Stem Cells and Spinal Fusion

Stephen R. Stephan, Linda E. Kanim and Hyun W. Bae

Int J Spine Surg published online 19 April 2021
https://www.ijssurgery.com/content/early/2021/04/21/8057

The International Journal of Spine Surgery
2397 Waterbury Circle, Suite 1,
Aurora, IL 60504, Phone: +1-630-375-1432

International Journal of Spine Surgery, Vol. 00, No. 00, 0000, pp. 000–000
https://doi.org/10.14444/8057

Stem Cells and Spinal Fusion

STEPHEN R. STEPHAN, MD,[1] LINDA E. KANIM, MA,[2] HYUN W. BAE, MD[1,2]

[1]*Department of Orthopaedic Surgery, Cedars-Sinai Medical Center, Los Angeles, California,* [2]*Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California*

ABSTRACT

Background: This manuscript is a review of the literature investigating the use of mesenchymal stem cells (MSCs) being applied in the setting of spinal fusion surgery. We mention the rates of pseudarthrosis, discuss current bone grafting options, and examine the preclinical and clinical outcomes of utilizing MSCs to assist in successfully fusing the spine.

Methods: A thorough literature review was conducted to look at current and previous preclinical and clinical studies using stem cells for spinal fusion augmentation. Searches for PubMed/MEDLINE and ClinicalTrials.gov through January 2021 were conducted for literature mentioning stem cells and spinal fusion.

Results: All preclinical and clinical studies investigating MSC use in spinal fusion were examined. We found 19 preclinical and 17 clinical studies. The majority of studies, both preclinical and clinical, were heterogeneous in design, due to different osteoconductive scaffolds, cells, and techniques used. Preclinical studies showed promising outcomes in animal models when using appropriate osteoconductive scaffolds and factors for osteogenic differentiation. Similarly, clinical studies have promising outcomes, but differ in their methodologies, surgical techniques, and materials used, making it difficult to adequately compare between the studies.

Conclusion: MSCs may be a promising option to use to augment grafting for spinal fusion surgery. MSCs must be used with appropriate osteoconductive scaffolds. Cell-based allografts and the optimization of their use have yet to be fully elucidated. Further studies are necessary to determine the efficacy of MSCs with different osteoconductive scaffolds and growth/osteogenic differentiation factors.

Level of Evidence: 3.

Special Issue

Keywords: stem cells, mesenchymal stem cells, MSC, spinal fusion, biologics, regenerative medicine, autograft, bone graft, scaffold

INTRODUCTION

Spinal fusion surgery is one of the most common procedures performed in the United States, with over 1 million cases performed annually.[1] In 2020, it is still reported as one of the most costly procedures, with an average cost of $120,000 per hospitalization.[2] Conditions treated with spinal fusion include various degenerative disorders, fractures, spinal tumors, and deformities of scoliosis, kyphosis, and more. Spinal fusions are performed when any structural or neurologic component of the spine is compromised, typically affecting abnormal motion, and likely producing pain and disability. Successful fusion involves new bone formation between 2 or more adjacent vertebrae, returning stability to the diseased segment of the spine.

A wide variety of spinal fusion procedures exist, with the anatomic location and pathology directing which surgical approach, stabilizing instrumentation, and procedure may maximize stability and rapid healing, while minimizing surgical trauma. As novel technologies progress influencing instrumentation, biomaterials, implants, and grafting techniques, new and less tissue-destructive approaches are being discovered/designed.

The incidence of pseudarthrosis, or nonunion, can be as high as approximately 25%–35% in spinal fusion surgery, which is highly dependent on the type of procedure, approach used, and patient factors, such as bone quality, health status, and comorbidities.[3] This is an extremely high incidence for such a widely and commonly performed, as well as expensive, procedure. When there is a failure of bone formation, unsuccessful fusion leads to the following: pain, instability, implant failure, reoperation, patient stress, and drastically increased costs.[4] Risk factors include cigarette smoking, age, female sex, excessive thoracolumbar kyphosis, and various

bone diseases, such as osteopenia and osteoporosis.[5–8]

Methods to prevent pseudarthrosis have become some of the most researched and invested-in aspects of spine surgery today. Traditional gold standard for bone grafting has been autologous bone harvest, collected from a donor site or the surgical site. Other options include allograft, synthetics, and growth factors such as recombinant human bone morphogenic protein (rhBMP)-2. With the acceleration of regenerative medicine and technology, we have seen the emergence of mesenchymal stem cells (MSCs) as a possible option for increasing fusion rates, as well as decreasing complications. In this manuscript, we present current bone grafting options and then focus on the use of stem cells to augment grafting options to reduce the potential for pseudarthrosis in spinal fusion surgery.

MATERIALS AND METHODS

This manuscript is a review of the literature, performed to be up to date up until January 2021. PubMed/MEDLINE databases were searched, as well as ClinicalTrials.gov, for any literature with relevant information pertaining to stem cells and their use in spinal fusion. Keywords that were used were as follows: spine fusion, spinal fusion, stem cells, MSCs, adipose derived stem cells, autologous bone, allogeneic stem cells. Pertinent studies that were included were largely focused on preclinical and clinical trials investigating the rate of fusion with the use of stem cells in spine surgery. The heterogeneity between studies did not allow for data and statistical analysis to show whether or not fusion rates differed, but the studies are summarized and left for conclusions to be made by the readers.

Bone Graft Review

The gold standard to achieve successful fusion is currently autologous bone (autograft) from either the iliac crest or local bone graft (LBG), found in or near the surgical site. Studies have shown both grafts to be equally effective for single-level fusions, but LBG was found to be unsatisfactory for multilevel procedures.[9] Autograft contains all 3 key elements to provide for successful spine fusion: osteoinductive factors such as cytokines and growth factors, osteoconductive materials such as collagen and minerals for a structural support scaffolding, and osteogenic components such as osteoblastic/preosteoblastic cells and bone marrow stem cells.[10]

Although successful fusion rates with autograft may be as high as 95%, bone available for harvest is limited, and quality varies depending on the patient bone health, age, smoking, diabetes, and other comorbidities. Additionally, autograft harvesting may lead to infection, donor site pain, blood loss, and risk of fracture.[11,12] These complications have been reported to be as high as 39% with iliac crest bone graft harvest.[13]

For these reasons, other modalities for grafting have been explored. Biologics and synthetics, osteogenic differentiation factors such as BMP-2, demineralized bone matrix (DBM), hydroxyapatite, provide combinations of osteoinduction and osteoconduction, but fail fundamentally as they are not osteogenic. Additionally, these products also have limitations and side effects of their own. Using these biological and synthetics as stand-alone substitutes for bone graft has not been fully explored, and would likely not provide the adequate stability and fusion ability as in conjunction with other modalities.[14–16] The unmet need for commonly used autograft substitutes has paved the way for the investigation of using stem cells for spinal fusion.

Stem Cells

Stem cells, first described by Friedenstein[17] in 1968, are defined as immature tissue precursor cells, which can differentiate into muscle, bone, tendons, fat, and other various stromal tissues.[18–21] They can be categorized into embryonic stem cells, induced pluripotent cells, and adult stem cells.

MSCs, which fall under the category of adult stem cells, have benefited from advancements in the field of regenerative medicine, and are the focus for use in spinal fusion procedures. The multipotent nature of individual MSCs was first described by Pittenger et al[22] in 1999. Research has shown that MSCs have osteogenic properties, can be modified to secrete osteoinductive factors, and can be implemented on an osteoconductive scaffold to successfully provide the 3 components for optimizing fusion and osteogenesis.[16] MSCs are able to differentiate into osteogenic cells and also exhibit paracrine effects. Additionally, they can be easily cultured and have a high ex-vivo expansive potential.[23,24]

MSCs can be derived from numerous adult tissues, including bone marrow, muscle, and subcu-

taneous fat,[25,26] and have been shown to resist immunologic rejection.[18,27] The most common source for MSCs in spinal fusion is bone marrow aspirate (BMA), followed by adipose tissue.[28–30] Clinical studies have explored BMA harvest sites, with vertebral bodies and iliac crests having robust harvests.[31] BMA is easily obtained in the supine position from the posterior iliac bone, or can be obtained easily through the surgical site, as well.[32] Studies have looked at regenerative capacity over time with various stem cell subtypes,[33–35] as well as regenerative capacity in older patients. Mazini et al[33] reported a maintained regenerative capacity in in vitro studies with adipose-derived stem cells, whereas bone marrow MSCs may start to lose expression of specific surface antigens in later passage.[33,36] Although demonstrated with in vitro studies, this information is difficult to understand and demonstrate in vivo and in the clinical setting.

Bone marrow MSCs have been studied to provide new treatment methods for arthritis, periodontal disease, intrinsic muscular dystrophy, and cardiac disease because of their ability to differentiate into different cell types.[18,22] Similarly, they have been shown to differentiate into cells of the osteogenic lineage within the appropriate conditions.[37,38] The adipose-derived MSCs can also be extracted via liposuction, which is typically less painful than bone marrow aspiration.[39,40] Lastly, allogeneic MSCs from matching donors have been used for patients with low bone volume, who are unable to produce enough of their own MSCs. Concerns have been expressed with allogeneic MSCs due to immune reactions in patients.[41]

MSCs present a lesser fraction of the total population of nucleated cells, under 0.01%[42,43] of cells when isolated from BMA, and an in-vitro expansion phase may be necessary to obtain sufficient stem cell numbers prior to implantation.[22] Several techniques for expansion exist, but problems such as sterility technique, culture time, medium used, as well as number of MSCs required are still yet to be established. Additionally, this source of cells may vary and not be as reliable in an elderly population, due to dissipation of the potency of the MSCs.[44]

Preclinical Results

To date, there has been a great deal of preclinical trials investigating the efficacy of stem cells in bony fusion with various animal spinal fusion models.[45,46] Many of these studies have investigated variations in growth factors and scaffold options to promote optimized bony fusion, with some studies even looking at genetically modified MSCs. As common in emerging topics, the results of these studies are variable, but the majority of studies are able to replicate outcomes between autograft and MSCs with supporting scaffolds in spinal fusion.[16,45,47–57] These studies are summarized in Table 1.

Numerous studies have shown the addition of MSCs to achieve superior rates of fusion when compared with autograft.[45,47,51,58] Nakajima et al[51] studied rabbit spines treated with MSCs cultured in osteogenic differentiation medium versus without differentiation medium and autograft, showing higher fusion rates in the first group. Minamide et al[45] demonstrated increased fusion rates in rabbits with bone marrow cells when compared with BMP and autograft. Similarly, the same group also showed higher fusion rates with bone marrow derived MSCs cultured in rhBMP-2 and fibroblast growth factor when compared with autograft. Bae et al[54] showed increased posterolateral intertransverse process fusion rates to 89% in rats treated with BMA on collagen sponges and subeffective concentrations of rhBMP-2 compared with 33%–50% with rhBMP-2 and collagen sponges alone. Additionally, Crowley et al[59] demonstrated various preclinical and clinical studies investigating MSCs implanted on biologic or synthetic scaffolds with effective results in promoting bony union.

Other studies have shown comparable results with engineered MSCs to autograft. Sheyn et al[58] and Hasharoni et al[60] demonstrated genetically modified MSCs expressing BMP-2 when placed in the paraspinal musculature induced spinal fusion in mice that were comparable with the fusion achieved with instrumentation, in regards to segment rigidity. Similar results were demonstrated when looking at MSCs seeded on an alginate scaffold with low doses of BMP-2.[16]

Although the majority of the preclinical models have focused on bone marrow derived MSCs, Miyazaki et al[55] compared bone marrow derived MSCs to adipose-derived MSCs, demonstrating no significant difference in fusion rates between the 2 types of MSCs in a rat model of posterolateral fusion. Similarly, Ammerman et al[61] demonstrated increased fusion rates with adipose derived MSCs in a posterolateral spinal fusion rabbit model.

Table 1. Preclinical studies of spinal fusion using stem cells.

Study	Animals	Conditions	Fusion, %
Fu et al[16]	24 rabbits	Autograft	92
		Alginate + MSC + BMP2	92
		Alginate + MSC	67
		Alginate + BMP2	0
Bae et al[54]	53 rats	rhBMP2/ACS + fresh syngeneic BMA transplant	89
		rhBMP2/2ACS only	50
		rhBMP2/1ACS only	33
		ACS + fresh syngeneic BMA transplant	0
		ACS only	0
Gupta et al[47]	24 sheep	TCP + bone marrow cells	33
		TCP + whole marrow	8
		TCP	0
		Autograft	25
Minamide et al[48]	30 rabbits	MSC-BMP-FGF	86
		MSC-FGF	43
		MSC-BMP	28
		MSC	0
		Autograft	57
Cinotti et al[49]	40 rabbits	Ceramic + MSC	85
		Ceramic + bone marrow	50
		Ceramic	30
		Autograft	25
Kai et al[50]	30 rabbits	Ceramic + cells	100
		Ceramic + cells + BMP	100
		Ceramic	50
		Autograft	67
Valdes et al[56]	53 rabbits	60M rhBMP6 stimulated OPC	62
		30M rhBMP6 stimulated OPC	54
		Autograft	55
		DBM	40
		Decortication alone	0
Minamide et al[45]	36 rabbits	BMP-HA	100
		High marrow cells	71
		Low marrow cells	0
		Autograft	57
Nakajima et al[51]	24 rabbits	Osteogenic MSC	80
		MSC	33
		Hydroxyapatite	0
		Autograft	67
Wang et al[52]	9 monkeys	MSC+ ceramic	67
		Ceramic	17
		Autograft	83
Cui et al[57]	52 rats	Bone marrow	50
		DI-BAG cells	100
		Matrix only	0
Cuenca-López et al[53]	34 sheep	HA + MSC	35
		HA	22
		Allograft	70
		Autograft	70
Miyazaki et al[55]	48 rats	Collagen + adipose-derived MSC + adeno-BMP2	100
		Collagen + marrow-derived MSC + adeno-BMP2	100
		Collagen + BMP2	100
		Collagen + adipose-derived MSC + adeno-LacZ	0
		Collagen + marrow-derived MSC + adeno-LacZ	0
		Collagen alone	0

Abbreviations: ACS, absorbable collagen sponges; Adeno-LacZ, study specific; BMA, bone marrow aspirate; BMP2, bone morphogenic protein; DBM, demineralized bone matrix; DI-BAG, study specific; FGF, fibroblast growth factor; HA, hydroxyapatite; MSC, mesenchymal stem cell; OPC, osteoprogenitor cells; TCP, tricalcium phosphate.

To summarize, preclinical trials demonstrate promising outcomes for MSCs in spinal fusion. It is difficult to compare different trials and perform statistical analysis, as these results are highly dependent on the use of specific growth factors and differentiation mediums to aid in bone formation, as well as the use of appropriate scaffoldings and animals. The efficacy of MSCs to promote spinal fusion without the addition of genetic engineering or additional growth factors has been less than ideal.[54,60,62] With the appropriate techniques, MSCs either approach or match the fusion rates achieved with autograft in preclinical models. As with any type of treatment, the question of how

Table 2. Clinical studies using stem cells for spinal fusion.

Study	Patients	Approach	Type	Conditions	Fusion, %
Gan et al[42]	41	PLF/TLF	Autologous	Enriched BMA + β-TCP	95.1
Hostin et al[63]	22	AIF	Autologous	Collagen + BMA w/cage	87
Kitchel[64]	25	PLF, IF	Autologous	Collagen + BMA	80
				Iliac crest bone graft	84
Neen et al[65]	50	PLF, TLF, 360	Autologous	Collagen/hydroxyapatite + BMA	PLF 93, IF 85
				Iliac crest bone graft	PLF 93, IF 92
Niu et al[66]	21	PLF	Autologous	LBG + BMA	85.7
				Iliac crest bone graft	90.5
Vaccaro et al[67]	73	PLF	Autologous	BMA + DBM	63
				Iliac crest bone graft	67
Bansal et al[68]	30	PLF	Autologous	Hydroxyapatite + TCP + BMA	100
				Iliac crest bone graft	96
Taghavi et al[69]	62	PLF	Autologous	Collagen + BMA	100
				LBG	100
Odri et al[70]	15	PLF	Autologous	BMC + BPCG + autologous bone	100
Hart et al[71]	40	PLF	Autologous	BMC + allograft	80
Ammerman et al[61]	23	TLIF	Allogeneic	Osteocel + DBM	91.3
McAfee et al[72]	25	XLIF	Allogeneic	Autograft/Osteocel	85
Caputo et al[73]	30	XLIF	Allogeneic	Osteocel + DBM	89.6
Tohmeh et al[74]	40	XLIF	Allogeneic	Osteocel + DBM	90.2
Kerr et al[62]	52	ALIF, TLIF, 360	Allogeneic	Osteocel	92.3
Peppers et al[75]	40	ACDF	Allogeneic	Trinity	91.4
Eastlack et al[76]	182	ACDF + plating	Allogeneic	Osteocel and PEEK interbody	87

Abbreviations: ACDF, anterior cervical discectomy and fusion; AIF, anterior interbody fusion; ALIF, anterior lumbar interbody fusion; BMA, bone marrow aspirate; BMC, bone marrow concentrate; BPCG, bisphasic phosphate ceramics graft; β-TCP, tricalcium phosphate scaffolding; DBM, demineralized bone matrix; IF, interbody fusion; LBG, local bone graft; PEEK, polyetheretherketone; PLF, posterolateral fusion; TCP, tricalcium phosphate; TLF, transforaminal lumbar fusion; TLIF, transforaminal lumbar interbody fusion; XLIF, extreme lateral interbody fusion.

these results will translate to clinical results is what is most important.

Clinical Results

Clinical studies examining the efficacy of MSCs on spinal fusion are more limited than preclinical trials. Most studies look at MSCs isolated from BMA, as it can be harvested from the iliac crest or vertebral body intraoperatively and then transplanted to the fusion site. Additionally, many of the clinical studies use different carrier scaffolds, making it difficult to compare between trials, but in general, utilizing MSCs for spinal fusion show fusion rates from 63%–100%.[42,61,61–76] Studies are shown in Table 2.

There are multiple prospective trials and also systemic reviews investigating outcomes of stem cells and spinal fusion, mostly with the use of computed tomography or plain radiographs. In a prospective study, Gan et al[42] reported on 41 patients with enriched BMA on a β-tricalcium phosphate scaffold achieving 95.1% fusion at 24-month follow-up. Another study reported an 87% successful fusion rate with 182 patients in a multicenter prospective trial.[51] Odri et al[70] achieved 100% fusion on 15 patients receiving MSCs with macroporous biphasic phosphate ceramic scaffolds and autologous bone.

A systematic review by Khashan et al[31] compiled results from 7 different clinical studies, 6 prospective and 1 randomized control trial. Studies contained at least 20 patients each and compared BMA on a scaffold to iliac crest and/or LBG.[31] Fusion rates for BMA with scaffolds ranged from 63%–100%, whereas LBG or iliac crest bone graft ranged from 67%–100%. The majority of these studies examined posterolateral fusion. The review concluded that there is still insufficient evidence to support the use of MSCs or BMA over autologous bone graft.

There are also studies involving allogeneic MSCs (Table 2). Peppers et al[75] reported on 40 patients undergoing anterior discectomy and fusion with Trinity Evolution Viable Cellular Bone Matrix, an allogeneic stem cell source, with 91.4% fusion rates. Another study reported 92.3% fusion rates for 52 patients with Osteocel, an allograft-based tissue containing live stem cells.[62] This fusion rate is higher in comparison with Osteocel when being used with DBM (89.6%) and autograft (85%). Osteocel has also shown promising outcomes in other studies, with fusion rates ranging between 87% and 92%.[61,62,73,76] These studies and products demonstrate high rates of fusion and may be options for patients who are unable to use their own MSCs for fusion.

Currently, as of January 2021, there are 11 active studies listed on ClinicalTrials.gov investigating the

Table 3. Current clinical trials.

ClinicalTrials.gov Identifier	Description	Design	Outcomes
NCT01552707[77]	Isolation and ex-vivo expansion of MSCs with Xcelia, then fixed to allogenic bone compared with bone iliac crest alone.	Prospective, RCT	Safety of Xcelia, feasibility of Xcelia, efficacy of spinal fusion
NCT02297256[78]	Bone marrow aspirate concentrate (BMAC) + allograft compared with iliac crest bone graft during posterior lumbar/lumbosacral spine fusion.	Prospective, RCT	Fusion status, Oswestry Disability Index (ODI), Short Form Health Survey (SF-12), numeric pain rating scale, length of stay
NCT02924571[79]	BMAC and allograft compared with rh-BMP2 for thoracolumbar spine fusion with interbody support.	Prospective, blinded, nonrandomized	ODI, SF-12, numeric pain rating scale
NCT03827096[80]	Bone marrow cell aspiration from iliac crest cultivated for 3 passages to expand and suspended on β-tricalcium phosphate foam to lumbar spine.	Single group assignment	Demonstrate absence of complications at the site of spinal fusion, ODI, efficacy of spinal fusion on x-ray and CT
NCT00996073[81]	Allogeneic mesenchymal precursor cells (NeoFuse) combined with MasterGraft Matrix compared with use of autologous iliac crest bone graft in lumbar interbody fusion site.	Prospective, multicenter, randomized	Determine safety, evaluate overall fusion success
NCT01097486[82]	Allogeneic mesenchymal precursor cells (NeoFuse) combined with MasterGraft Matrix compared with use of autologous iliac crest bone graft in multilevel anterior cervical discectomy and fusion.	Prospective, multicenter, randomized, single-blinded	Determine safety, evaluate overall fusion success
NCT02070484[83]	Stem cell allograft (NuCel) compared with demineralized bone matrix.	Randomized, parallel assignment	ODI, evaluation of fusion via CT
NCT00941980[84]	Stem cells attached to allograft bone matrix (Osteocel Plus) in subjects undergoing posterior lumbar interbody fusion surgery compared with historic autograft control.	Prospective, nonrandomized multicenter	Evaluate fusion rates, complications, radiographic outcome, surgical time, blood loss
NCT00948831[85]	Osteocel Plus in subjects undergoing anterior lumbar interbody fusion.	Prospective, nonrandomized multicenter	Evaluate fusion rates, complications, radiographic outcome, surgical time, blood loss
NCT00947583[86]	Osteocel Plus in subjects undergoing transforaminal lumbar interbody fusion.	Prospective, nonrandomized multicenter	Evaluate fusion rates, complications, radiographic outcome, surgical time, blood loss
NCT00951938[87]	Allogeneic cancellous bone matrix with viable osteoprogenitor cells, MSCs, and demineralized cortical bone (Trinity Evolution) in patients undergoing ACDF.	Case-only, prospective	Fusion rates, pain, complications

Abbreviations: BMP2, bone morphogenic protein; CT, computed tomography; MSC, mesenchymal stem cell; RCT, randomized controlled trial.

effects of stem cells on spinal fusion (Table 3). As time goes on, with expanded popularity of stem cells increasing fusion rates, we will likely see more studies investigating clinical outcomes associated with MSCs compared with autologous bone graft. Ultimately, with the heterogeneity of clinical studies at this time, it is difficult to directly compare fusion rates with autologous bone graft, but the studies are overall promising.

DISCUSSION

Successfully achieving spinal fusion is highly dependent on having osteogenic, osteoconductive, and osteoinductive factors available. Traditionally, autologous bone harvesting from the surgical site or iliac crest have been the standard of care, but complications, donor site morbidity, and limited quantities of bone have brought other options into the spotlight.

MSCs have the potential to become widely used as bone graft augmentation and for achieving successful spinal fusion. It is believed that stem cells contribute to the fusion process and improve union through their osteogenic and osteoinductive properties within the fusion site, although the primary contribution is still unknown. Although they are not yet on the path of becoming the gold standard for achieving successful fusion, MSCs have gained interest due to ease of use, ability to harvest intraoperatively, and the regenerative capabilities. At this time, multiple factors need to be optimized, such as: intrinsic and extrinsic expression of growth factors and cytokines, the optimization of choosing the material and construction of scaffoldings for the cells to be supported, and finding the most beneficial

area of stromal cell harvest, while also minimizing the morbidity of the procedure. MSCs cannot be used alone to promote spinal fusion; they must be used in conjunction with, at minimum, a scaffolding to hold them in place.

There are a significant amount of preclinical studies, which show comparable outcomes when using MSCs to achieve successful spinal fusion. These studies are heterogeneous in nature, using different animal models, various scaffolds, and also various growth factors and harvesting mediums for the cells. Although many types of combinations have been examined, we do not know the optimal combination that will translate to success in the clinical realm. Even if this perfect combination of factors, cells, and scaffold is discovered, we also may not be sure if it is a one-size-fits-all for every patient.

In clinical models, we have seen studies with fusion rates of 63%–100%. Most studies demonstrated at least approximately equal fusion rates, but again, just as with preclinical models, different studies used different combinations of growth factors and scaffolds. Additionally, numerous studies look at the use of BMA, rather than just the MSCs isolated from BMA. Clinical trials involving allogeneic MSCs have shown promise in patients, such as elderly, who may be limited in the number of viable cells available from liposuction or BMA. Lastly, we also are not sure how many of these cells continue to be viable after placement. Newer technologies and techniques are required to quantify viable cells and ensure their survival after implantation.

As future studies are started and planned, we should look to standardize certain aspects, that way we can compare between different studies. Similarly, we can start looking at patient demographics, approaches, and the pathology behind the reason for spinal fusion, to further understand what combination of scaffold and MSCs will work in each setting. Additionally, as we start to understand these factors, cost analyses and other outcome studies will become just as important as fusion rates. Lastly, future studies need to address the regenerative capacity of stem cells over time. Although in vitro studies exist, it would be important to the field to understand the temporal benefit of in vivo use of MSCs in spinal fusion.

In summary, the future of spinal fusion may be heading in the direction of using MSCs, synthetics, and proteins such as BMP-2 to improve outcomes. Preclinical results with various proteins, growth factors, and scaffolds have shown promising results. Clinical trials, including prospective studies, have shown that MSCs with the appropriate harvesting, growth factors, and scaffoldings can provide comparable fusion rates to autograft. As new studies begin to emerge, and as regenerative medicine and technology advance, we may see MSCs becoming a staple of spinal fusion surgeries.

REFERENCES

1. Centers for Disease Control and Prevention. Table 116. https://www.cdc.gov/nchs/data/hus/2013/116.pdf. Accessed October 9, 2020.

2. McCarthy IM, Hostin RA, Ames CP, et al. Total hospital costs of surgical treatment for adult spinal deformity: an extended follow-up study. *Spine J*. 2014;14(10):2326–2333.

3. Kim YJ, Bridwell KH, Lenke LG, Rhim S, Cheh G. Pseudarthrosis in long adult spinal deformity instrumentation and fusion to the sacrum: prevalence and risk factor analysis of 144 cases. *Spine*. 2006;31(20):2329–2336. doi:10.1097/01.brs.0000238968.82799.d9

4. Dickson DD, Lenke LG, Bridwell KH, Koester LA. Risk factors for and assessment of symptomatic pseudarthrosis after lumbar pedicle subtraction osteotomy in adult spinal deformity. *Spine*. 2014;39(15):1190–1195. doi:10.1097/BRS.0000000000000380

5. Hermann P, Webler M, Bornemann R, et al. Influence of smoking on spinal fusion after spondylodesis surgery: a comparative clinical study. *Technol Health Care*. 2016;24. doi:10.3233/THC-161164

6. Buchlak QD, Yanamadala V, Leveque J-C, Sethi R. Complication avoidance with pre-operative screening: insights from the Seattle spine team. *Curr Rev Musculoskelet Med*. 2016;9(3):316–326. doi:10.1007/s12178-016-9351-x

7. Kim YJ, Bridwell KH, Lenke LG, Rinella AS, Edwards C, Edward C. Pseudarthrosis in primary fusions for adult idiopathic scoliosis: incidence, risk factors, and outcome analysis. *Spine*. 2005;30(4):468–474. doi:10.1097/01.brs.0000153392.74639.ea

8. Keaveny TM, Yeh OC. Architecture and trabecular bone—toward an improved understanding of the biomechanical effects of age, sex and osteoporosis. *J Musculoskelet Neuronal Interact*. 2002;2(3):205–208.

9. Sengupta DK, Truumees E, Patel CK, et al. Outcome of local bone versus autogenous iliac crest bone graft in the instrumented posterolateral fusion of the lumbar spine. *Spine (Phila Pa 1976)*. 2006;31(9):985–991.

10. Khan SN, Cammisa FPJ, Sandhu HS, Diwan AD, Girardi FP, Lane JM. The biology of bone grafting. *J Am Acad Orthop Surg*. 2005;13(1):77–86.

11. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. *Spine*. 2002;27(16 suppl 1):S26–S31. doi:10.1097/00007632-200208151-00007

12. Ito K, Imagama S, Ito Z, et al. Screw fixation for atlantoaxial dislocation related to Down syndrome in children

younger than 5 years. *J Pediatr Orthop Part B*. 2017;26(1):86–90. doi:10.1097/BPB.0000000000000299

13. Sasso RC, LeHuec JC, Shaffrey C; Spine Interbody Research Group. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. *J Spinal Disord Tech*. 2005;18 Suppl:S77–S81. doi:10.1097/01.bsd.0000112045.36255.83

14. Park JJ, Hershman SH, Kim YH. Updates in the use of bone grafts in the lumbar spine. *Bull Hosp Jt Dis 2013*. 2013;71(1):39–48.

15. Spivak JM, Hasharoni A. Use of hydroxyapatite in spine surgery. *Eur Spine J*. 2001;10(suppl 2):S197–S204. doi:10.1007/s005860100286

16. Fu T-S, Wang I-C, Lu M-L, Hsieh M-K, Chen L-H, Chen W-J. The fusion rate of demineralized bone matrix compared with autogenous iliac bone graft for long multi-segment posterolateral spinal fusion. *BMC Musculoskelet Disord*. 2016;17. doi:10.1186/s12891-015-0861-2

17. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Prolif*. 1970;3(4):393–403. doi:10.1111/j.1365-2184.1970.tb00347.x

18. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol*. 2007;213(2):341–347. doi:10.1002/jcp.21200

19. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8(4):315–317. doi:10.1080/14653240600855905

20. Nguyen LH, Duenas V, Chen MY, Jandial R. Progenitor cells: role and usage in bone tissue engineering approaches for spinal fusion. *Adv Exp Med Biol*. 2012;760:188–210. doi:10.1007/978-1-4614-4090-1_12

21. Pneumaticos SG, Triantafyllopoulos GK, Chatziioannou S, Basdra EK, Papavassiliou AG. Biomolecular strategies of bone augmentation in spinal surgery. *Trends Mol Med*. 2011;17(4):215–222. doi:10.1016/j.molmed.2010.12.002

22. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143–147. doi:10.1126/science.284.5411.143

23. Morelli C, Barbanti-Brodano G, Ciannilli A, Campioni K, Boriani S, Tognon M. Cell morphology, markers, spreading, and proliferation on orthopaedic biomaterials. An innovative cellular model for the "in vitro" study. *J Biomed Mater Res A*. 2007;83(1):178–183. doi:10.1002/jbm.a.31262

24. Manfrini M, Fiorini M, Barbanti-Brodano G, Pressato D, Tognon M. New generation of orthopaedic mimetic bioceramics assayed with human mesenchymal stem cells. *Eur Musculoskelet Rev*. 2011;6:96–99.

25. Zheng B, Cao B, Crisan M, et al. Prospective identification of myogenic endothelial cells in human skeletal muscle. *Nat Biotechnol*. 2007;25(9):1025–1034. doi:10.1038/nbt1334

26. Crisan M, Yap S, Casteilla L, et al. A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell*. 2008;3(3):301–313. doi:10.1016/j.stem.2008.07.003

27. Lyons AB, Parish CR. Determination of lymphocyte division by flow cytometry. *J Immunol Methods*. 1994;171(1):131–137. doi:10.1016/0022-1759(94)90236-4

28. Liu X, Feng Q, Bachhuka A, Vasilev K. Surface modification by allylamine plasma polymerization promotes osteogenic differentiation of human adipose-derived stem cells. *ACS Appl Mater Interfaces*. 2014;6(12):9733–9741. doi:10.1021/am502170s

29. Steinert AF, Rackwitz L, Gilbert F, Nöth U, Tuan RS. Concise review: the clinical application of mesenchymal stem cells for musculoskeletal regeneration: current status and perspectives. *Stem Cells Transl Med*. 2012;1(3):237–247. doi:10.5966/sctm.2011-0036

30. Veronesi F, Salamanna F, Tschon M, Maglio M, Nicoli Aldini N Fini M. Mesenchymal stem cells for tendon healing: what is on the horizon? *J Tissue Eng Regen Med*. 2017;11(11):3202–3219. doi:10.1002/term.2209

31. Khashan M, Inoue S, Berven SH. Cell based therapies as compared to autologous bone grafts for spinal arthrodesis. *Spine*. 2013;38(21):1885–1891. doi:10.1097/BRS.0b013e3182a3d7dc

32. Risbud MV, Shapiro IM, Guttapalli A, et al. Osteogenic potential of adult human stem cells of the lumbar vertebral body and the iliac crest. *Spine*. 2006;31(1):83–89. doi:10.1097/01.brs.0000193891.71672.e4

33. Mazini L, Rochette L, Amine M, Malka G. Regenerative capacity of adipose derived stem cells (ADSCs), comparison with mesenchymal stem cells (MSCs). *Int J Mol Sci*. 2019;20(10). doi:10.3390/ijms20102523

34. Wagner W, Wein F, Seckinger A, et al. Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. *Exp Hematol*. 2005;33(11):1402–1416. doi:10.1016/j.exphem.2005.07.003

35. Cuevas-Diaz Duran R González-Garza MT Cardenas-Lopez A Chavez-Castilla L Cruz-Vega DE Moreno-Cuevas JE. Age-related yield of adipose-derived stem cells bearing the low-affinity nerve growth factor receptor. *Stem Cells Int*. 2013;2013:372164. doi:10.1155/2013/372164

36. McIntosh K, Zvonic S, Garrett S, et al. The immunogenicity of human adipose-derived cells: temporal changes in vitro. *Stem Cells*. 2006;24(5):1246–1253. doi:10.1634/stemcells.2005-0235

37. Ohgushi H, Goldberg VM, Caplan AI. Heterotopic osteogenesis in porous ceramics induced by marrow cells. *J Orthop Res*. 1989;7(4):568–578. doi:10.1002/jor.1100070415

38. Tibbitt MW, Anseth KS. Hydrogels as extracellular matrix mimics for 3D cell culture. *Biotechnol Bioeng*. 2009;103(4):655–663. doi:10.1002/bit.22361

39. Lad SP, Bagley JH, Karikari IO, et al. Cancer after spinal fusion: the role of bone morphogenetic protein. *Neurosurgery*. 2013;73(3):440–449. doi:10.1227/NEU.0000000000000018

40. Tannoury CA, An HS. Complications with the use of bone morphogenetic protein 2 (BMP-2) in spine surgery. *Spine J*. 2014;14(3):552–559. doi:10.1016/j.spinee.2013.08.060

41. Crevensten G, Walsh AJL, Ananthakrishnan D, et al. Intervertebral disc cell therapy for regeneration: mesenchymal stem cell implantation in rat intervertebral discs. *Ann Biomed Eng*. 2004;32(3):430–434. doi:10.1023/b:abme.0000017545.84833.7c

42. Gan Y, Dai K, Zhang P, Tang T, Zhu Z, Lu J. The clinical use of enriched bone marrow stem cells combined with porous beta-tricalcium phosphate in posterior spinal fusion. *Biomaterials*. 2008;29(29):3973–3982. doi:10.1016/j.biomaterials.2008.06.026

43. Logeart-Avramoglou D, Anagnostou F, Bizios R, Petite H. Engineering bone: challenges and obstacles. *J Cell Mol Med*. 2005;9(1):72–84. doi:10.1111/j.1582-4934.2005.tb00338.x

44. Jing W, Smith AA, Liu B, et al. Reengineering autologous bone grafts with the stem cell activator WNT3A. *Biomaterials*. 2015;47:29–40. doi:10.1016/j.biomaterials.2014.12.014

45. Minamide A, Yoshida M, Kawakami M, et al. The use of cultured bone marrow cells in type I collagen gel and porous hydroxyapatite for posterolateral lumbar spine fusion. *Spine*. 2005;30(10):1134–1138. doi:10.1097/01.brs.0000162394.75425.04

46. Werner BC, Li X, Shen FH. Stem cells in preclinical spine studies. *Spine J*. 2014;14(3):542–551. doi:10.1016/j.spinee.2013.08.031

47. Gupta MC, Theerajunyaporn T, Maitra S, et al. Efficacy of mesenchymal stem cell enriched grafts in an ovine posterolateral lumbar spine model. *Spine*. 2007;32(7):720–726; discussion 727. doi:10.1097/01.brs.0000258863.40984.32

48. Minamide A, Yoshida M, Kawakami M, et al. The effects of bone morphogenetic protein and basic fibroblast growth factor on cultured mesenchymal stem cells for spine fusion. *Spine*. 2007;32(10):1067–1071. doi:10.1097/01.brs.0000261626.32999.8a

49. Cinotti G, Patti AM, Vulcano A, et al. Experimental posterolateral spinal fusion with porous ceramics and mesenchymal stem cells. *J Bone Joint Surg Br*. 2004;86(1):135–142.

50. Kai T, Shao-qing G, Geng-ting D. In vivo evaluation of bone marrow stromal-derived osteoblasts-porous calcium phosphate ceramic composites as bone graft substitute for lumbar intervertebral spinal fusion. *Spine*. 2003;28(15):1653–1658. doi:10.1097/01.BRS.0000083168.37329.B4

51. Nakajima T, Iizuka H, Tsutsumi S, Kayakabe M, Takagishi K. Evaluation of posterolateral spinal fusion using mesenchymal stem cells: differences with or without osteogenic differentiation. *Spine*. 2007;32(22):2432–2436. doi:10.1097/BRS.0b013e3181573924

52. Wang T, Dang G, Guo Z, Yang M, Li Y. [Lumbar interbody fusion using autologous bone marrow mesenchymal stem cell-calcium phosphate ceramic composite in rhesus monkey]. *Zhonghua Wai Ke Za Zhi*. 2006;44(12):843–847.

53. Cuenca-López MD, Andrades JA, Gómez S, et al. Evaluation of posterolateral lumbar fusion in sheep using mineral scaffolds seeded with cultured bone marrow cells. *Int J Mol Sci*. 2014;15(12):23359–23376. doi:10.3390/ijms151223359

54. Bae HW, Zhao L, Kanim LE, Wong P, Marshall D, Delamarter RB. Bone marrow enhances the performance of rhBMP-2 in spinal fusion: a rodent model. *J Bone Joint Surg Am*. 2013;95(4):338–347. doi:10.2106/JBJS.K.01118

55. Miyazaki M, Zuk PA, Zou J, et al. Comparison of human mesenchymal stem cells derived from adipose tissue and bone marrow for ex vivo gene therapy in rat spinal fusion model. *Spine*. 2008;33(8):863–869. doi:10.1097/BRS.0b013e31816b45c3

56. Valdes M, Moore DC, Palumbo M, et al. rhBMP-6 stimulated osteoprogenitor cells enhance posterolateral spinal fusion in the New Zealand white rabbit. *Spine J*. 2007;7(3):318–325. doi:10.1016/j.spinee.2006.02.005

57. Cui Q, Ming Xiao Z Balian G Wang GJ. Comparison of lumbar spine fusion using mixed and cloned marrow cells. *Spine*. 2001;26(21):2305–2310. doi:10.1097/00007632-200111010-00003

58. Sheyn D, Rüthemann M, Mizrahi O, et al. Genetically modified mesenchymal stem cells induce mechanically stable posterior spine fusion. *Tissue Eng Part A*. 2010;16(12):3679–3686. doi:10.1089/ten.TEA.2009.0786

59. Crowley C, Wong JM-L, Fisher DM, Khan WS. A systematic review on preclinical and clinical studies on the use of scaffolds for bone repair in skeletal defects. *Curr Stem Cell Res Ther*. 2013;8(3):243–252. doi:10.2174/1574888x11308030009

60. Hasharoni A, Zilberman Y, Turgeman G, Helm GA, Liebergall M, Gazit D. Murine spinal fusion induced by engineered mesenchymal stem cells that conditionally express bone morphogenetic protein-2. *J Neurosurg Spine*. 2005;3(1):47–52. doi:10.3171/spi.2005.3.1.0047

61. Ammerman JM, Libricz J, Ammerman MD. The role of Osteocel Plus as a fusion substrate in minimally invasive instrumented transforaminal lumbar interbody fusion. *Clin Neurol Neurosurg*. 2013;115(7):991–994. doi:10.1016/j.clineuro.2012.10.013

62. Kerr EJ, Jawahar A, Wooten T, Kay S, Cavanaugh DA, Nunley PD. The use of osteo-conductive stem-cells allograft in lumbar interbody fusion procedures: an alternative to recombinant human bone morphogenetic protein. *J Surg Orthop Adv*. 2011;20(3):193–197.

63. Hostin R, O'Brien M, McCarthy I, et al. Retrospective study of anterior interbody fusion rates and patient outcomes of using mineralized collagen and bone marrow aspirate in multilevel adult spinal deformity surgery. *Clin Spine Surg*. 2016;29(8):E384–E388. doi:10.1097/BSD.0b013e318292468f

64. Kitchel SH. A preliminary comparative study of radiographic results using mineralized collagen and bone marrow aspirate versus autologous bone in the same patients undergoing posterior lumbar interbody fusion with instrumented posterolateral lumbar fusion. *Spine J*. 2006;6(4):405–411; discussion 411–412. doi:10.1016/j.spinee.2005.09.013

65. Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing healos with autograft. *Spine*. 2006;31(18):E636–E640. doi:10.1097/01.brs.0000232028.97590.12

66. Niu C-C, Tsai T-T, Fu T-S, Lai P-L, Chen L-H, Chen W-J. A comparison of posterolateral lumbar fusion comparing autograft, autogenous laminectomy bone with bone marrow aspirate, and calcium sulphate with bone marrow aspirate: a prospective randomized study. *Spine*. 2009;34(25):2715–2719. doi:10.1097/BRS.0b013e3181b47232

67. Vaccaro AR, Stubbs HA, Block JE. Demineralized bone matrix composite grafting for posterolateral spinal fusion. *Orthopedics*. 2007;30(7):567–570. doi:10.3928/01477447-20070701-06

68. Bansal S, Chauhan V, Sharma S, Maheshwari R, Juyal A, Raghuvanshi S. Evaluation of hydroxyapatite and beta-tricalcium phosphate mixed with bone marrow aspirate as a bone graft substitute for posterolateral spinal fusion. *Indian J Orthop*. 2009;43(3):234–239. doi:10.4103/0019-5413.49387

69. Taghavi CE, Lee K-B, Keorochana G, Tzeng S-T, Yoo JH, Wang JC. Bone morphogenetic protein-2 and bone marrow aspirate with allograft as alternatives to autograft in instrumented revision posterolateral lumbar spinal fusion: a minimum two-year follow-up study. *Spine*. 2010;35(11):1144–1150. doi:10.1097/BRS.0b013e3181bb5203

70. Odri GA, Hami A, Pomero V, et al. Development of a per-operative procedure for concentrated bone marrow adjunction in postero-lateral lumbar fusion: radiological, biological and clinical assessment. *Eur Spine J*. 2012;21(12):2665–2672. doi:10.1007/s00586-012-2375-z

71. Hart R, Komzák M, Okál F, Náhlík D, Jajtner P, Puskeiler M. Allograft alone versus allograft with bone marrow

concentrate for the healing of the instrumented posterolateral lumbar fusion. *Spine J*. 2014;14(7):1318–1324. doi:10.1016/j.spinee.2013.12.014

72. McAfee PC, Shucosky E, Chotikul L, Salari B, Chen L, Jerrems D. Multilevel extreme lateral interbody fusion (XLIF) and osteotomies for 3-dimensional severe deformity: 25 consecutive cases. *Int J Spine Surg*. 2013;7:e8–e19. doi:10.1016/j.ijsp.2012.10.001

73. Caputo AM, Michael KW, Chapman TM, et al. Extreme lateral interbody fusion for the treatment of adult degenerative scoliosis. *J Clin Neurosci*. 2013;20(11):1558–1563. doi:10.1016/j.jocn.2012.12.024

74. Tohmeh AG, Watson B, Tohmeh M, Zielinski XJ. Allograft cellular bone matrix in extreme lateral interbody fusion: preliminary radiographic and clinical outcomes. *ScientificWorldJournal*. 2012;2012:263637. doi:10.1100/2012/263637

75. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution® Viable Cellular Bone Matrix) in patients undergoing two-level anterior cervical discectomy and fusion. *J Orthop Surg*. 2017;12(1):67. doi:10.1186/s13018-017-0564-5

76. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel Plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine*. 2014;39(22):E1331–E1337. doi:10.1097/BRS.0000000000000557

77. Safety Study of Mesenchymal Stem Cells and Spinal Fusion. ClinicalTrials.gov.identifier: NCT01552707. Updated January 21, 2020. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT01552707

78. Prospective Study of Thoracolumbar Spinal Fusion Graft (BMAC). ClinicalTrials.gov.identifier: NCT02297256. Updated June 5, 2020. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT02297256

79. BMAC & Allograft vs BMP-2. ClinicalTrials.gov.identifier: NCT02924571. Updated November 9, 2020. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT02924571

80. Utilization of Autologous Mesenchymal Cells in Posterolateral Spinal Fusion in Degenerative Spine Disease (AMSC-DSD-001). ClinicalTrials.gov.identifier: NCT03827096. Updated January 18, 2020. Access January 5, 20201. https://clinicaltrials.gov/ct2/show/NCT03827096

81. Safety and Preliminary Efficacy Study of NeoFuse in Subjects Requiring Lumbar Interbody Fusion. ClinicalTrials.gov.identifier: NCT00996073. Updated June 29, 2020. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT00996073

82. Safety and Preliminary Efficacy Study of NeoFuse in Subjects Undergoing Multi-Level Anterior Cervical Discectomy. ClinicalTrials.gov.identifier: NCT01097486. Updated August 16, 2019. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT01097486

83. Human Amniotic Tissue-derived Allograft, NuCel, in Posterolateral Lumbar Fusions for Degenerative Disc Disease. ClinicalTrials.gov.identifier: NCT02070484. Updated September 28, 2018. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/results/NCT02070484

84. Osteocel Plus in Posterior Lumbar Interbody Fusion (PLIF). ClinicalTrials.gov.identifier: NCT00941980. Updated January 8, 2014. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT00941980

85. Osteocel Plus in Anterior Lumbar Interbody Fusion (ALIF). ClinicalTrials.gov.identifier: NCT00948831. Updated April 21, 2015. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT00948831

86. Osteocel Plus in Transforaminal Lumbar Interbody Fusion (TLIF). ClinicalTrials.gov.identifier: NCT00947583. Updated January 8, 2014. Accessed January 5, 2021. https://clinicaltrials.gov/ct2/show/NCT00947583

87. Trinity Evolution in Anterior Cervical Discectomy and Fusion (ACDF). ClinicalTrials.gov.identifier: NCT00941938. Updated April 8, 2014. Accessed January 5, 2021. https://www.clinicaltrials.gov/ct2/show/results/NCT00951938?view=results

Disclosures and COI: The authors received no funding for this study and report no conflicts of interest.

Corresponding Author: Hyun W. Bae, MD, Professor of Surgery, Department of Orthopaedic Surgery, Cedars Sinai Medical Center, Director of Education, Cedars Sinai Spine Center, 444 S. San Vicente Blvd, STE 950, Los Angeles, CA 90048. Phone: (310) 423-7340; Email: hyun.bae@cshs.org.

Published 0 Month 2021