51] This group found that revision discectomy and fusion was comparable to revision discectomy alone in terms of reoperation rates, intraoperative dural tears, and functional outcomes. Their analysis included the El Shalzly et al[50] study as well as the Liu et al study.[24] Of interest, all patients who had a revision discectomy alone but then incurred a second recurrence underwent additional fusion at the time of revision surgery. Though not highlighted in the abstract, the authors found significantly better ODI scores with fusion among 6 studies.

Onyia and Menon also performed a systematic review on this topic.[52] They reviewed the Fu et al[48], Aghayee et al[53], Liu et al[24], and El Shazly et al[50] studies. They again recognized a higher rate of new postoperative neurological deficit and dural tears with discectomy alone. They did not note any difference in functional outcomes scores or pain. The authors concluded that fusion "should not be undertaken in all recurrences" but considered as an option in instability, deformity, or if associated radiculopathy is present.

In an update of previously published neurosurgical guidelines, Wang et al reiterated support that lumbar fusion is an option in patients with a herniated disc (not necessarily recurrent) who have evidence of chronic, axial back pain, work as manual laborers, have severe degenerative changes, or instability with radiculopathy.[54] In a revision setting, fusion was recommended as an option in the presence of instability or chronic axial low back pain.

In **item 7,** fusion in conjunction with facet joint excision is considered an indicated procedure. Recent evidence has suggested advantages with fusion compared to facet cyst excision alone. Xu et al reviewed the records of 167 patients who underwent surgery for a symptomatic facet cyst.[55] Seventy-four had cysts excision with fusion, while 90 underwent cyst excision without fusion. They found a significantly higher rate of recurrent cyst formation and recurrent back pain in the nonfusion patients. Notwithstanding these data, the Coverage Committee recognizes that not all synovial facet cysts will require fusion. However, even in the absence of preoperative static or dynamic instability, fusion is reasonably indicated for the treatment of this clinical entity. Of note, there is a very high rate of adhesions between the facet cyst and the underlying dural sac, making complete excision of the cyst difficult without more extensive resection of the facet joint itself, which can lead to iatrogenic destabilization.

Literature Update

A number of recent studies examining the outcomes of facet cyst excision with and without fusion have been published. Bruder et al reported on a large cohort of patients who underwent decompression alone for a synovial cyst of the lumbar spine.[56] They found a higher than expected rate of dural tear (8.5%) with nearly ¾ of the cases showing adherence between the cyst and the dura. More importantly, 7% of patients had cyst recurrence and 9% underwent a secondary operation for stabilization for instability. While the authors concluded that decompression alone was adequate in most cases, they did note that the role of fusion continues to be debated.

Campbell et al performed a systematic review of the literature regarding operative treatment of facet cysts in the lumbar spine.[57] From 50 studies, they concluded that decompression procedures had lower rates of recurrence than percutaneous procedures (just as cyst aspiration). They could draw no conclusions regarding the role of fusion because of a paucity of evidence. They did note that 4% of patients underwent a fusion in a delayed fashion.

In another systematic review, Ramhmdani et al included 17 studies that focused on patients who had concurrent spondylolisthesis, facet arthropathy, and degenerative disc disease at the same level as a facet cyst.[58] They found that those with spondylolisthesis were 11.5 times more likely to undergo a reoperation that involved a fusion. This, they concluded, indicated that facet cysts are a sign chronic instability that may benefit from fusion at the index procedure.

In one of the only comparisons of fusion and nonfusion procedures for this diagnosis, van Dijke et al reviewed the outcomes of 314 patients who underwent surgery.[59] They found a higher rate of recurrent radiculopathy without fusion compared to fusion (25% vs 9.4%) with bivariate analysis. Adjusting for confounders, this difference was not statistically different, however. This group concluded that the decision for fusion should be based on the presence of instability.

In **item 8,** there are specific criteria detailed to indicate lumbar fusion for the treatment of discogenic back pain, presumably from degenerative disease. The Coverage Committee recognizes this is a highly controversial indication for fusion. The literature has conflicting evidence regarding the relative benefits of operative versus nonoperative treatment for this condition. In one randomized controlled trial, Brox et al found that fusion was no better than cognitive interventions and exercises at 2 years.[60] Notwithstanding the methodological critiques of the study, including the low patient numbers and a fusion method that most would consider to be less than ideal (ie, it did not include interbody fusion), the group did find statistically better improvements in leg pain in the operative group compared to the nonoperative group, though this was not the primary focus of treatment. In a subsequent publication of the 4-year outcomes of this study, there were still no differences between the groups. Similar conclusions were drawn from a study by Fairbank et al, which also compared surgery to a cognitive program.[61] Of note, the surgical group included many nonfusion procedures, so it remains difficult to generalize the results to fusion. Contrastingly, Fritzell et al found statistically better outcomes with fusion compared to a relatively unstructured nonoperative treatment program, the latter being the main focus of criticism.[62] What is lacking from all of these studies were clear-cut radiographic criteria, barring the requirement of having so-called spondylosis. The Coverage Committee has reviewed other nonrandomized studies that have indicated better outcomes when stricter radiographic and patient-centered inclusion criteria are used. In a prospective study commonly cited as evidence against fusion, Parker et al documented poor overall results in a group of so-called highly selected patients with discogenic low back pain (evaluated by MRI and discography), finding only 56% of patients being extremely satisfied with surgery.[63] However, if workman compensation cases are excluded, 90% of patients were extremely satisfied with the procedure. In a retrospective study of similarly highly select patients, Moore et al found that 87% of patients improved after an anterior-posterior fusion procedure for single level discogenic low back pain.[64]

In reviewing the various randomized controlled trials comparing fusion to artificial disc replacement that have demonstrated equivalency between the two procedures, it becomes apparent that, in a select group of patients with strict radiographic and clinical inclusion criteria, fusion for discogenic low back pain can be a moderately effective procedure. Based on analysis of this breadth of literature, the Coverage Committee developed a list of strict and rigorous criteria for fusion in this patient population. Based on the current level of evidence, as well as reasonable clinical judgment, only single level fusions for isolated single level degenerative disease noted on an MRI (with associated Modic changes) in nonsmoking patients without significant psychiatric disorder would be indicated after at least 6 months of failure of nonoperative treatment.

Literature update

Bydon et al performed a systematic review and meta-analysis of RCTs comparing operative and nonoperative treatment of so-called discogenic low back pain (LBP).[65] From analysis of 3 eligible studies, they found that pooled ODI scores were more improved in the fusion group but not to a point that would be considered clinically significant. They concluded that further evidence is needed comparing a specific surgical technique (instead of a variety of methods as has been used in prior studies) and a structured physical therapy program. They also noted that both fusion and nonoperative care should be considered acceptable treatments.

Mirza et al reported 1-year outcomes of a prospective, observational study comparing operative to nonoperative care of discogenic LBP.[66] Importantly, the study had well defined inclusion criteria that included 1- or 2-level disc degeneration, predominant axial LBP, and at least 6 months duration. In all, 495 patients were enrolled in the study, 86 of which had surgery (80% of which were fusions). With baseline differences accounted for, there was a 5.4 point average greater improvement in the surgical group as measured by the Roland Morris Disability Questionnaire. As measured by a composite score, the 1-year success rate was 33% in the operative group and 15% in the nonoperative group.

In **item 9**, a number of studies were reviewed that have documented acceptable outcomes from repair (ie, redo fusion) of a pseudarthrosis in the lumbar spine. In general, the studies demonstrate in an appropriately selected patient who has failed nonoperative treatment, that a revision surgery for pseudarthrosis repair can decrease symptoms and improve quality of life. Adogwa et al (2013), in a review of 17 patients from an institutional database, found that the VAS back pain and ODI scores significantly improved with revision surgery for pseudarthrosis at 2 years follow-up.[67] The diagnostic criteria this group used for pseudarthrosis were lack bridging bone across motions segments (on CT or plain films) or pedicle screw halos and motion on dynamic radiographs, corresponding mechanical low back pain, and prior attempted fusion at the level. At least 6 months of nonoperative care was required prior to surgery. In another study from the same group, Adogwa et al in 2011 reported the outcomes of a larger cohort of 47 patients who underwent pseudarthrosis repair in the lumbar spine.[68] The investigators reported significant improvements in VAS back pain, and SF-12 physical health scores at 2-year follow-up, while Zung Depression Scale scores and SF-12 mental component scores were not significantly improved. The inclusion and diagnostic criteria were the same as that in the 2013 study, with a minimum of 6 months of nonoperative care required prior to revision surgery. In a study specific to pseudarthrosis repair in 19 patients who previously underwent a stand-alone PLIF with a metallic cage, Cassinelli et al reported a 94% solid fusion rate and improvement in seven of eight of the SF-36 subcategories, though significant in only two subcategories.[69] Importantly, ODI scores were not significantly improved. This group did not clearly specify the preoperative criteria for pseudarthrosis. The range of time between initial PLIF and revision surgery was 9 months to 40 months. Other groups have reported the outcomes of pseudarthrosis repair following surgery adult deformity surgery, Pateder et al documented a 90 percent fusion rate with redo fusions for adult scoliosis with 80 percent of patients reporting that they would have the surgery again.[70] Harimaya et al, in a series of 33 patients who underwent revision surgery for failed lumbosacral fixation for adult deformity, highlighted the importance of strong caudal fixation, such as iliac screws, to avoid pseudarthrosis.[71] In this case, the diagnosis of pseudarthrosis is heralded by curve/correction decompensation and hardware breakage or pull-out, which may obviate a period of nonoperative care prior to considering revision surgery.

Literature update

In a more recent study that was published in 2 parts, Adogwa et al reviewed the results of 69 patients aged 65 years and older who underwent a revision decompression and fusion for pseudarthrosis (17 patients), same-level recurrent stenosis (24 patients), or adjacent segment disease with nerve compression (28 patients).[67, 72] Through various measures, they found significant improvements in quality of life, pain, and disability measures for all 3 conditions. Of note, the mean time between the index and revision surgery was 3.5 years.

Dede et al, among 66 patients who underwent pseudarthrosis repair in the lumbar spine, found better outcomes if the index surgery was for spondylolisthesis compared to degenerative disc disease.[73] Mobbs et al, in a series of patients who underwent ALIF for treatment of a failed posterior fusion, only considered patients who were at least 9 months from their index surgery.[74] In a study of 60 patients with either adjacent segment disease or pseudarthrosis after an index fusion, patients with adjacent segment disease had better outcomes than those with pseudarthrosis.[75]

References

1. Kelleher MO, Timlin M, Persaud O, Rampersaud YR. Success and failure of minimally invasive decompression for focal lumbar spinal stenosis in patients with and without deformity. Spine (Phila Pa 1976). 2010;35(19):E981–E987. doi:10.1097/BRS.0b013e3181c46fb4
2. Kim HJ, Iyer S. Proximal Junctional Kyphosis. J Am Acad Orthop Surg. 2016;24(5):318–326. doi:10.5435/JAAOS-D-14-00393
3. NASS Coverage Committee. *Lumbar Laminectomy Coverage Recommendation.* North American Spine Society; 2014.
4. NASS Coverage Committee. *Lumbar Discectomy Coverage Recommendation.* North American Spine Society; 2014.
5. Ackshota N, Nash A, Bussey I, et al. Outcomes of multilevel vertebrectomy for spondylodiscitis. Spine J. 2019;19(2):285-292. doi: 10.1016/j.spinee.2018.06.361.
6. Blizzard DJ, Hills CP, Isaacs RE, Brown CR. Extreme lateral interbody fusion with posterior instrumentation for spondylodiscitis. J Clin Neurosci. 2015;22(11):1758-1761. doi: 10.1016/j.jocn.2015.05.021.
7. Madhavan K, Vanni S, Williams SK. Direct lateral retroperitoneal approach for the surgical treatmet of lumbar discitis and osteomyelitis. Neurosurg Focus. 2014;37(2):E5. doi: 10.3171/2014.6.FOCUS14150.
8. Patel NB, Dodd ZH, Voorhies J, Horn EM. Minimally invasive lateral transpsoas approach for spinal discitis and osteomyelitis. 2015;22(11):1753-1757. doi: 10.1016/j.jocn.2015.03.061.
9. Timothy J, Pal D, Akhunbay-Fudge C, et al. Extreme lateral interbody fusion (XLIF) as a treatment for acute spondylodiscitis: Leeds spinal unit experience. J Clin Neurosci. 2019;59:213-217. doi: 10.1016/j.jocn.2018.10.63.
10. Gorensek M, Kosak R, Travnik L, Vengust R. Posterior instrumentation, anterior column reconstruction with single posterior approach for treatment of pyogenic osteomyelitis of thoracic and lumbar spine. Eur Spine J. 2013;22(3):633-641. doi: 10.1007/s00586-012-2487-5.
11. Heary RF, Agarwal N, Agarwal P, Goldstein IM. Surgical Treatment With Thoracic Pedicle Screw Fixation of Vertebral Osteomyelitis With Long-Term Follow-Up. Oper Neurosurg (Hagerstown). 2019 Nov 1;17(5):443-451.
12. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 Aug 20-26;366(9486):643-8.
13. Schoenfeld AJ, Losina E, Ferrone ML, et al. Ambulatory status after surgical and nonsurgical treatment for spinal metastasis. Cancer. 2019. doi: 10.1002/cncr.32140.
14. Wood K, Buttermann G, Mehbod A, Garvey T, Jhanjee R, Sechriest V. Operative compared with nonoperative treatment of a thoracolumbar burst fracture without neurological deficit. A prospective, randomized study. J Bone Joint Surg Am. 2003 May; 85-A(5):773-81.
15. Wood KB, Buttermann GR, Phukan R, et al. Operative compared with nonoperative treatment of a thoracolumbar burst fracture without neurological deficit: a prospective randomized study with follow-up at sixteen to twenty-two years. J Bone Joint Surg Am. 2015;97(1):3-9. doi: 10.2106/JBJS.N.00226.
16. Schwab F, Farcy JP, Bridwell K, et al. A clinical impact classification of scoliosis in the adult. Spine 2006 Aug 15; 31(18):2109-14.
17. Glassman SD, Berven, S., Bridwell, K., Horton, W., Dimar, JR. Correlation of radiographic parameters and clinical symptoms in adult scoliosis. Spine 2005 Mar 15; 30(6):682-8.
18. Mac-Thiong JM, Transfeldt EE, Mehbod AA, et al. Can c7 plumbline and gravity line predict health related quality of life in adult scoliosis? Spine 2009 Jul 1; 34(15):E519-27.
19. Lafage V, Bharucha NJ, Schwab F et al. Multicenter validation of a formula predicting postoperative spinopelvic alignment. J Neurosurg Spine 2012 Jan; (16)1:15-21.
20. Glassman SD, Carreon LY, Shaffrey CI, et al. The costs and benefits of nonoperative management for adult scoliosis. Spine 2010 Mar 1; 35(5):578-82.
21. Kelly MP, Lurie JD, Yanik EL, et al. Operative Versus Nonoperative Treatment for Adult Symptomatic Lumbar Scoliosis. J Bone Joint Surg Am. 2019;10(4):338-352. doi: 10.2106/JBJS.18.00483.
22. Choi SH, Son SM, Goh TS, Park W, Lee JS. Outcomes of Operative and Nonoperative Treatment in Patients with Adult Spinal Deformity with a Minimum 2-Year Follow-Up: A Meta-Analysis. World Neurosurg. 2018:120:e870-e876. doi: 10.1016/j.wneu.2018.08.179.
23. Teles AR, Mattei TA, Righesso O, Falavigna A. Effectiveness of Operative and Nonoperative Care for Adult Spinal Deformity. Global Spine J. 2017;7(2):170-178. doi: 10.1177/2192568217699182.
24. Liu S, Schwab F, Smith JS, et al. Likelihood of reaching minimal clinically important difference in adult spinal deformity: a comparison of operative and nonoperative treatment. Ochsner J. 2014; 14(1):67-77.
25. Scheer J, Hostin R, Robinson C, et al. Operative Management of Adult Spinal Deformity Results in Significant Increases in QALYs Gained Compared to Nonoperative Management. Spine. 2018:43(5): 339-347. doi: 10/1097/BRS.0000000000001626.
26. Smith JS, Lafage V, Shaffrey CI, et al. Outcomes of Operative and Nonoperative Treatment for Adult Spinal Deformity: A Prospective, Multicenter, Propensity-Matched Cohort Assessment With Minimum 2-Year Follow-up. Neurosurgery. 2016;78(6):851-861. doi: 10.1227/NEU.0000000000001116.
27. Herkowitz, HN; Kurz LT. Degenerative lumbar spondylolisthesis with spinal stenosis. A prospective study comparing decompression with decompression and intertransverse process arthrodesis. J Bone Joint Surg Am 1991 Jul; 73(6):802-8.
28. NASS Evidence-Based Clinical Guidelines Committee. *Evidence-Based Clinical Guidelines on Degenerative Spondylolisthesis.* North American Spine Society; 2014.
29. Weinstein JN, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. N Engl J Med. 2007 May 31; 356(22):2257-70.

30. Försth P, Ólafsson G, Carlsson T, et al. A Randomized, Controlled Trial of Fusion Surgery for Lumbar Spinal Stenosis. N Engl J Med. 2016;374(15):1413-1423. doi: 10.1056/NEJMoa1513721.
31. Ghogawala Z, Dziura J, Butler WE, et al. Laminectomy plus Fusion versus Laminectomy Alone for Lumbar Spondylolisthesis. N Engl J Med. 2016;374(15):1424-1434. doi: 10.1056/NEJMoa1508788.
32. Ghogawala Z, Resnick DK, Glassman SD, Dziura J, Shaffrey CI, Mummaneni PV. Randomized controlled trials for degenerative lumbar spondylolisthesis: which patients benefit from lumbar fusion?, J Neurosurg Spine. 2017;26(2):260-266. doi: 10.3171.2016.8.SPINE16716.
33. Burgstaller JM, Porchet F, Steurer J, Wertli NM. Arguments for the choice of surgical treatments in patients with lumbar spinal stenosis – a systematic appraisal of randomized controlled trials. BMC Musculoskelet Disord. 2015;16:96. doi: 10.1186/s12891-015-0548-8.
34. Yavin D, Casha S, Wiebe S, et al. Lumbar Fusoin for Degenerative Disease: A Systematic Review and Meta-Analysis. Neurosurgery. 2017;80(5):701-715. doi: 10.1093/neuros/nyw162.
35. Inose H, Kato T, Yuasa M, et al. Comparison of Decompression, Decompression Plus Fusion, and Decompression Plus Stabilization for Degenerative Spondylolisthesis: A Prospective, Randomized Study. Clin Spine Surg. 2018;31(7):E347-E352. doi: 10.1097/BSD.0000000000000659.
36. Isaacs RE, Sembrano JN, Tohmeh AG. Two-Year Comparative Outcomes of MIS Lateral and MIS Transforaminal Interbody Fusion in the Treatment of Degernative Spondylolisthesis: Part II: Radiographic Findings. Spine (Phila Pa 1976). 2016;41 Suppl 8:S133-144. doi: 10.1097/BRS.0000000000001472.
37. Moller H, Hedlund R. Surgery versus conservative management in adult isthmic spondylolisthesis –a prospective, randomized study: part 1. Spine. 2000 Jul 1; 25(13):1711-5.
38. White MM, Panjabi AA 3rd. Basic biomechanics of the spine. Neurosurgery. 1980 Jul;7(1):76-93.
39. Frobin W, Brinckmann P, Leivseth G, Biggemann, Reikeras O. Precision measurement of segmental motion from flexion-extension radiographs of the lumbar spine. Clin Biomech 1996 Dec; 11 (8):457-465.
40. Abumi K, Panjabi MM, Kramer KM, Duranceau J, Oxland T, Crisco JJ. Biomechanical evaluation of lumbar spinal stability after graded facetectomies. Spine. 1990 Nov; 15(11):1142-7.
41. Watters, WC. If, when and how to fuse when treating lumbar degenerative stenosis. Semin Spine Surg. 2011 Dec; 23(4):218-221.
42. Dazley JM, et al. Recurrent lumbar spinal stenosis: etiology and surgical management. Sem Spine Surg. 25:283.294.
43. Chen WJ, Lai PL, Niu CC, Chen LH, Fu TS, Wong CB. Surgical treatment of adjacent instability after lumbar spine fusion. Spine. 2001 Nov 15; 26(22):E519-524.
44. Takeshima T, Kambara K, Miyata S, Ueda Y, Tamai S. Clinical and radiographic evaluation of disc excision for lumbar disc herniation with and without posterolateral fusion. Spine. 2000 Feb 15; 25(4):450-6.
45. Otani K, Kikuchi S, Sato K, et al. Does the fusion of a lumbar disc herniation improve the clinical outcome? An investigation with a minimum 10-year follow-up. J Spinal Disord Tech. 2014 June;27(4):196-201.
46. McCulloch JA, Weiner BK. Microsurgery in the lumbar intertransverse interval. Instr Course Lect. 2002; 51:233-41.
47. Tender GC, Baratta RV, Voorhies RM. Unilateral removal of pars interarticularis. J Neurosurg Spine. 2005 Mar; 2(3):279-88.
48. Drazin D, Ugiliweneza B, Al-Khouja L, et al. Treatment of Recurrent Disc Herniation: A Systematic Review. Cureus. 2016;8(5):e622. doi: 10.7759/cureus.622.
49. Fu TS, Lai PL, Tsai TT, Niu CC, Chen LH, Chen WJ. Long-term results of disc excision for recurrent lumbar disc herniation with or without posterolateral fusion. Spine (Phila Pa 1976). 2005;30(24):2830–2834. doi:10.1097/01.brs.0000190393.15369.94
50. El Shazly AA, El Wardany MA, Morsi AM. Recurrent lumbar disc herniation: A prospective comparative study of three surgical management procedures. Asian J Neurosurg. 2013;8(3):139-146. doi: 10.4103/1793-5482.121685.
51. Kerezoudis P, Goncalves S, Cesare JD, et al. Comparing outcomes of fusion versus repeat discectomy for recurrent lumbar disc herniation: A systemic review and meta-analysis. Clin Neurol Neurosurg. 2018;171:70-78. doi: 10.1016/j.clineuro.2018.05.023.
52. Onyia CU, Menon SK. The debate on most ideal technique for managing recurrent lumbar disc herniation: a short review. Br J Neurosurg. 2017;31(6):701-708. doi: 10.1080/02688697.2017.1368451.
53. Aghayee HN, Azhari S, Heidarnejad F. The outcomes of surgical treatment of recurrent lumbar disk herniation with discectomy alone and discectomy with 9. posterolateral interbody fusion. Novel Biomed. 2014;2:10-7.
54. Wang JC, Dailey AT, Mummaneni PV, et al. Guideline update for the performance of fusion proceudres for degernerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy. 2014;21(1):48-53. doi: 10.3171/2014.4.SPINE14271.
55. Xu R, et al. Factors associated with recurrent back pain and cyst recurrence after surgical resection of one hundred ninety-five spinal synovial cysts: analysis of one hundred sixty-seven consecutive cases. Spine 2010 May 1; 35(10):1044-53.
56. Bruder M, Cattani A, Gessler F, et al. Synovial cysts of the spine: long-term follow-up after surgical treatment of 141 cases in a single-center series and comprehensive literature review of 2900 degenerative spinal cysts. J Neurosurg Spine. 2017;27(3):256-267. doi: 10.3171/2016.12.SPINE16756.
57. Campbell RJ, Mobbs RJ, Rao PJ, Phan K. Interventions for Lumbar Synovial Facet Joint Cysts: A Comparison of Percutaneous, Surgical Decompression and Fusion Approaches. World Neurosurg. 2017;98:492-502. doi: 10.1016/j.wneu.2016.11.044.
58. Ramhmdani S, Ishida W, Perdomo-Pantoja A, Witham TF, Lo SL, Bydon A. Synovial Cyst as a Maker for Lumbar Instability: A Systemic Review and Meta-Analysis. World Neurosurg. 2019;122:e1059-e1068. doi: 10.1016/j.wneu.2018.10.228.
59. van Dijke M, Janssen Sj, Cha TD, et al. Comparison of Decompression With and Without Fusion for Patients With Synovial Facet Cysts. Clin Spine Surg. 2017;30(10):E1399-E1404. doi: 10.1097/BSD.0000000000000449.

60. Brox JI, Sorensen R, Friis A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. Spine. 2003 Sep 1; 28(17):1913-21.
61. Fairbank J, Frost H, Wilson-MacDonald J, et al. Randomised controlled trial to compare surgical stabilization of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilization trial. BMJ. 2005 May 28; 330(7502):1233.
62. Fritzell P, Hagg O, Wessberg P, Norwall A, Swedish Lumbar Spine Study Group. 2001 Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine. 2001 Dec 1; 26(23):2521-32.
63. Parker LM, Murrell SE, Boden SD, Horton WC. The outcome of posterolateral fusion in highly selected patients with discogenic low back pain. Spine. 1996 Aug 15; 21(16):1909-16.
64. Moore KR, Pinto MR, Butler LM. Degenerative disc disease treated with combined anterior and posterior instrumentation. Spine. 2002 Aug 1; 27(15):1680-6.
65. Bydon M, De la Garza-Ramos R, Macki M, Baker A, Gkaslan AK, Bydon A. Lumbar fusion versus nonoperative management for treatment of discogenic low back pain: a systematic review and meta-analysis of randomized controlled trials. J Spinal Disord Tech. 2014;27(5):297-304. doi: 10.1097/BSD.0000000000000072.
66. Mirza SK, Deyo RA, Heagerty PJ, Turner JA, Martin BI, Comstock BA. One-year outcomes of surgical versus nonsurgical treatments for discogenic back pain: a community-based prospective cohort study. Spine J. 2013;13(11):1421-1433. doi: 10.1016/j.spinee.2013.05.047.
67. Adogwa O, Carr, RK, Kudyba K, et al. Revision lumbar surgery in elderly patients with symptomatic pseudarthrosis, adjacent-segment disease, or same-level recurrent stenosis. Part 1. Two-year outcomes and clinical efficacy: clinical article. J Neurosurg Spine. 2013 Feb;18(2):139-46.
68. Adogwa O, Parker SL, Shau D, et al. Long-term outcomes of revision fusion for lumbar pseudarthrosis: clinical article. J Neurosurg Spine 2011 Oct;15(4):393-8.
69. Cassinelli EH, Wallach E, Hanscom B, Vogt M, Kang JD. Prospective clinical outcomes of revision fusion surgery in patients with pseudoarthrosis after posterior lumbar interbody fusions using stand-alone metallic cages. Spine J. 2006 Jul-Aug; 6(4):428-34.
70. Pateder DB, et al. Spinal fusion after revision surgery for pseudarthrosis in adult scoliosis. Spine. 2006 May 15; 31(11):E314-9.
71. Harimaya K, Mishiro T, Lenke LG, Bridwell KH, Koester LA, Sides BA. Etiology and revision surgical strategies in failed lumbosacral fixation of adult spinal deformity constructs. Spine. 2011 Sep 15; 36(20):1701-10.
72. Adogwa O, Owens R, Karikari I, et al. Revision lumbar surgery in elderly patients with symptomatic pseudoarthorsis, adjacent-segment disease, or same-level recurrent stenosis. Part 2. A cost effectiveness analysis: clinical article. J Neurosurg Spine. 2013;18(2):147-153. doi: 10.3171/2012.11.SPINE12226.
73. Dede O, Thuillier D, Pekmezci M, et al. Revision surgery for lumbar pseudarthrosis. Spine J. 2015;15(5):977-982. doi: 10.1016/j.spinee.2013.05.039.
74. Mobbs RJ, Phan K, Thayaparan GK, Rao PJ. Anterior Lumbar Interbody Fusion as a Salvage Technique for Pseudarthrosis following Posterior Lumbar Fusion Surgery. Global Spine J. 2016;6(1):14-20. doi: 10.1055/s-0035-1555656.
75. Suh SP, Jo YH, Jeong HW, Choi WR, Kang CN. Outcomes of Revision Surgery Following Instrumented Posterolateral Fusion in Degenerative Lumbar Spinal Stenosis: A Comparative Analysis between Pseudoarthrosis and Adjacent Segment Disease. Asian Spine J. 2017;11(3):463-471. doi: 10.4184/asj.2017.11.3.463.

Authors

NASS Coverage Committee
Co-Chairs: Co-Chairs: Scott Kreiner, MD, & Mitchell Reiter, MD

Members:

Okezie K. Aguwa, MD
Jamie Baisden, MD, FACS
Deb Bhowmick, MD
R. Dale Blasier, MD
Christopher M. Bono, MD
Mohamad Bydon, MD
R.S. Cowan, MD
Justin M. Dazley, MD
Donald Dietze, MD
John Easa, MD
Jason Friedrich, MD
Gary Ghiselli, MD
John Glaser, MD
Zoher Ghogawala, MD, FACS
Sterling Haring, DO, MPH
James Harrop, MD
Timothy Holt, MD
Scott Horn, DO
Heidi M. Hullinger, MD
Steven Hwang, MD
D.J. Kennedy, MD
Kevin Khalsa, MD
Ajit Krishnaney, MD
Anthony Lapinsky, MD
Paul Matz, MD
E. Kano Mayer, MD
David Reese O'Brien, MD
Sunil J. Panchal, MD, DABPM
Charles Reitman, MD
Timothy Sanford, MD
Sunny Sharma, MD
Matthew Smuck, MD
Jeffrey Summers, MD
William Tontz, MD
Eeric Truumees, MD
Thomas H. Xu, MD

Financial Statement

These Coverage Recommendations were developed in their entirety by the North American Spine Society (NASS). All participating authors have disclosed potential conflicts of interest consistent with NASS' disclosure policy.

Author Disclosures

Aguwa, Okezie K.: Consulting: New Era Orthopaedics (B).
Baisden, Jamie : Nothing to Disclose
Bhowmick, Deb A.: Speaking and/or Teaching Arrangements: Medtronic Inc. (B).
Blasier, R. Dale: Other: AAOS (Travel Expense Reimbursement, Member of Committee on Coding, Coverage and Reimbursement).
Bono, Christopher M.: Consulting: United Health Care (B); Device or Biologic Distribution Group (Physician-Owned Distributorship): Elsevier (B), Wolters Kluwer (A); Other: The Spine Journal (NASS) (F).
Bydon, Mohamad : Nothing to Disclose
Cowan, R. Scott: Speaking and/or Teaching Arrangements: LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement).
Dazley, Justin M.: Consulting: Clariance (C).
Dietze, Donald: Consulting: Joimax Spine (None, I have not received any remuneration to date.), Osseus Fixation Devices (B).
Easa, John E: Nothing to Disclose
Friedrich, Jason: Consulting: MCG Health (B, Divested as of 11/1/2018., Outside 12-Month Requirement).
Ghiselli, Gary: Board of Directors: Colorado Orthopedic Society (No compensation, volunteer position); Device or Biologic Distribution Group (Physician-Owned Distributorship): Impulse Neuromonitoring, Neurointerpretive Services (E), New Era Orthopedics (B); Private Investments: DiFusion (100,000 Shares, 9%).
Glaser, John A.: Nothing to Disclose
Haring, Sterling: Scientific Advisory Board: Centers For Disease Control And Prevention (A); Trips/Travel: American Association Of Medical Colleges (Travel Expense Reimbursement, Outside 12-Month Requirement).
Harrop, James S.: Board of Directors: PNS, (treasurer), LSRS (treasurer), CSRS (secretary), AOSNA (research Chair); Consulting: Depuy Ethicon Spine (B, Paid directly to institution/employer); Fellowship Support: NREF (A, Paid directly to institution/employer); Research Support (Investigator Salary): AONA Spine (B, Paid directly to institution/employer); Research Support (Staff and/or materials): AO Spine/NACTN (C, Paid directly to institution/employer); Speaking and/or Teaching Arrangements: Globus (C).
Holt, Timothy A.: Speaking and/or Teaching Arrangements: SI Bone (E, Paid directly to institution/employer).
Horn, Scott I.: Board of Directors: Spine Intervention Society (Travel expenses); Other Office: CPT Advisor for SIS (Volunteer position. Travel expenses.); Speaking and/or Teaching Arrangements: AAPMR (Travel expenses), NASS (Travel expenses.), SIS (AMA CPT advisor, Health Policy Chair, Travel expenses).
Hullinger, Heidi M.: Trips/Travel: AAOS (American Academy of Orthopaedic Surgeons) (Travel Expense Reimbursement, Serve as AAOS delegate to AMA).
Hwang, Steven W.: Board of Directors: Ronald McDonald house (None); Consulting: Globus (B), Nuvasive (B); Speaking and/or Teaching Arrangements: Zimmer-Biomet (B); Stock Ownership: Auctus (7.50%); Trips/Travel: NASS (A).
Kennedy, D.J.: Board of Directors: AAPM&R (Member at Large AAPM&R Board of Directors), Spine intervention Society (Non-renumerative position of influence. Member at Large AAPM&R Board of Directors); Consulting: State Farm Auto Insurance (B); Speaking and/or Teaching Arrangements: Spine Intervention Society (Travel expenses); Trips/Travel: AAPM&R (A), Spine Intervention Society (A).
Khalsa, Kevin: Nothing to Disclose
Kreiner, Scott: Speaking and/or Teaching Arrangements: Spine Intervention Society (Travel expenses Reimbursed).
Krishnaney, Ajit A.: Consulting: Stryker (C).
Lapinsky, Anthony S.: Device or Biologic Distribution Group (Physician-Owned Distributorship): RTI Surgical (C).
Massey, Michael : Nothing to Disclose
Matz, Paul G.: Nothing to Disclose
Mayer, E. Kano A.: Private Investments: Lanai Health Solutions (30.00%); Speaking and/or Teaching Arrangements: North America Spine Society (B, Trips, Travel and Honorarium Teaching); Stock Ownership: Infinite Orthopedics (1.00%, Novel Orthopedic device awaiting FDA approval that does not have spine indication and no conflict with role in spine); Trips/Travel: AMA (Travel Expense Reimbursement).
O'Brien, David Reese: Nothing to Disclose

Panchal, Sunil J.: Speaking and/or Teaching Arrangements: RTI (B), Stimwave (B).
Reiter, Mitchell F.: Other: None (Future Compensation Expected, My professional partner and I have applied for a patent for an allergy testing device.)
Reitman, Charles A.: Board of Directors: NASS (Travel Expense Reimbursement); Other: NASS (Nonfinancial, Committeee leadership); Scientific Advisory Board: Clinical Orthopaedics And Related Research (B, Paid directly to institution/employer).
Sanford, Timothy : Nothing to Disclose
Sharma, Sunny : Nothing to Disclose
Smuck, Matthew: Board of Directors: Spine Intervention Society (None); Consulting: Consultant & expert witness - State Farm (F), Spine Biopharma (Future Compensation Expected); Grants: Relievant Medsystems (F, Paid directly to institution/employer), Re-Walk (E, Paid directly to institution/employer); Private Investments: Vivametrica (15.00%); Scientific Advisory Board: BlueJay Mobile-Health (Stock options), NuSpine (Stock options); Stock Ownership: BlueJay Mobile-Health (<1%), NuSpine (<1%); Trips/Travel: Spine Intervention Society, Board of Directors (B, Travel Expenses).
Summers, Jeffrey T.: Other Office: Biomerieux (Salary, Paid directly to institution/employer).
Tontz, William L.: Trips/Travel: Stryker (B).
Truumees, Eeric: Board of Directors: Seton Family of Doctors (None); Other Office: AAOS (Editor-in-Chief of AAOS Now); Research Support (Staff and/or materials): Medtronic (C, Paid directly to institution/employer), Pfizer (E, Outside 12-Month Requirement, Paid directly to institution/employer), Relievant (F, Paid directly to institution/employer), Seikagaku Corporation (C, Paid directly to institution/employer), Stryker Spine (B, Outside 12-Month Requirement, Paid directly to institution/employer), Vertex Pharma (D, Outside 12-Month Requirement, Paid directly to institution/employer); Trips/Travel: AAOS (Travel Reimbursement (B)).
Whetstone, Kirk E: Nothing to Disclose
Xu, Thomas H.: Trips/Travel: Nevro (A).

Comments

Comments regarding the coverage recommendations may be submitted to coverage@spine.org and will be considered in development of future revisions of the work.

Disclosure Key

Direct or indirect remuneration: royalties, stock ownership, private investments, consulting, speaking and/or teaching arrangements, trips/travel. ***Position held in a company:*** board of directors, scientific advisory board, other office. ***Support from sponsors:*** endowments, research–investigator salary, research–staff and/or materials, grants, fellowship support. ***Other***

Degree of support:

Level A. $100 to $1000	Level F. $100,001 to $500,000
Level B. $1,001 to $10,000	Level G. $500,001 to $1M
Level C. $10,001 to $25,000	Level H. $1,000,001 to $2.5M
Level D. $25,001 to $50,000	Level I. greater than $2.5M
Level E. $50,001 to $100,000	

NASS COVERAGE POLICY RECOMMENDATIONS

Minimally Invasive Sacroiliac Joint Fusion

NASS® ADVANCING GLOBAL SPINE CARE

DEFINING APPROPRIATE COVERAGE POSITIONS

North American Spine Society 7075 Veterans Blvd. Burr Ridge, IL 60527
spine.org

COVERAGE COMMITTEE

NASS Coverage Policy Recommendations

NASS Coverage Committee

North American Spine Society
Coverage Policy Recommendations

7075 Veterans Boulevard
Burr Ridge, IL 60527 USA
(630) 230-3600
www.spine.org

ISBN 1-929988-73-7

Introduction

North American Spine Society (NASS) coverage policy recommendations are intended to assist payers and members by proactively defining appropriate coverage positions. Historically, NASS has provided comment on payer coverage policy upon request. However, in considering coverage policies received by the organization, NASS believes proactively examining medical evidence and recommending credible and reasonable positions may be to the benefit of both payers and members in helping achieve consensus on coverage before it becomes a matter of controversy. This coverage recommendation reflects the best available data as of October 24, 2019; information and data available after October 24, 2019, is thus not reflected in this recommendation and may warrant deviations from this recommendation, if appropriate.

Methodology

The coverage policies put forth by NASS use an evidence-based approach to spinal care when possible. In the absence of strict evidence-based criteria, policies reflect the multidisciplinary experience and expertise of the authors in order to reflect reasonable standard practice indications in the United States.

NASS Coverage Policy Methodology

Scope and Clinical Indications

Low back pain (LBP) is the leading cause of global disability.[1] The sacroiliac joint (SIJ) represents a specific and identifiable cause of LBP. The SIJ is the cause of chronic LBP in 15-30% of patients, with a higher prevalence in older patients, those with a history of lumbosacral fusion, trauma, spondyloarthropathy, and/or maximal pain below the L5 vertebra.[2-14] Although no single physical exam maneuver has a high predictive value for diagnosing SIJ pain[2,15,16] the following criteria predict a positive response to a diagnostic intra-articular anesthetic block in 70-80% of patients: maximal pain below L5 and positive findings on at least 3 of 6 provocation tests (1. Patrick's or FABER, 2. Gaenslen, 3. thigh thrust, 4. sacral thrust, 5. distraction, 6. compression).[17-20] With the exception of acute inflammatory sacroiliitis or advanced arthritis, most patients will not demonstrate imaging abnormalities.[21] The reference standard for the diagnosis of SIJ pain remains a positive response to a fluoroscopically-guided intra-articular injection of local anesthetic.

Fusion of the SIJ was initially described as a treatment option in 1925. Given the depth and anatomic location of the SIJ, significant morbidity was associated with open fusion approaches and limited usage of these procedures. Over the past few decades, techniques utilizing trans-iliac approaches to fuse the SIJ have been developed. Minimally invasive technology has been applied to these approaches and has resulted in the development of minimally invasive SIJ fusion procedures in recent years. This Coverage Recommendation is limited to the insertion of, usually more than one, structural device traversing the SIJ intended to fuse to the bone or lead to the fusion of the joint itself.

Minimally invasive SIJ fusion is indicated for the treatment of SIJ pain for patients with low back/buttock pain who meet ALL of the following criteria:

1. Have undergone and failed a minimum 6 months of intensive nonoperative treatment that must include medication optimization, activity modification, and active therapeutic exercise targeted at the lumbar spine, pelvis, SIJ and hip including a home exercise program.
2. Patient's report of nonradicular, typically unilateral, pain that is maximal below the L5 vertebrae, localized over the posterior SIJ, and consistent with SIJ pain.

3. A physical examination typically demonstrating localized tenderness with palpation over the sacral sulcus (Fortin's point, ie, at the insertion of the long dorsal ligament inferior to the posterior superior iliac spine or PSIS) or the absence of tenderness elsewhere (eg, greater trochanter, lumbar spine, coccyx) that would explain the patient's symptoms.
4. Positive response to a cluster of at least 3 provocative tests (1. Patrick's or FABER, 2. Gaenslen, 3. thigh thrust, 4. sacral thrust, 5. distraction, 6. compression). Note that the thrust tests may not be recommended in pregnant patients or those with connective tissue disorders.
5. Absence of generalized pain behavior (eg, somatoform disorder) or generalized pain disorders (eg, fibromyalgia).
6. At least 75% reduction of pain, documented by pain diary, for the expected duration of the anesthetic used following an image-guided, contrast-enhanced intra-articular SIJ injection on 2 separate occasions.
7. A trial of at least one therapeutic intra-articular SIJ injection (ie, corticosteroid injection). Please see *NASS Coverage Policy Recommendation Sacroiliac Joint Injections and Radiofrequency Ablation*.[22]
8. Diagnostic imaging studies that include ALL of the following:
    a. Imaging (plain radiographs and a CT or MRI) of the SIJ that excludes the presence of destructive lesions (eg, tumor, infection) or autoimmune arthropathy that would not be properly addressed by percutaneous SIJ fusion.
    b. Imaging of the pelvis (AP plain radiograph) to rule out concomitant hip pathology that would better explain the patient's symptoms.
    c. Imaging of the lumbar spine (CT or MRI) to rule out neural compression or other degenerative condition that, in combination with the patient's history, physical, and other testing would more likely be the source of their low back or buttock pain.

Minimally invasive SIJ fusion for SIJ pain is **NOT** indicated in ANY of the following scenarios:

1. Any case that does not fulfill ALL of the above criteria.
2. Presence of systemic arthropathy such as ankylosing spondylitis or rheumatoid arthritis.
3. Presence of generalized pain behavior (eg, somatoform disorder) or generalized pain disorder (eg, fibromyalgia).
4. Presence of infection or tumor.

Coverage Recommendation

The NASS Coverage Committee recommends coverage for minimally invasive SIJ fusions when **all** 8 criteria have been met. Minimally invasive SIJ Fusions have been shown to be relatively safe[23-27] with a minimal EBL, low infection rate, low complication rate, and low revision surgery rates.[28] Much of the literature is subjected to potential bias since there is a high rate of industry sponsored data, however, multiple SIJ fusion devices have shown similar results.[29] The clinical efficacy for SIJ Fusion in appropriately selected patients has been shown to be more effective than nonoperative care and more cost effective.

Rational for Coverage Recommendations

Patient Selection: The challenges associated with identifying patients with SIJ pain by history and physical exam alone has been well studied.[30] No single historical finding is diagnostic of SIJ pain, but the following are common: unilateral pain, maximal pain below the L5 vertebrae, pain aggravated with sitting and transitions from sitting to standing, history of trauma, referred pain to the buttock, groin, thigh and occasionally below the knee.[3] The utility of physical exam findings has been more extensively evaluated in multiple studies, reviews and meta-analyses.[2,17-21,31-34] Studies agree that no single physical exam maneuver is reliable for diagnosis of SIJ pain[2,17-21], but a combination of provocative maneuvers can achieve a PPV of 70-80% for predicting at least a 50% improvement on a diagnostic intra-articular SIJ injection.[17,19,21,35] No combination of tests can predict an 80% or greater response.[2,34] History and physical exam cannot effectively differentiate between pain from the SIJ itself versus pain from the dorsal ligaments or both.[36] Based on the available evidence, it is reasonable to select patients for all types of diagnostic SIJ procedures on the basis of having maximal pain below the L5 vertebrae and at least 3 positive provocation maneuvers (1. Patrick's or FABER, 2. Gaenslen, 3. thigh thrust, 4. sacral thrust, 5. distraction, 6. compression) and lack of a better explanation for symptoms (eg, discogenic and/or radicular pain).[17-21,32,37,38]

Value of Radiographic Findings: While various imaging modalities can identify structural abnormalities of the SIJ, imaging abnormalities are not needed for a diagnosis of SIJ pain or for responsiveness to SIJ injections.[39] Plain radiographs and CT can identify late stage sacroiliitis or SIJ arthropathy. A positive bone scan can increase the likelihood that the SIJ is the source of pain, but a negative bone scan does not reduce the probability.[21] An MRI is more sensitive than bone scan or plain radiographs for early detection of sacroiliitis and may be useful for monitoring treatment response in patients with inflammatory spondyloarthropathy.[37,40,41] However, in the nonspondyloarthropathy population that makes up the vast majority of patients with LBP, neither MRI, nor any other imaging modality, has proven better than clinical selection to predict responsiveness to diagnostic SIJ injections. Furthermore, imaging findings have not been shown to be better than diagnostic injections for predicting responsiveness to therapeutic SIJ procedures. Thus, imaging is considered to be helpful in identifying patients who might benefit from further evaluations such as a diagnostic injection, though the absence of abnormalities on imaging does not negate the appropriateness of performing the procedure.

Utility of Diagnostic Injections: History, physical exam and imaging studies are inadequate for confirmation of SIJ pain[31], at least in patients without spondyloarthropathy. Multiple studies and reviews have evaluated the utility of single and dual anesthetic blocks for the diagnosis of SIJ pain.[15,17,19,31-32,36-37,42,43] A single SIJ injection of anesthetic, with or without steroid, carries with it a false positive rate of 20-54%.[15,17,31,44] Due to the high false positive rates from a single injection and relatively low prevalence of SIJ pain, true confirmation of SIJ pain requires at least 75% improvement using comparative anesthetic blocks. While many of the studies on SIJ fusion have relied on 50% relief from a single diagnostic block as an indicator for fusion,[45-50] it is known that relaxing positive anesthetic block criteria from 75% down to 50% will significantly increase the observed prevalence of SIJ pain and increase treatment failures.

Minimally Invasive Fusion: Lorio and Rashbaum[29] reviewed minimally invasive SIJ fusions with different implants and different approaches and overall identified a high success rate with improved validated outcome scores, low revision rates, and low adverse events.

A systematic review and meta-analysis by Lingutla et al[43] revealed statistical and clinical improvement in all outcomes: VAS pain, SF-36 ODI, and Majeed scores with a mean follow up of 17.6 months using MIS and open techniques in both

prospective and retrospective fashion using a variety of surgical approaches. In total 276 studies were identified in this review and after strict inclusion strategies, 6 studies were included in the meta-analysis for a total of 407 patients.

A multicenter study using both open and minimally invasive SIJ fusions compiled data on 263 patients: 149 were treated with open SIJF and 114 patients with MIS SIJ fusion. The MIS patients on average were 10 years older than the open SIJF, but the MIS Group showed statistically significant improvement in operative EBL, operative time, and lower length of hospitalization. VAS scores at 12 months postoperative were 3.5 points lower in the MIS vs open SIJ fusion groups. Compared to open SIJ fusion, MIS SIJ fusion had significantly better pain relief and improved perioperative outcome measures.[51]

David Polly et al[49] looked at the 2-year randomized control trial of MIS SIJF compared to nonoperative management for a SIJ dysfunction. They determined that MIS SIJF with triangular titanium implants had a larger improvement in pain disability and quality of life compared to those treated nonoperatively, and that the improvements persisted to 24 months.[49]

A systematic literature review by Zaidi et al[28] found for MIS patients near 84% had excellent outcomes, reoperation rate was near 6% for MIS vs near 15% for open SIJ, with a major complication rate of 5-20% in the MIS group as compared to the open group.

Shamrock et al [27] reviewed 14 studies with 720 patients. A total of 99 patients had bilateral MIS SIJF. A surgical complication rate of 11.11% was identified with 25 adverse events due to implant placement (3.05%) with nerve root impingement being the most commonly observed device related complication.

MIS SIJ fusion was found to be cost effective compared to nonsurgical treatment. Cher et al[52] used data from 2 prospective RCT and looked to 5-year health quality and costs after MIS SIJF triangular titanium implants. MIS SIJF provided potential cost savings/quality gained compared to nonsurgical treatment after a treatment period of greater than 13 years.

Conclusion

Overall MIS SIJF in properly selected patients, despite a difficult diagnosis or selection effort, has shown clinical improvement, improved QOL, relatively safe and cost-effective treatment for long-term strategy in the treatment of SIJ pain and dysfunction.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2018;392(10159):1789-1858.
2. Dreyfuss P, Michaelsen M, Pauza K, McLarty J, Bogduk N. The value of medical history and physical examination in diagnosing sacroiliac joint pain. *Spine (Phila Pa 1976).* 1996;21:2594-602.
3. Young S, Aprill C, Laslett M. Correlation of clinical examination characteristics with three sources of chronic low back pain. *Spine J.* 2003;3:460-5.
4. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med.* 2011;12:224-33.
5. DePalma MJ, Ketchum JM, Saullo TR. Etiology of chronic low back pain in patients having undergone lumbar fusion. *Pain Med.* 2011;12:732-9.
6. Depalma MJ, Ketchum JM, Trussell BS, Saullo TR, Slipman CW. Does the location of low back pain predict its source? *PM R.* 2011;3:33-9.
7. Katz V, Schofferman J, Reynolds J. The sacroiliac joint: a potential cause of pain after lumbar fusion to the sacrum. *J Spinal Disord Tech.* 2003;16:96-9.
8. Laplante BL, Ketchum JM, Saullo TR, DePalma MJ. Multivariable analysis of the relationship between pain referral patterns and the source of chronic low back pain. *Pain Physician.* 2012;15:171-8.
9. Liliang PC, Lu K, Liang CL, Tsai YD, Wang KW, Chen HJ. Sacroiliac joint pain after lumbar and lumbosacral fusion: findings using dual sacroiliac

joint blocks. *Pain Med.* 2011;12:565-70.
10. Maigne JY, Planchon CA. Sacroiliac joint pain after lumbar fusion. A study with anesthetic blocks. *Eur Spine J.* 2005;14:654-8.
11. DePalma MJ, Ketchum JM, Saullo TR. Multivariable analyses of the relationships between age, gender, and body mass index and the source of chronic low back pain. *Pain Med.* 2012;13:498-506.
12. Weksler N, Velan GJ, Semionov M, et al. The role of sacroiliac joint dysfunction in the genesis of low back pain: the obvious is not always right. Arch Orthop Trauma Surg. 2007;127:885-8.
13. Chou LH, Slipman CW, Bhagia SM, et al. Inciting events initiating injection-proven sacroiliac joint syndrome. *Pain Med.* 2004;5:26-32.
14. Fortin JD, Aprill CN, Ponthieux B, Pier J. Sacroiliac joint: pain referral maps upon applying a new injection/arthrography technique. Part II: Clinical evaluation. *Spine (Phila Pa 1976).* 1994;19:1483-9.
15. Maigne JY, Aivaliklis A, Pfefer F. Results of sacroiliac joint double block and value of sacroiliac pain provocation tests in 54 patients with low back pain. *Spine (Phila Pa 1976).* 1996;21:1889-92.
16. Schwarzer AC, Aprill CN, Bogduk N. The sacroiliac joint in chronic low back pain. *Spine (Phila Pa 1976).* 1995;20:31-7.
17. Laslett M, Aprill CN, McDonald B, Young SB. Diagnosis of sacroiliac joint pain: validity of individual provocation tests and composites of tests. *Man Ther.* 2005;10:207-18.
18. Laslett M, Young SB, Aprill CN, McDonald B. Diagnosing painful sacroiliac joints: A validity study of a McKenzie evaluation and sacroiliac provocation tests. *Aust J Physiother.* 2003;49:89-97.
19. van der Wurff P, Buijs EJ, Groen GJ. A multitest regimen of pain provocation tests as an aid to reduce unnecessary minimally invasive sacroiliac joint procedures. *Arch Phys Med Rehabil.* 2006;87:10-4.
20. Szadek KM, van der Wurff P, van Tulder MW, Zuurmond WW, Perez RS. Diagnostic validity of criteria for sacroiliac joint pain: a systematic review. *J Pain.* 2009;10:354-68.
21. Hancock MJ, Maher CG, Latimer J, et al. Systematic review of tests to identify the disc, SIJ or facet joint as the source of low back pain. *Eur Spine J.* 2007;16:1539-50.
22. NASS Coverage Committee. *NASS Coverage Policy Recommendations for Sacroiliac Joint Injections.* 1st ed. Burr Ridge: North American Spine Society Publications; 2020.
23. Ashman B, Norvell DC, Hermsmeyer JT. Chronic sacroiliac joint pain: fusion versus denervation as treatment options. *Evid Based Spine Care J.* 2010;1:35-44.
24. Kancherla VK, McGowan SM, Audley BN, Sokunbi G, Puccio ST. Patient Reported Outcomes from Sacroiliac Joint Fusion. *Asian Spine J.* 2017;11:120-126.
25. Kube RA, Muir JM. Sacroiliac Joint Fusion: One Year Clinical and Radiographic Results Following Minimally Invasive Sacroiliac Joint Fusion Surgery. *Open Orthop J.* 2016;10:679-689.
26. Nystrom B, Gregebo B, Taube A, Almgren SO, Schillberg B, Zhu Y. Clinical outcome following anterior arthrodesis in patients with presumed sacroiliac joint pain. *Scand J Pain.* 2017;17:22-29.
27. Shamrock AG, Patel A, Alam M, Shamrock KH, Al Maaieh M. The safety profile of percutaneous minimally invasive sacroiliac joint fusion. *Global Spine J.* 2019;9:874-880.
28. Zaidi HA, Montoure AJ, Dickman CA. Surgical and clinical efficacy of sacroiliac joint fusion: a systematic review of the literature. *J Neurosurg Spine.* 2015;23:59-66.
29. Lorio MP, Rashbaum R. ISASS policy statement - minimally invasive sacroiliac joint fusion. *Int J Spine Surg.* 2014;8:25.
30. Dreyfuss P, Henning T, Malladi N, Goldstein B, Bogduk N. The ability of multi-site, multi-depth sacral lateral branch blocks to anesthetize the sacroiliac joint complex. *Pain Med.* 2009;10:679-88.
31. Kennedy DJ, Engel A, Kreiner DS, Nampiaparampil D, Duszynski B, MacVicar J. Fluoroscopically guided diagnostic and therapeutic intra-articular sacroiliac joint injections: a systematic review. *Pain Med.* 2015;16:1500-18.
32. MacVicar J, Kreiner DS, Duszynski B, Kennedy DJ. Appropriate use criteria for fluoroscopically guided diagnostic and therapeutic sacroiliac interventions: results from the spine intervention society convened multispecialty collaborative. *Pain Med.* 2017;18:2081-95.
33. Laslett M, McDonald B, Tropp H, Aprill CN, Oberg B. Agreement between diagnoses reached by clinical examination and available reference standards: a prospective study of 216 patients with lumbopelvic pain. BMC Musculoskelet Disord. 2005;6:28.
34. Schneider BJ, Huynh L, Levin J, Rinkaekan P, Kordi R, Kennedy DJ. Does immediate pain relief after an injection into the sacroiliac joint with anesthetic and corticosteroid predict subsequent pain relief? *Pain Med.* 2018;19:244-51.
35. Telli H, Telli S, Topal M. The validity and reliability of provocation tests in the diagnosis of sacroiliac joint dysfunction. *Pain Physician.* 2018;21(4):E367-E76.
36. King W, Ahmed SU, Baisden J, et al. Diagnosis and treatment of posterior sacroiliac complex pain: a systematic review with comprehensive analysis of the published data. *Pain Med.* 2015;16:257-65.
37. Manchikanti L, Singh V, Pampati V, et al. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician.* 2001;4:308-16.
38. Petersen T, Laslett M, Juhl C. Clinical classification in low back pain: best-evidence diagnostic rules based on systematic reviews. *BMC Musculoskelet Disord.* 2017;18:188.
39. Hansen HC, McKenzie-Brown AM, Cohen SP, Swicegood JR, Colson JD, Manchikanti L. Sacroiliac joint interventions: a systematic review. *Pain Physician.* 2007;10:165-84.

NASS coverage recommendations should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment is to be made by the physician and patient in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution. The coverage recommendations ***do not represent a "standard of care,"*** *nor are they intended as a fixed treatment protocol. It is anticipated that there will be patients who will require less or more treatment than the average. It is also acknowledged that in atypical cases, treatment falling outside these criteria will sometimes be necessary. This document should not be seen as prescribing the type, frequency or duration of intervention. Treatment and accompanying payment should be based on this information in addition to an individual patient's needs as well as the doctor's professional judgment and experience. This document is designed to function as a guide and should not be used as the sole reason for denial of treatment and services. It is not intended to supersede applicable ethical standards or provisions of law. This is not a legal document.*

40. Blum U, Buitrago-Tellez C, Mundinger A, et al. Magnetic resonance imaging (MRI) for detection of active sacroiliitis--a prospective study comparing conventional radiography, scintigraphy, and contrast enhanced MRI. *J Rheumatol.* 1996;23:2107-15.
41. Simopoulos TT, Manchikanti L, Singh V, et al. A systematic evaluation of prevalence and diagnostic accuracy of sacroiliac joint interventions. *Pain Physician.* 2012;15:E305-E44.
42. Liliang PC, Lu K, Weng HC, Liang CL, Tsai YD, Chen HJ. The therapeutic efficacy of sacroiliac joint blocks with triamcinolone acetonide in the treatment of sacroiliac joint dysfunction without spondyloarthropathy. *Spine (Phila Pa 1976).* 2009; 34:896-900.
43. Lingutla KK, Pollock R, Ahuja S. Sacroiliac joint fusion for low back pain: a systematic review and meta-analysis. *Eur Spine J* 2016;25:1924-1931.
44. Chou LH, Slipman CW, Bhagia SM, et al. Inciting events initiating injection-proven sacroiliac joint syndrome. *Pain Med.* 2004;5:26-32.
45. Polly DW, Cher DJ, Wine KD, et al. Randomized controlled trial of minimally invasive sacroiliac joint fusion using triangular titanium implants vs nonsurgical management for sacroiliac joint dysfunction: 12-month outcomes. *Neurosurgery.* 2015;77(5):674-690; discussion 690-671.
46. Whang P, Cher D, Polly D, et al. Sacroiliac joint fusion using triangular titanium implants vs. Non-surgical management: six-month outcomes from a prospective randomized controlled trial. *Int J Spine Surg.* 2015;9:6.
47. Duhon BS, Bitan F, Lockstadt H, et al. Triangular titanium implants for minimally invasive sacroiliac joint fusion: 2-year follow-up from a prospective multicenter trial. *Int J Spine Surg.* 2016;10:13.
48. Duhon BS, Cher DJ, Wine KD, Kovalsky DA, Lockstadt H, Group SS. Triangular titanium implants for minimally invasive sacroiliac joint fusion: a prospective study. *Global Spine J.* 2016;6(3):257-269.
49. Polly DW, Swofford J, Whang PG, et al. Two-year outcomes from a randomized controlled trial of minimally invasive sacroiliac joint fusion vs. Non-surgical management for sacroiliac joint dysfunction. *Int J Spine Surg.* 2016;10:28.
50. Sturesson B, Kools D, Pflugmacher R, Gasbarrini A, Prestamburgo D, Dengler J. Six-month outcomes from a randomized controlled trial of minimally invasive SI joint fusion with triangular titanium implants vs conservative management. *Eur Spine J.* 2016;10:28.
51. Smith AG, Capobianco R, Cher D, Rudolf L, Sachs D, Gundanna M, et al. Open versus minimally invasive sacroiliac joint fusion: a multi-center comparison of perioperative measures and clinical outcomes. Ann Surg Innov Res. 2013;7:14.
52. Cher DJ, Frasco MA, Arnold RJ, Polly DW. Cost-effectiveness of minimally invasive sacroiliac joint fusion. *Clinicoecon Outcomes Res.* 2016;8:1-14.

Authors

NASS Coverage Committee
Co-Chairs: Co-Chairs: Scott Kreiner, MD, & Mitchell Reiter, MD

Members:

Jamie Baisden, MD, FACS
R. Dale Blasier, MD
Christopher M. Bono, MD
Mohamad Bydon, MD
R.S. Cowan, MD
Justin M. Dazley, MD
Donald Dietze, MD
John Easa, MD
Jason Friedrich, MD
Gary Ghiselli, MD
John Glaser, MD
Sterling Haring, DO, MPH
James Harrop, MD
Heidi M. Hullinger, MD
Steven Hwang, MD
D.J. Kennedy, MD
Kevin Khalsa, MD
Ajit Krishnaney, MD
Anthony Lapinsky, MD
Michael Massey, MD
Paul Matz, MD
E. Kano Mayer, MD
David Reese O'Brien, MD
Sunil J. Panchal, MD, DABPM
Charles Reitman, MD
Timothy Sanford, MD
Byron Schneider, MD
Sunny Sharma, MD
Matthew Smuck, MD
Jeffrey Summers, MD
William Tontz, MD
Eeric Truumees, MD
Thomas H. Xu, MD

Financial Statement

These Coverage Recommendations were developed in their entirety by the North American Spine Society (NASS). All participating authors have disclosed potential conflicts of interest consistent with NASS' disclosure policy.

Author Disclosures

Baisden, Jamie: Other: ASIA (Nonfinancial, Surgery Committee), Globus Medical (A, Outside 12-Month Requirement), LSRS (None, Membership Committee), SI-BONE (A, Outside 12-Month Requirement); Trips/Travel: Synthes (A, Outside 12-Month Requirement).
Blasier, R. Dale: Other: AAOS (Travel Expense Reimbursement, Member of Committee on Coding, Coverage and Reimbursement).
Bono, Christopher M.: Consulting: United Health Care (B); Other: The Spine Journal (NASS) (F); Royalties: Elsevier (B), Wolters Kluwer (A).
Bydon, Mohamad : Nothing to Disclose

Cowan, R. Scott: Speaking and/or Teaching Arrangements: LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement), LDR (A, Outside 12-Month Requirement).
Dazley, Justin M.: Consulting: Clariance (C).
Dietze, Donald: Consulting: Joimax Spine (Future Compensation Expected), Osseus Fixation Devices (B).
Easa, John E: Nothing to Disclose
Friedrich, Jason: Consulting: MCG Health (B, Outside 12-Month Requirement).
Ghiselli, Gary: Board of Directors: Colorado Orthopedic Society (None); Consulting: Johnson & Johnson (C); Device or Biologic Distribution Group (Physician-Owned Distributorship): Impulse Neuromonitoring, Neurointerpretive Services (E), New Era Orthopedics (B).
Glaser, John A.: Nothing to Disclose
Haring, Sterling: Scientific Advisory Board: Centers For Disease Control And Prevention (A); Trips/Travel: American Association Of Medical Colleges (Travel Expense Reimbursement, Outside 12-Month Requirement).
Harrop, James S.: Board of Directors: PNS (Treasurer), LSRS (Treasurer), CSRS (Secretary), AOSNA (Research Chair); Consulting: DePuy Ethicon Spine (B, Paid directly to institution/employer); Fellowship Support: NREF (A, Paid directly to institution/employer); Research Support (Investigator Salary): AONA Spine (B, Paid directly to institution/employer); Research Support (Staff and/or materials): AOSpine/NACTN (C, Paid directly to institution/employer); Scientific Advisory Board: Abbvie (B); Speaking and/or Teaching Arrangements: Globus (C).
Hullinger, Heidi M.: Trips/Travel: AAOS (Travel Expense Reimbursement, Delegate to AMA).
Hwang, Steven W.: Board of Directors: Ronald McDonald House (None); Consulting: NuVasive (C); Speaking and/or Teaching Arrangements: Zimmer Biomet (C); Stock Ownership: Auctus (7.50%); Trips/Travel: NASS (A).
Kennedy, D.J.: Board of Directors: AAPM&R (Nonfinancial, Member at Large), Spine Intervention Society (Nonfinancial, Member at Large); Consulting: State Farm Auto Insurance (B); Speaking and/or Teaching Arrangements: Spine Intervention Society (Travel Expense Reimbursement); Trips/Travel: AAPM&R (Travel Expense Reimbursement), Spine Intervention Society (Travel Expense Reimbursement).
Khalsa, Kevin: Nothing to Disclose
Kreiner, Scott: Research Support (Staff and/or materials): Abbott (Future Compensation Expected, Paid directly to institution/employer); Speaking and/or Teaching Arrangements: Spine Intervention Society (Travel Expense Reimbursement).
Krishnaney, Ajit A.: Consulting: Stryker (C).
Lapinsky, Anthony S.: Device or Biologic Distribution Group (Physician-Owned Distributorship): RTI Surgical (C).
Massey, Michael : Nothing to Disclose
Matz, Paul G.: Consulting: Norcal Mutual Insurance Company (B); Private Investments: Alumni Ventures Group (F, It is a blind trust. A power-of-attorney is signed by me so that the fiduciaries of the investment fund do the vetting and investing.).
Mayer, E. Kano A.: Consulting: Turning Point (Future Compensation Expected); Other: Wharton, Levin, Ehrmantraut & Klein, P.A (B, Outside 12 month Requirement); Private Investments: Lanai Health Solutions (30.00%); Speaking and/or Teaching Arrangements: North America Spine Society (B); Stock Ownership: Infinite Orthopedics (1%); Trips/Travel: AMA (Travel Expense Reimbursement).
O'Brien, David Reese: Nothing to Disclose
Panchal, Sunil J.: Speaking and/or Teaching Arrangements: RTI (B), Stimwave (B).
Reiter, Mitchell F.: Other: DR Innovations (Future Compensation Expected, 40%. My professional partner and I have invented and received a patent for a wearable device named Sensiband that tests people for allergies to the metals commonly used in medical implants. This device itself is not an implant used in spinal surgery. Sensiband is FDA registered as a class I medical device.); Private Investments: CreOsso (4%).
Reitman, Charles A.: Board of Directors: NASS (Travel Expense Reimbursement); Other: NASS (Nonfinancial, Committeee leadership); Scientific Advisory Board: Clinical Orthopaedics And Related Research (B, Paid directly to institution/employer).
Sanford, Timothy : Nothing to Disclose
Schneider, Byron J.: Consulting: AIM Specialty (B), State Farm (C); Grants: SIS (E, Paid directly to institution/employer); Speaking and/or Teaching Arrangements: AAPM (Travel Expense Reimbursement), NASS (A, Travel, Reimbursement, and Honorarium for speaking/teaching).
Sharma, Sunny : Nothing to Disclose
Smuck, Matthew: Board of Directors: Spine Intervention Society (None); Consulting: Consultant & expert witness - State Farm (F), Spine Biopharma (Future Compensation Expected); Grants: Relievant Medsystems (F, Paid directly to institution/employer), ReWalk (E, Paid directly to institution/employer); Private Investments: Vivametrica (15.00%); Scientific Advisory Board: BlueJay Mobile-Health (Stock options), NuSpine (Stock options); Stock Ownership: BlueJay Mobile-Health (<1%), NuSpine (<1%); Trips/Travel: Spine Intervention Society, Board of Directors (B, Travel Expenses).
Summers, Jeffrey T.: Consulting: First Choice (A, Paid directly to institution/employer), Newsouth Neurospine (A, Paid directly to institution/employer); Other Office: Biomerieux (Salary, Family Relationship); Trips/Travel: SIS (A, Travel Expense Reimbursement).
Tontz, William L.: Nothing to Disclose

Truumees, Eeric: Board of Directors: Seton Family of Doctors (None); Other Office: AAOS (Editor-in-Chief of AAOS Now); Research Support (Staff and/or materials): Medtronic (C, Paid directly to institution/employer), Pfizer (E, Outside 12-Month Requirement, Paid directly to institution/employer), Relievant (F, Paid directly to institution/employer), Seikagaku Corporation (C, Paid directly to institution/employer), Stryker Spine (B, Outside 12-Month Requirement, Paid directly to institution/employer), Vertex Pharma (D, Outside 12-Month Requirement, Paid directly to institution/employer); Trips/Travel: AAOS (Travel Reimbursement (B).
Xu, Thomas H.: Trips/Travel: Nevro (A).

Comments

Comments regarding the coverage recommendations may be submitted to coverage@spine.org and will be considered in development of future revisions of the work.

Welcome to Boston and NASS 2021

Welcome to the vibrant city of Boston and the 36th Annual Meeting of the North American Spine Society!

Following last year's virtual meeting, spine specialists are again converging in-person at NASS 2021, engaging in four days of pioneering educational programming, motivating and thought-provoking speakers, and valuable networking opportunities with fellow spine professionals.

"After last year's hiatus, I think everyone is looking to reconnect with colleagues, collaborators, and researchers in a more engaged and interpersonal way," said co-chair Andrew Schoenfeld, MD, orthopedic surgeon at Boston's Brigham and Women's Hospital. "Beyond the cutting-edge research and technological advancements that attendees can experience in the symposia and abstract sessions, as well as on the exhibit floor, the ability to engage in dynamic discussions in real time during sessions and behind the scenes are the added benefits of an in-person meeting that cannot be matched in a virtual setting."

Also serving as NASS 2021 program cochairs are E. Kano Mayer, MD, physiatrist at Seton Spine and Scoliosis Center in Austin, Texas, and Michael P. Steinmetz, MD, neurosurgeon at Cleveland Clinic in Ohio.

The program committee received 1,150 total abstract submissions, of which 424 (37%) were accepted. Program offerings encompass 239 surgical abstracts and 185 medical abstracts as well as hands-on courses, symposia, surgical technique cadaver demonstrations and new technological offerings from industry.

"The greatest challenge was truly selecting which abstracts and symposia to place on the conference platform because of how much really great material and ideas had been sent in for consideration," Dr. Schoenfeld said. "We really were benefitting from an embarrassment of riches in this context."

Additionally, Dr. Schoenfeld highlighted the 23 Best Papers sessions. "These are likely to be the highest impact and influential articles that we will see in print in the most important spine, orthopedic and neurosurgical publications in the next nine to 12 months," he said, adding that these sessions provide the opportunity to "get a head start and advanced notice on these new advances before seeing them come out in the journals."

This year's Presidential Guest Speaker is Steven Pinker, cognitive scientist, provocative speaker and author of the acclaimed *Enlightenment Now: The Case for Reason, Science, Humanism, and Progress*. Don't miss his Thursday morning talk, in which Pinker will challenge attendees to look past negative headlines, explore data showing that the world is getting better, and explain the conviction that reason and science can enhance human flourishing.

The Technical Exhibition also returns and will feature hundreds of exhibitors' new and innovative spine care technologies and equipment with hands-on learning experiences and demonstrations. The exhibition also contains the Solution Showcase with "Lunch & Learn" opportunities, the Surgical Innovation Labs with demonstrations and workshops, and The Learning Place, where attendees can view ePosters and meet select ePoster authors. Be sure to allow time for exploration and networking in this venue.

Speaking of networking opportunities, plan to stop by tonight's NASS Social Hour, and enjoy the daily

morning and afternoon networking breaks.

While excitement abounds at meeting in person again this year, NASS 2021 also offers a hybrid meeting format with a virtual component for those who cannot attend in Boston. Virtual attendees will still have the high-quality NASS Annual Meeting experience they have come to expect, according to Dr. Schoenfeld.

"They will be able to experience all symposia and sessions in real time or as recorded content, and they will be able to submit questions and interact with session moderators. It will be as close to in real life as you can get without actually being present at the venue," he said.

Additionally, meeting attendees with general registration who may have missed a session can access

OnDemand archived recordings including abstract presentations, symposia and ePosters.

Reflecting on the value of reconvening at the Annual Meeting, Dr. Schoenfeld summarized, "The educational content at NASS is second to none. As someone who lives in academic medicine on the daily, the interpersonal interactions, both planned and off the cuff, are what I missed most and what I think the real value of attending in-person meetings may be."

Enjoy exploring Boston. Discover and reconnect at NASS 2021. And welcome back!

The Future of Healthcare in the Spotlight

Wednesday morning's plenary session on the "Future of Healthcare" was designed to facilitate understanding of many of the recent, current and pending changes and advances in the health care field as well as to provide a glimpse into what to expect in the future.

Moderator Michael P. Steinmetz, MD, opened the session by acknowledging several broad areas of change before introducing his co-moderator, Karthik Madhavan, MD, who built on a series of foundational thoughts regarding disruptive change in normal processes.

Dr. Madhavan used the frequently cited example of how the traditional cab business was impacted by ride sharing applications, outlining a series of set "phases" in the disruption process.

"Why is this important?" he asked. "It's because we see a similar story with health insurance, and we are paying the price for it."

Pointing to significant cost increases in the ride share experience, Dr. Madhavan asserted that, when health insurance was starting out, it provided good incentives to both customers and doctors, while accepting nearly every procedure.

"Now, over a period of time, they see that they have the customer base and they dictate which procedures they approve and which ones they don't."

Pointing to how this has impacted medical practices, he urged the audience to "Love your job, not your hospital, because you never know when your hospital is going to stop loving you."

Piyush Kalakoti, MD, provided a prerecorded presentation focused on "The Cost of Current Hospitalizations and Resource Utilization." Pointing to a number of current trends in spine surgery, he drew on a variety of studies, as well as census data, to assert that the volume of spine fusion surgeries will more than double over the next two decades, which will mandate myriad changes in areas from policy to training.

Acknowledging that he comes from a slightly different background than many of the audience members, Gerry Stanley, MD, P-CEO, based his presentation, "What Does the Affordable Health Care Act Expansion Mean for Spine Surgery?" on his own experience in areas like employer sponsored versus employer owned plans, pointing to challenges in companies where 38% of costs go to health care and observing how that sort of reality places physicians "on a collision course with health care."

He highlighted five ways that employers are addressing health care costs – providers / facilities, diagnostics, drugs, technology and therapies – offering examples in each area where "incredibly disruptive companies" are emerging to address needs. He urged physicians to "explore the gray space" between each of those areas, developing new capabilities that replace "a hammer that sees a world of nails" with an "entire kit of new tools" to solve problems.

Daniel T. Laich, DO, joined the panel to address "Hospital vs ASC: Which One is Receptive for Disruption?" While personally questioning aspects of the ride sharing disruption model, Laich presented a slightly different perspective on disruptive innovation that included the need for an enabling technology combined with an innovative business model and coherent value network.

In another prerecorded presentation, Ryan Grant, MD, presented his perspective on "The Future of Integrated, Virtual Care and the Evaluation of Virtual Care as it Pertains to Spine and Musculoskeletal Care."

"Telehealth for MSK care has a lot more power than many people realize," he said, pointing to the need to "meet the patient where they are" and utilizing multiple technologies to provide "a more engaging patient experience."

He observed that medicine is often boring for patients but quickly added that technology can make it more fun and educational.

Offering the example of how avatar technology allows people to interact with future versions of themselves, he characterized it as "a powerful motivator," asserting, "real behavior change requires medicine to really hear their patients."

With some planned panel members unable to attend NASS 2021 or participate remotely, the moderator called on Stanley to provide his extemporaneous comments on the evolving Walmart health care strategy, which was described as "one of the most disruptive forces that is going to hit health care."

Kurt Eichholz, MD, FACS, concluded the formal panel presentations with a prerecorded overview of recent and potential Medicare cost cuts, highlighting upcoming cuts in the "nine to 10 percent range" and urging the audience to get involved to try to stop the cuts that he predicted would lead to "significant delays in care and worse outcomes."

Not surprisingly, the dynamic presentations provided fertile ground for follow-up questions from the audience.

Robotic Technology Is a Growing Presence in Spine Surgery

As with any new technology, the introduction and increasing popularity of robot-guided lumbar instrumented fusion in minimally invasive surgery has the potential to improve safety and accuracy of pedicle screw placement, but also the potential of introducing early complications. A series of abstract presentations on Wednesday afternoon addressed the new technology while balancing a range of risk and patient benefits.

Under the broad heading of "Robotics: Thorocolumbar Surgery," moderators Eric W. Nottmeier, MD and Chetan K. Patel, MD guided attendees through a half dozen robotic-related abstract presentations represented by four different authors.

Calista Dominy, BS, opened the session with a look at her team's exploration of "Trends in total charges and utilization of computer assisted navigation in thoracolumbar spine surgery."

"Computer-assisted navigation is a surgical assistive technology that has been developed and applied to orthopedics over the past 20 years," she explained, adding that the new technology is "particularly useful in spinal surgery for improved visualization of the patient's anatomy."

Their presentation noted the growth of computerassisted navigation, pointing to their examination of 27,093 total thoracolumbar cases that have utilized the technology, with 2,169 cases in 2015, 5,171 in 2016, 9,045 in 2017 and 10,708 in 2018.

In her conclusions, Dominy pointed to "a significant upward trend in the use of computer-assisted navigation over time," adding, "This points to a potential rising adoption of this technology for lumbar spinal surgery. And this is important to keep in mind because it could mean more spine surgeons will train with and use this technology as the time goes on, in their operating rooms. Another lens to look at this through is the fact that, as this navigation becomes more implemented into surgical care, this could lead to patients potentially seeking out surgeons who do use this kind of technology in their own practice."

In the remote presentation, "Optimizing safety in robotic lumbar instrumented fusions: a risk factor analysis of robotic failures," Kimberly Ashayeri, MD, from NYU Langone Health, highlighted her team's exploration of a study objective to "assess the pitfalls experienced by a single institution, identify risk factors for robot failures, and determine an optimized operating room workflow to present robot-related complications."

Dr. Ashayeri also presented a second abstract, titled "Robotic pedicle screw placement has a dynamic learning curve based on spine surgery invasiveness index."

Two other abstracts were presented by Peter G. Passias, MD, also with NYU Langone Health. The first, titled "Identification of optimal frailty and deformity ranges to achieve maximum improvement from adult spinal deformity corrective surgery," sought to assess whether the ability to improve health-related quality of life measures reaches a maximum according to patient frailty and radiographic severity. The second abstract, "Do no harm: a retrospective analysis of the initial risk of complications in robotic spine surgery," explored the potential risks of robotic spinal surgery during the current technology adjustment period to aid in decision-making and better patient care.

Additional abstract topics presented virtually ranged from trends in robot related complications, to a comparative look at how robotic vs freehand screw placement affects patient-reported outcomes.

President Looks to Spine Technology Future

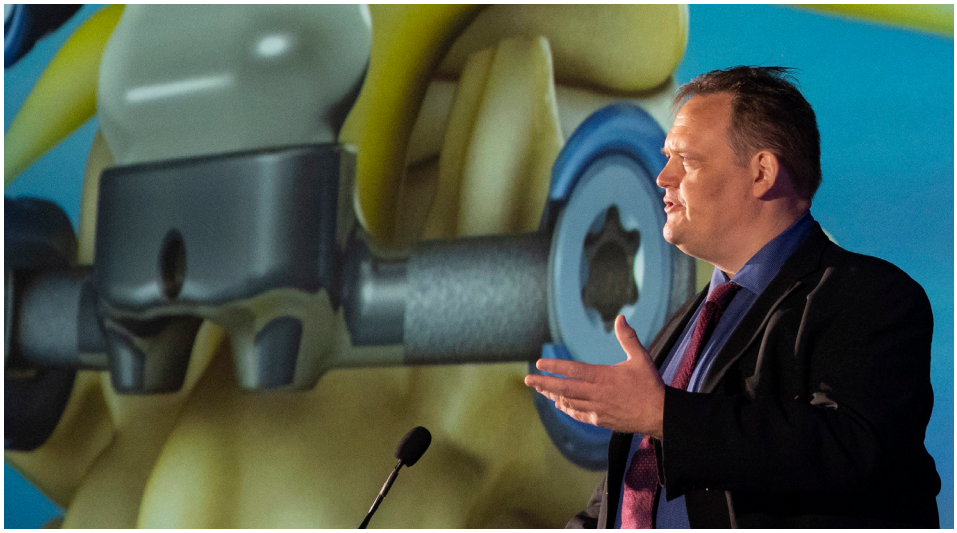
With his entrance greeted by a standing ovation from NASS members, Dr. Eeric Truumees characterized 2020 as "an interesting year," adding that it has been "a great honor to serve as President of NASS."

"After that roller-coaster year and some of the challenges of putting on a meeting that is both in-person and virtual, I thought about who would actually come to this meeting and why," he said. "What are they going to get out of it? Well, as someone who has been to a number of meetings here and abroad, I can tell you that our program committee has put together an outstanding program of new research and symposia to help us digest that work. NASS also has one of the best spine trade floors in the world. And it really gives us not only the opportunity to socially network with our colleagues, but for many of us, the real reason we are here is to improve our knowledge base and skill sets and bounce new ideas off people we trust."

Building on a theme of improved knowledge and new technologies, Dr. Truumees shared his reflections on the change, innovation and new technologies that have come into practice over the course of his career.

He said that his early professional vision of future innovation had been something of "a straight road," acknowledging that the subsequent reality presented a pathway more complicated and winding than he expected, with progress accompanied by a few "treacherous twists and turns" along the way. Fortunately, he identified a reality of "smaller missteps over time" with smaller potholes in the road.

He pointed to early career developments like kyphoplasty and



vertebroplasty, accompanied by the introduction and of PMMA in discoplasty and rheumatoid arthritis reconstruction.

"But PMMA is far from the biggest change in my practice over the last 20 years," he said, identifying microdiscectomy and supporting hardware developments and characterizing endoscopic discectomy "a hot topic" about which he wants to learn more.

The NASS President said that advancing approaches to the spine led to other developments, like dynamic screw systems, posterior dynamic systems and rigid stabilization techniques.

Describing several recent improvements in the area of fixation, he added, "Modern systems go in like butter compared to those earlier systems."

"With all of these procedures, advances in enabling technologies like high-speed burrs allowed controlled resection of bone in relatively smaller spaces," he said. "And then more recently there are devices like the BoneScalpel, promoted as a means to efficiently cut bone while protecting soft tissue."

The continuing innovation road described by Dr. Truumees also included technologies like interoperative navigation systems, spinal robotics, virtual reality and other adjuncts for surgical procedures.

Shifting to the future of spine care, he said that biologics are certainly "a buzzword" today but balanced hope against his belief that the technology "is not quite there yet."

But other technologies also offer new promise, with specific identification of new surgical frames to allow safer positioning and lower blood loss for major surgery, new diagnostic tools and lower radiation imaging systems.

Dr. Truumees ended with his personal thoughts surrounding a rational process for incorporating new technologies and characterizing five different types of technology adopters: innovators, early adopters, early majority, late majority and laggards. Crediting specific traits and results to each category, he expressed the need to create a systematic approach to technology adoption.

"Spine care is advancing," he concluded. "And it has the potential for great help."

Presidential Guest Speaker Spotlights Rationality

In the first live lecture he's given in more than 18 months, Steven Pinker, Harvard Professor and NASS 2021 Presidential Guest Speaker, used his Thursday morning address to challenge the audience on the topic of "Rationality: What It Is; Why It Seems Scarce and Why That Matters."

Referring to his latest book, *Rationality,* which was published earlier this week, the experimental cognitive psychologist asserted that the subject matter presents something of a puzzle.

"On one hand, we clearly belong to a rational species," he said. "We have discovered the secrets of the universe. We have walked on the moon. We have discovered the secrets of life and mind. We have fought back against the horsemen of the apocalypse. We have reduced the frequency of war and the human toll of famine.

We have decimated extreme poverty and reduced child mortality." He continued, "At the same time, the majority of Americans aged 18 to 24 think that astrology is very or sort of scientific. And large proportions believe in conspiracy theories, such as COVID-19 is a plot by Bill Gates to implant microchips in people's arms to control population."

Elaborating on the basic theme, he began by offering a definition of rationality as "the use of knowledge to attain goals," a definition that led to a follow-on query of how knowledge can be used to attain goals.

Pinker said that the answer is in normative models of reason and how they help people to avoid various fallacies. As examples, he cited logic, probability, Bayes' Rule, rational choice, Signal Detection Theory, Game Theory and Causal Inference.

Asking rhetorically if people tend to follow these normative models of rationality, he offered examples from logic and Bayesian Inference, in which some respondents could end up embracing fallacies.

"The big question, and one which I suspect many of you have been waiting for, is: If people can be rational, why does humanity seem to be losing its mind?"

Pointing to the fact that it is not a simple phenomenon, he offered several reasons, ranging from what he identified as "motivated reasoning" to "realist versus mythological beliefs."

Focusing on the topic of beliefs, he added, "For most of us, for most of our history, whether a belief is literally true is only one out of several possible reasons for endorsing it."

Pinker said that all of this serves to raise another question: How can people be more rational?

He asserted that rationality should represent "the fourth 'R'" of the traditional "three Rs of learning," adding that norms of rationality should be promoted, that beliefs should be tested and not guarded and that it should be seen as a positive thing to change your mind.

He summarized three reasons why rationality matters, including positive life and financial outcomes, the driving of material progress and the driving of moral progress.

Pinker concluded with the admonition that the power of rationality to guide moral progress is of a piece with its power to guide material progress and wise choices in our lives.

His presentation was followed by an enthusiastic series of questions and clarification requests from the engaged audience.

Meet the 2021 SpineLine 20 Under 40 Class

By Jeff Karzen and Kelly Campbell, MS

SpineLine is excited to share articles on this year's 20 Under 40 winners, highlighting some of the best and brightest NASS members under the age of 40. This is the fourth year of the 20 Under 40 campaign, and it has been a rousing success. Honorees have been selected to join NASS committees, received media publicity in their local communities and have been terrific representatives of some of the rising stars in spine care.

Winners are selected by the *SpineLine* editorial board and based on career accomplishments thus far, involvement with NASS and contributions in the community. If you would like to be considered for the 2022 20 Under 40 class, please fill out an application form at https://spineline.survey.fm/20-under-40-application. If you would like to nominate a colleague, please complete the nomination form at https://spineline.survey.fm/nominations-for-20-under-40. Candidates must be born on January 1, 1982 or after to be eligible.

Brenton Pennicooke Commited to Diversity, Equity, Inclusion in Spine Care

From an early age, Brenton Henry Pennicooke knew he wanted to make his parents' hard work as immigrants pay off. His father built a business from the ground up and his mother developed a career as a drug addiction counselor and social advocate. Both parents exemplified resilience, perseverance, and hard work, which Dr. Pennicooke aspires to emulate everyday as a neurosurgeon. With their work ethic instilled in him, he became the first African-American neurosurgery attending at Washington University in St. Louis.

The importance of what he's accomplished isn't lost on him, and he is committed to equity, diversity and inclusion in medicine on all sides. "My primary mode of giving back to my local community is by coordinating formal opportunities for underrepresented students to work with the neurosurgery department to observe surgical cases and conduct research, actively recruit and retain students from underrepresented backgrounds, and pursue internal and external funding to support collaborative programs and research on treating patients from backgrounds that are underrepresented within medicine."

His research interests further this work, as he is using machine learning to better address disparities in spine care. Through his own personal reading, he learned how large data is leveraged to drive innovation and optimization at tech companies and in the financial sector, and thought that those principles could be applied to spine care. During his neurosurgery residency research year, he learned new skills by collaborating with computer scientists, data scientists and operational engineers.

When he's not in practice or researching, Dr. Pennicooke and his wife are avid hikers who enjoy sharing the outdoors with their daughter.

Chris Alcala Returns to Puerto Rico to Expand the Puerto Rico Spine Center

When Dr. Chris Alcala was seven years old, his 35-year-old father developed cauda equina syndrome as a result of lumbar disc herniation. He went from being an avid athlete to wheelchair bound for almost a full year. As a child who was thrust into a part of the home physical therapy team, Dr. Alcala knew he would dedicate his life to helping people who were like his dad, and teaching others to do so.

For the past several years, Dr. Alcala would return to Puerto Rico a few times a year to provide pro bono surgical, research and educational assistance to the Puerto Rico Spine Center and the University of Puerto Rico Orthopedic Surgery program. After seven years as attending staff surgeon at the Twin Cities Spine Center fellowship program, Dr. Alcala decided to return to Puerto Rico this summer to further develop and expand the Puerto Rico Spine Center with four other surgeons, two interventional pain management specialists and one PM&R doctor. His goal is to continue to expand the first multidisciplinary spine program in the country and one of the few in Latin America. He feels blessed to achieve this with the educational back-up of his partners at the Twin Cities Spine Center, his professional home. He notes, "there is a longstanding relationship that started more than 30 years ago between the Twin Cities Spine Center and Puerto Rico when the first fellow from PR did his training at the center. Now with me moving back home and joining the Puerto Rico Spine Center with the advice of my extended family at the Twin Cities Spine Center, I see it as a dream come true to give back to my country and provide access to high value spine care. We are building an educational and research bridge between both institutions to move forward our field and subsequently, patient care."

When he's not busy with work, Dr. Alcala spends time with his wife (an orthopedic hand surgeon) and two young children.

SpineLine's 20 Under 40

Call to Service Guides Jeffrey Mullin's Career

For Jeffrey Mullin, choosing neurosurgery as his specialty was the culmination of a life-long desire to serve others combined with his attraction to the physical and intellectual demands. He notes, "immense knowledge of the delicate anatomy and physiology with the continual honing of high-level technical abilities all merged to improve patients' lives in a tangible way."

Now in practice in Buffalo, that call to service manifests in remarkable ways. When he saw members of his community unable to access care, he collaborated with his hospital system and now runs a clinic where he provides spine care to the un- and under-insured. The people who visit often need help navigating the system and Mullin and his team provide support.

Dr. Mullin's patients are the benefactors of his dedication. Colleagues note that he is the first in the hospital to round on all his patients, and he takes time to explain complex concepts with empathy and compassion. About his relationship with patients, Dr. Mullin explains, "the patient-physician bond is meaningful to me. Patients are placing their health in my hands… I provide patients with my undivided focus to bring what I consider to be the optimal targeted surgery for each specific patient and his/her associated pathology."

He also serves as the Associate Program Director for the residency program and Co-Fellowship Director for the Spine Fellowship at the University of Buffalo Neurosurgery program. Colleagues say he takes time to understand how his students learn so he can provide an optimal educational experience. As a result, his trainees have been awarded $70,000 over the past two years in research funding. Dr. Mullin's own research interests include spine biomechanics, cervical pedicle screws and proximal junctional tethers.

When not serving patients and training physicians, Dr. Mullin enjoys spending time with his wife Katherine and five daughters.

Aditya Raghunandan's Navy Background Provides Leadership, Career Goals

As a first generation immigrant and thrill seeker, Aditya Raghunandan found meaning and excitement in his early career as a US Navy flight surgeon. For eight years and three separate tours, he ensured the nation's aviators were able to perform at levels akin to those of professional athletes.

"As Navy flight surgeons, we fly with our aviators to understand firsthand the grueling environment they have to operate under, so I accumulated a little over 400 hours of flight time in 16 different types of aircraft," he says.

Because of his experience in keeping aviators flight-ready by optimizing musculoskeletal care and mitigating biophychosocial stressors, Dr. Raghunandan pursued medical training in sports and spine medicine to help individuals move past injuries and disabilities and reach their full potential. He was awarded a four-year scholarship to attend medical school.

Dr. Raghunandan has served in leadership positions in the local, regional and national levels. Seeing a need for residents to contribute more to the American Medical Society of Sports Medicine, he sent a proposal to the organization president and was named the inaugural president of the Sports Medicine Resident Council. Under his leadership, the group launched initiatives that increased mentorship, research, social media and online didactic activities.

His career goals are informed by his early experience, citing he'd like to "utilize my experience caring for the biopsychosocial needs of aviators and apply the specialized skill set of a musculoskeletal specialist to the unique health and environmental challenges surrounding astronauts and space flight."

When he's not serving his patients, Dr. Raghunandan can be found running, finding great new restaurants, and spending time with his wife and young daughter.

SpineLine's 20 Under 40

Military Background Paves Way for Simone Maybin's Success

Growing up in a military family, Simone Maybin lived in several different countries and experienced many unique cultures from a young age.

Years later, she enrolled at the Air Force Academy in Colorado Springs, CO., where she was an athlete and cadet leader while learning the time management skills that would serve her well in future endeavors.

"My time in the military affected me in such a major way, I could write a book," said Maybin, a physical medicine and rehabilitation physician at Conway Medical Center in South Carolina. "In summary I will say the greatest lessons are: 1) the conditions could always be worse 2) barriers don't ever make me hesitate in my efforts and 3) relationship-building is the key to success."

After college, Maybin became a professional bodybuilder, competing in 19 competitions over nine years. Although she has taken time off recently due to a challenging fellowship and COVID-19 restrictions, Maybin plans to compete again.

"The thing I most proudly admit is I was 100% natural the entire journey in a non-drug tested federation," she said. "I did this to be an example to others. The most rewarding part is inspiring others to take control of their health and establish a healthy balance."

As a woman of color, Maybin has embraced being a role model for other young women who might not see many physicians who look like them.

"I've also been different in that way and I have been equipped over the years with tips from mentors, my parents and colleagues," Maybin said. "It takes an Army to get where I am and nothing I earned has been alone. I hope to be part of many other young girls' Army and help them to reach their dreams."

Training Fellows is Rewarding for Orthopedic Surgeon Raymond Hah

As an orthopedic surgeon at the University of Southern California's Keck Medicine, Raymond Hah devotes an ample amount of time to working with up and coming physicians.

"Training the next generation of spine surgeons is very important to me as it ultimately has an exponentially larger impact on people than my own clinical practice," Hah said. "Most important is teaching them the right indications and correct patient selection for surgery. I also think it is important for them to see a wide range of surgical techniques, so they have the introduction to see what is best for them in their practice."

Dr. Hah grew up around medicine in Southern California, albeit with different types of patients. His father, Bill Hah, has been a veterinarian for several decades and still runs a busy practice. The younger Hah says he learned two valuable lessons early on from his father.

"The importance of a strong work ethic and to never shy away from any task, no matter how small," Hah said. "I realized that cleaning a kennel is just as important to running a hospital as the surgeries and medical evaluations. I think that idea tremendously influences the way that I work even to this day, especially in the operating room."

From an early age, Dr. Hah decided a career in medicine would be his path. After high school, he enrolled in a combined undergraduate and MD program and was passionate about pursuing his goal of becoming a physician.

It is safe to say the hard work has paid off.

SpineLine's 20 Under 40

Philip Louie Is Taking Patient Engagement into the Future

Dr. Philip Louie's interest in spine care came when his once energetic grandmothers began to struggle to walk without pain. The promise of providing patients with a return to their activities and quality of life was an exciting one for him. As a full-fledged physician, Dr. Louie has been able to council those grandmothers to seek treatment, and with minor interventions they are back to walking the sidewalks with grace and determination.

Engaging with patients is a passion of Dr. Louie's. While in residency, he and fellow resident Kevin Campbell, MD, noticed that they consistently were asked the same few questions. They sent a series of daily text messages and exercise videos to coach peri- and postoperative patients through their recovery. This led to them starting a company, STREAMD, that runs as a perioperative chatbot on an artificial intelligence and machine learning platform that takes patients from preoperative to the postoperative recovery period.

Dr. Louie is an active researcher who has published more than 100 papers on training, machine learning and AI to provide individualized care, psychosocial factors associated with treatment, and health care costs and value issues.

Since the onset of COVID-19, Dr. Louie has been giving back to the community he came from via the Chinatown-International District Business Improvement Area of Seattle. Unfortunately, much of that work has been in the form of cleaning vandalism, aiding in public safety and helping businesses find funding to stay afloat through the pandemic.

Within NASS, Dr. Louie is a frequent presenter at NASS conferences and a member of *SpineLine's* editorial board. His free time is spent with his family at local parks and beaches, and supporting Seattle's sports teams.

A Love for Research Leads José A. Canseco to a Surgeon-Scientist Career

For José A. Canseco, MD, PhD, a passion for spine care was ignited as an undergraduate at Rice University while he was conducting research in musculoskeletal bioengineering. While at Harvard Medical School, he solidified his plan to become an orthopedic surgeon and research scientist. His doctoral research at M.I.T. was on ligament regeneration using co-cultures of mesenchymal stem cells and ACL fibroblasts to enhance primary ligament repair.

Dr. Canseco's current research interests, sparked by the mentorship of Dr. Christopher Kepler, are understanding neurogenic inflammation and its role in discogenic back pain. As a clinician-scientist, his goal is in developing innovative conservative management approaches for disc-related back pain based on currently available biologics for neurogenic pain syndromes. From a basic science perspective, he hopes to explore alternative inflammatory pathways to understand the molecular basis of disc degeneration and its relationship to discogenic back pain. His long-range goals include developing a comprehensive surgical acumen to provide excellent patient care and pursuing a career as a surgeon-scientist. Presently, Dr. Canseco is an orthopedic spine surgeon at the Rothman Institute and an assistant professor at Thomas Jefferson University. He serves as a principal investigator in the Laboratory for Translational Spine Science focusing on therapies that can be applied in the clinic and operating room.

Dr. Canseco recognizes the importance of giving back and has volunteered his time at Puentes de Salud, a nonprofit clinic for medically underserved Latino populations in South Philadelphia. He hopes to continue his volunteerism as his career progresses.

When he's not engaging in research or seeing patients, Dr. Canseco can be found with his wife and three children at the beach, and deep-sea fishing with his in-laws.

SpineLine's 20 Under 40

Aju Bosco Is a Trendsetter for Orthopedic Surgeons in India

In 2015, Aju Bosco became the first orthopedic surgeon from the government sector of the state of Tamil Nadu, India to pursue the board-certified spine surgery clinical fellowship. Doing so allowed Bosco to be trained under the country's finest spine surgeons at Ganga Hospital in Coimbatore, the largest private spine care hospital in the country.

"As the first board-certified spine surgeon to be appointed as the assistant professor in the only orthopedic spine surgery unit in the government sector of my state, I believe that I am in a key position to transform the lives of thousands with spine ailments, not just by utilizing the skills that I have acquired during my fellowship but also by inspiring my resident physicians to pursue a career in spine surgery," Bosco said. "I am proud to be able to offer specialized spine care to underprivileged patients free of cost under the government scheme, who cannot afford the high cost of such treatment in private sector hospitals."

Bosco is the son of two general physicians, Drs. John and Rita Bosco. Seeing physicians up close every day made Bosco eager to follow his parents' path.

"My mother instilled in me the respect and passion for the medical profession from an early age," Bosco said. "My father is a passionate physician, and he treats a third of his patients free of cost since the day he started practicing medicine. I grew up seeing the altruistic and selfless service of my parents to the underprivileged community in my neighborhood. I have inherited from my parents the qualities of altruism and passion for the profession, which I believe are the two most important attributes of a good physician."

Bosco believes in offering "holistic expert spine care that is available, accessible and affordable to the entire society" by integrating technology and developing a system that will make expert spine care accessible to the underprivileged and remote areas of the community.

Lindsey Ross Breaks Down Barriers as a Minority, Female Surgeon

As a neurosurgeon at Cedars-Sinai in her hometown of Los Angeles, Lindsey Ross understands clearly that she is carrying a torch of sorts for women of color.

"It is rare that I see other surgeons that look like me," Ross said. "For that matter, neither have my patients, my colleagues, the people who work in the hospital or the administrators I work for. It can feel overwhelming at times, where my every breath and move and is attempting to break down walls, barriers, and sterotypes. My success is a step forward in progress and success for all women and women of color."

Ross' unique experience extends beyond LA, however. In 2016-17, she served as a White House Fellow, a prestigious position where she worked for the Secretary of U.S. Department of Health and Human Services that also included roundtable discussions with top government leaders.

"I served during the transition from President Obama to President Trump, which was a special time in history," Ross said. "The experience was unparalleled. I enjoyed learning about public health policy, finance and leadership at the highest federal level. I also had the opportunity to meet many leaders of our country not only in health care but in the judicial system, economic, communications and national security. This is a view into our great country that few are afforded."

As for being a physician in the ever-changing modern health care landscape, Ross says she focuses on compassion, competency and creativity.

"This is my mantra and drives all of my decisions from the time I wake up until I go to sleep," she said. "I always want to do what's best for my patients and I will go above and beyond for them."

SpineLine's 20 Under 40

Aria Nouri, MD, MSc, Finds Success as Researcher, Reviewer and Neurosurgeon

What's in a name? For neurosurgeon Aria Nouri, a great deal. In the process of researching his master's thesis, he found inconsistencies in the literature pertaining to "cervical spondylotic myelopathy." Either it wasn't always the same condition or included a broader group of pathologies (eg, ossification of the posterior longitudinal ligament). The lack of clear definition prompted him to propose a more descriptive name with a clear definition, which ultimately led to the chapter, "Degenerative Cervical Myelopathy: Epidemiology, Genetics, and Pathogenesis" in his thesis, *The Role of Magnetic Resonance Imaging in Predicting Surgical Outcome in Patients with Degenerative Cervical Myelopathy*, which he worked on with his advisor and mentor, Michael Fehlings, MD, PhD, FRCSC, FACS. Despite early hesitation, the term "Degenerative Cervical Myelopathy" has been adopted in AOSpine's guidelines on the management of DCM, and the recent RECODE-DCM initiative survey found surgeons and patients both supported DCM as the index terminology for the condition.

Dr. Nouri's contribution to spine research continues through his more than 70 published papers and as a top-rated peer reviewer for a number of spine-related journals. He recommends to new reviewers that their reviews should aim to "make the paper the best possible version of itself. Comments to authors should focus not just on pointing out problems or weaknesses but also provide suggestions on how those problems can be rectified or diminished. I think it is important to look at literature referenced, seeing what papers have and more importantly, have not been cited, will provide a quick look into how well the paper is placed into the context of the 'current state of the art.'"

When he is not seeing patients or researching, Dr. Nouri enjoys soccer and basketball, listening to audiobooks, and traveling.

Eiman Shafa Embraces the Future Via Robotics

Growing up in Iran at the height of the Iran-Iraq War, Eiman Shafa saw his young uncle come home with a spinal cord injury. "I recall as a young boy wanting to make him better," he notes. "Looking back, this sad event encouraged me along a journey to address spine pathology."

The family immigrated to New Jersey when Dr. Shafa was 9 years old. Despite having to learn English, his childhood was essentially that of any native American's. When it was time for college, he studied in Nashville before returning for a residency five minutes from his childhood home. His fellowship was at Twin Cities Spine Center, where he is now an orthopedic surgeon, Director of Education, and Medical Director of Spine for Allina Health.

An avid researcher, Dr. Shafa's primary focuses are robotic spine surgery and minimally invasive techniques. Of his practice's robotic spine program, he says "I believe robotic assistance will be used in our procedures commonly over the years to come but the technology is currently advanced enough to enable all surgeons to work efficiency, and with accuracy and reproducibility. The most impactful part of robotic surgery currently is the detail to which a surgery can be planned ahead of the incision time."

Dr. Shafa has recently joined NASS' Section on Robotics and Navigation. "I am eager to contribute to the ideas that will guide thoughtful adoption of the technology for surgeon colleagues and guide industry engineers to design robotic capabilities from the clinical perspective for surgical decision-making to completion of the surgical procedure."

In his free time, Dr. Shafa can be found learning taekwondo from his wife who has earned two blackbelts, taking on a wood working project, and keeping up with his 2-year-old daughter.

SpineLine's 20 Under 40

Catherine Olinger Learns to Balance Motherhood and Surgery

The demands of being a surgeon are rigorous. Likewise for being the mother of a young child.

Combining the two? Well, that can be downright daunting. But Catherine Olinger has embraced the challenge, mastering the time management skills required to excel as an orthopedic surgeon at the University of Iowa while also teaming with her husband to care for their 8-year-old son.

"There are days that require finishing care for my patients as opposed to picking up my son from school," Olinger said. "There have been commitments regarding my career that have been prioritized over family and the balance between the two can be lopsided at times. However, my husband and I are a team and our son is our number one priority."

Olinger's son, Eddie, was born while she was in medical school at Creighton University. Her husband is in the Army and there are days when sacrifices must be made to care for their son.

"There were times I was not participating in every single conference, staying up late to read and volunteering for the worst calls shifts to make sure my family was cared for," she said. "I also think that my son is my greatest accomplishment and my family is most important to me. Without them, I wouldn't be where I am today. Making it all work definitely involves being aligned as a family to what values are important on a daily basis."

Olinger, who wanted to be a meteorologist as a child, found her career path in graduate school when she worked in pathology and surgery.

"I encourage people who think they want to be doctors to find ways to experience the health care field first hand," Olinger said.

Spine Care Is a Family Thing for Michael McCarthy

As the son and younger brother of spine surgeons, Michael McCarthy's training started on weekends at his father's practice: carrying charts, helping with research and observing surgeries. "The influence of these two individuals have shaped my career path providing me with tangible examples of how to be an excellent surgeon, parent, sibling and caring human."

His teenage and college years provided further confirmation that Dr. McCarthy would follow in his father and sister's footsteps. In high school, he volunteered at a camp for children with muscular dystrophy and cerebral palsy. While playing football for Boston College, observing the human body's capabilities solidified his interest in biomechanics and orthopedics.

Owing to his early mentorship experiences, Dr. McCarthy recently published an article in the *Journal of the American Academy of Orthopaedic Surgery* assessing how trainees can reach peak performance. The research informs his own work with trainees as he now "pays forward" his mentorship experiences. In addition to medical education research, Dr. McCarthy also has research interests in cervical spine surgery and the impact of COVID-19 on spine surgery.

In his practice, Dr. McCarthy collaborates with his patients to provide patient-centered care using evidence-based treatments. He specializes in minimally invasive, degenerative, tumor and deformity care, and believes "spine surgery is on the precipice of a significant change as enabling technologies continue to improve surgeons' ability to address spine issues in the least impactful manner."

When not in his busy Carmel, Indiana practice, Dr. McCarthy can be found with his wife and three children participating in his favorite activities: hiking, traveling and fishing. The family also gives back through community outreach programs and their church.

SpineLine's 20 Under 40

Partnership with SPINE20 is Paramount for Koji Tamai

Koji Tamai was among the main authors of the first scientific paper from SPINE20, an international advocacy group founded in 2019 by NASS, EuroSpine, German Spine Society and Saudi Spine Society to globally improve spine care and prevention.

Tamai, an orthopedic surgeon in Osaka, Japan, says his work with SPINE20 has been an important initiative for him.

"In my opinion, SPINE20 constitutes critical work that I am accomplishing to serve as a bridge for Asian countries," Tamai said. "In the near future, I would like to become a person that connects Asian countries to SPINE20, eventually resulting in improving the local spinal care level in every Asian country."

As a child, Tamai suffered from extreme atopic dermatitis and was hospitalized frequently. He said the experience was a driving force for his interest in medicine.

"As far as I can remember, I had already decided to become a doctor," he said. "In my elementary school graduation essay, I described my dream to become a medical doctor. After achieving this dream, I met great spine surgeons including my current superior, Nakamura. They had excellent personalities and exhibited strong professionalism, which led me to decide to become a spinal surgeon."

Tamai has made several trips to the US, including a year-long fellowship with USC Spine Center. There, he learned differences in the insurance systems as well as the contrasting styles of doctor-patient relationships between the US and Japan, bolstering his world views.

Ice Hockey Injury Put Life in Perspective for Alexander Satin

Alexander Satin played center and left wing in competitive ice hockey, and was on a New York state championship team in high school. He has terrific memories of playing hockey for outstanding coaches and alongside talented teammates.

However, a separated left shoulder injury during his senior year of high school took Satin's focus off the ice.

"The injury definitely put a lot of things in perspective for me," Satin said. "While many hockey players take gap years after high school, it became very apparent that my path was to go to college and pursue a premedical course. I had an excellent orthopedic surgeon who helped me through the injury. He spent a lot of time with me and was very reassuring. Mentally, it was very important to me that I return for the end of the season. This experience definitely piqued my interest in orthopedic surgery and is something that I think of while treating injured patients today, particularly young athletes."

Today, Satin is an orthopedic surgeon at Texas Back Institute, where he says advancing medicine and improving spine care are embedded in the TBI culture.

"We always say that if we are doing things the same way in 20 years, then we did something wrong," Satin said. "To that end, I think research is fundamental to advancing patient care. Whether it is understanding risk factors for complications or determining the best surgical approach, research provides us with answers to important clinical questions. I hope to follow in my senior partners' footsteps and safely introduce new technology that improves clinical outcomes through rigorous clinical studies."

SpineLine's 20 Under 40

Gene Tekmyster Thrives Treating Elite Athletes

Having been an athlete and all-around active individual, Gene Tekmyster spent his undergraduate years as an athletic trainer. The satisfaction he got in safely returning athletes to competition set him on his career path. He notes "spine medicine and spine injuries have always been the toughest of injuries to deal with... I wanted to be able to provide the athletes I was caring for with answers and treatment options that will allow them to return to their respective sports."

Now as a practicing physician at the USC Spine Center at Keck Medicine, Dr. Tekmyster is part of the team that cares for athletes from the LA Kings of the NHL and the USC Trojans. He is also a team physician for the US Ski and Snowboard team as well as continuing to care for athletes of all levels in the community.

His philosophy of care is that the goal of treatment should be optimization and return to the patient's pre-injury function. Noting that every patient's situation is unique, he prioritizes "an individual treatment plan that can be implemented to allow for optimal outcomes and functional improvement."

Dr. Tekmyster gives back to his community by providing event coverage for events like road races, triathlons, and high school sporting events. He also conducts educational seminars on injury prevention and caring for athletic injuries.

In his free time, Dr. Tekmyster can be found with his family, teaching his toddler how to ride a bike and enjoying outdoor activities like cycling, hiking and skiing. He's also an avid weightlifter who has obtained a coaching certification in Olympic weightlifting.

Research Always at the Forefront for Gregory Schroeder

Gregory Schroeder may be in the early stages of his orthopedic surgery career, but he has already authored or co-authored a whopping 217 peer-reviewed articles.

"I think research is important, because it allows what we do not only to affect our patients, but to help patients throughout the world, and it helps push spine care forward," Schroeder said. "Hopefully, this will lead to better care for patients in the future."

With many authored papers to choose from, Dr. Schroeder says he has two that stick out: 1) "Is it necessary to extend a multilevel posterior cervical decompression and fusion to the upper thoracic spine?" published in *Spine* in 2016 and 2) "Utilization of time-driven activity-based costing to determine the true cost of a single or 2-level anterior cervical discectomy and fusion" published in Clinical Spine Surgery in 2018.

Dr. Schroeder practices at the Rothman Institute near Philadelphia, and is also an assistant professor of orthopedic surgery at Thomas Jefferson University. An Indiana native, he says medicine was always something he found interesting, but it wasn't until a friend in college was diagnosed with cancer that he decided to pursue a career in the medical field.

"The most rewarding part of being a physician is seeing the patients return to clinic after the postoperative pain has subsided, and their nerve pain is gone," he said. "The most challenging part is explaining to patients that they have significant pain, but there is nothing further that I can offer them."