REVIEW

The Controversy Surrounding Bone Morphogenetic Proteins in the Spine: A Review of Current Research

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Bone morphogenetic proteins have been in use in spinal surgery since 2002. These proteins are members of the TGF-beta superfamily and guide mesenchymal stem cells to differentiate into osteoblasts to form bone in targeted tissues. Since the first commercial BMP became available in 2002, a host of research has supported BMPs and they have been rapidly incorporated in spinal surgeries in the United States. However, recent controversy has arisen surrounding the ethical conduct of the research supporting the use of BMPs. Yale University Open Data Access (YODA†) recently teamed up with Medtronic to offer a meta-analysis of the effectiveness of BMPs in spinal surgery. This review focuses on the history of BMPs and examines the YODA research to guide spine surgeons in their use of BMP in spinal surgery.

INTRODUCTION

The frequency of spinal fusion procedures has significantly increased over the last 15 years, concurrent with the increasing popularity and use of osteobiologics to improve fusion. Lumbar and cervical fusion are the most common spine surgeries performed in the United States, with a combined annual rate of approximately 450,000 operations [1]. Although there have been numerous advances in surgical fixation techniques, nonunion still occurs in 10 percent to 15 percent of patients [2]. Despite advancements in materials and constructs, instrumentation remains only a temporizing measure — biologic processes are re-
quired to solidify an arthrodesis for long-term fusion success.

Successful fusion is contingent upon multiple host and graft characteristics. Low bone density, alcohol abuse, cigarette smoking, and long fusions are known risk factors for nonunion. To augment spinal fusion, bone graft is often used, and bone graft material must have sufficient osteoconductive and osteoinductive activities to promote healing. For healing to occur, osteogenic cells lay down new bone on an acceptable scaffolding (osteococonductivity) and stimulate differentiation of stem cells or osteoprogenitor cells into osteoblasts (osteoinduction). Given the critical role graft materials play in driving successful fusion, substantial research efforts have focused upon methods to augment this biologic process in order to achieve stable fusion in circumstances which otherwise would be unfeasible.

Autograft, most commonly taken from the iliac crest, remains the gold-standard graft material as it naturally possess both osteoinductive and osteoconductive properties and is associated with a low risk of infection and rejection. However, autograft is associated with several disadvantages, including increased procedure time, limited donor site availability, and donor site pain — with rates that vary significantly in the literature [3-7]. Allograft circumvents donor site morbidity but has been associated with increased rates of infection and rejection and has poor osteoconductive properties [8,9]. These limitations, combined with a nontrivial incidence of nonunion, have stimulated research into potential alternatives or improvements, including bone morphogenetic proteins (BMPs) and bone marrow aspirate (BMA). BMPs have traditionally been preferred over BMA as head-to-head studies have shown the superiority of BMPs in animal models [10].

BMPs are a unique group of cytokines with osteoinductive activity that belong to the transforming growth factor beta (TGF-β) super-family [11]. In 1965, Urist demonstrated the ability of BMPs to induce ectopic differentiation of cartilage and bone in rodents [12]. New bone production required for a solid fusion occurs as a result of a series of complex cascades involving osteoprogenitor cells and numerous osteogenic growth factors and competing effects of osteoclastic and osteoblastic cells. BMPs function through a variety of pathways that include the initiation of an increase in alkaline phosphatase and parathyroid hormone levels, as well as an increase in expression of osteocalcin (a marker for differentiated osteoblasts). When bound to transmembrane receptors on mesenchymal stem cells, BMPs induce differentiation into osteoprogenitor cells and form new bone.

Following the sequencing and cloning of BMP genes in the early 1990s, mass production of different BMPs became feasible. In the past decade, 20 individual human recombinant BMPs (rhBMPs) possessing various bone and cartilage stimulation characteristics have been identified [13]. Numerous trials and case series have since evaluated the use of these biologics as adjuvants or alternatives to autograft in spinal fusion. The results and complications of these studies have varied with regard to the specific subtype of rhBMP used, anatomic location of fusion, surgical approach, and the specific authors conducting the studies [4].

Early positive results subsequently led to the Food and Drug Administration (FDA) approval of rhBMPs for use in human surgery [3]. Although the FDA approved usage in the spine is limited to a specific carrier, approach, and range of levels, clinical off-label use of these compounds is rampant. In their 2009 study, Cahill et al. reported that by 2006, rhBMP was used in 25 percent of all fusion procedures in the United States and 40 percent of lumbar fusions [14]. While the liberal usage of rhBMPs has led to improved success rates for many procedures, serious, unforeseen complications have been encountered. Given that much of the off-label use of rhBMPs occurs outside the context of a clinical trial, the true incidence of bad outcomes is unknown. Furthermore, a majority of early studies were industry sponsored and performed by surgeons with high levels of investment in the success of BMP. As more independent re-
search has become available, it has been clear that the early studies were flawed in their research design and biased in their outcomes.

Much remains unknown about these powerful compounds. The risk of uncontrolled bone formation, BMP antibody formation, bone resorption, immunogenicity, urethrogenital complications, and malignancies have yet to be fully characterized. All of this on the recent backdrop of research controversy makes it difficult for clinicians to understand the proper use of BMP in a clinical setting. Therefore, we have undertaken to provide a review that examines the evidence for and against BMP, chronicles the controversy surrounding BMP, and provides insight into new research in a better effort to provide clinicians with a working framework in which to apply BMP in their clinical practices.

**CONTROVERSY IN COMPLICATION RATES WITH rhBMP-2 USE**

Despite BMPs’ widespread use, controversy about its effectiveness remains. Controversy surrounds conflicting studies on the success and failure of rhBMP-2 and whether it is superior to autograft from the iliac crest as well as underreporting of adverse side effects in early clinical trials of rhBMP-2 [15,16]. Starting in 2006, independent research groups started to report serious side effects of rhBMP-2 use, with complication rates ranging from 20 to 70 percent [4]. The most notable complications included retrograde ejaculation, seroma formation, bone overgrowth, osteolysis, and an increased risk of cancer. Serious side effects began arising in BMP usage in the cervical spine with large seroma formations placing pressure on airways and causing major postoperative morbidity and mortality complications. In June 2008, the FDA placed a warning on BMP use in the cervical spine due to severe dysphagia postoperatively [17].

Soon after the FDA warning, additional concerns arose with the *Wall Street Journal* reporting that Medtronic was under investigation by the federal government for off-label use of INFUSE (rhBMP-2) [18]. Additional lawsuits were also reported, claiming damages on behalf of the federal government with evidence from former Medtronic employees alleging illegal marketing, including “indictments paid to doctors to use INFUSE” [4]. Even worse, an early study showing the effective use of rhBMP-2 was retracted by the *Journal of Bone and Joint Surgery* after allegations of research misconduct and fraud by the author [19]. It was later reported that the author had significant financial ties to the manufacturer of rhBMP-2 [20]. To say the least, the reputation of rhBMP-2 was tarnished, and the clinical use of BMP was questioned.

In an effort to sort out the madness and provide true evidence-based medicine for the use of rhBMP-2, Medtronic agreed to team up with the Yale University Open Data Access Project (YODA). In this collaboration, Medtronic offered to provide all of its clinical data to the Yale investigators who would independently analyze and interpret the data of all known clinical trials of rhBMP-2. In June 2013, the first two systematic reviews and meta-analyses from this collaboration were reported in the *Annals of Internal Medicine* [15,16].

The reports had four important findings. First, the reports found that in aggregate, the current data does not show a significant improvement in fusion rates with rhBMP-2 as compared to autograft iliac crest bone graft. Second, both BMP-2 and iliac crest bone graft are associated with similar rates of retrograde ejaculation and neurological complications when used in anterior interbody lumbar fusion or posterolateral fusion. This seems to not be associated with the graft material but inherent to the patient population. Third, there is clear evidence that BMP-2 usage leads to high rates of complication in anterior cervical procedures and high rates of ectopic bone formation in posterior lumbar interbody procedures. And fourth, although there is a slight risk of cancer with the use of BMP-2, the absolute risk remains very small and therefore most likely clinically insignificant (Table 1).
The findings of the Yale University Open Data Access project mark an important new milestone in clinical research by combining the resources of an invested company with the independent review of an academic institution. In light of these findings, we have undertaken to offer both the history of BMPs’ development alongside recent YODA evidence to offer clinical practice guidelines for five major spinal surgery applications in the following sections.

**TYPES OF BMPs**

Although 20 different BMPs have been discovered, only BMP-2 is currently FDA approved and available in recombinant form for use in human spine surgery. BMP-7, or OP-1, was previously given a Humanitarian Device Exemption and ultimately was not approved by the FDA. Additionally, growth differentiation factor 5 (GDF-5), a member of the TGF-β superfamily and closely related to BMPs, has also been preliminarily tested in humans.

**rhBMP-2**

In 1997, a prospective randomized control trial evaluating the use of rhBMP-2 was conducted under an FDA-approved investigational device exemption (IDE) [21]. In this pilot study, the rhBMP-2 (Genetics Institute, Cambridge, MA) was delivered on an absorbable collagen sponge (ACS) carrier (Integra Life Sciences, Plainsboro, NJ) and placed into a titanium interbody fusion device (LT-Cage; Medtronic Sofamor Danek). The authors concluded that fusion not only occurred, but occurred more reliably in the patients who received rhBMP-2 [21]. In a multicenter follow-up study, InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, TN) and autograft were compared for clinical and radiographic fusion following anterior lumbar interbody fusion (ALIF). Successful radiographic fusion was achieved in 94.5 percent of the experimental group versus 88.7 percent in the control group at 2-year follow-up. In the control group, 32 percent of patients reported graft site discomfort and 16 percent were bothered by its appearance at 2-year follow-up [3]. Citing this work as a pivotal study, Medtronic was granted FDA approval in 2003 for the use of rhBMP-2 in conjunction with the LT-CAGE™ Lumbar Tapered Fusion Device for ALIF. Contraindications included pregnancy, material allergy, infection, and previous tumor near the site of implantation.

Although only specifically tested and FDA approved for ALIF, off-label, or “physician-directed application,” of InFUSE is widespread. Publication of initial clinical results indicating superior fusion rates compared to autograft and no complications encouraged many surgeons to begin using rhBMP-2 off-label — initially restricted to patients with known risk factors for nonunion and later with more generalized use. It is easy to see why as patients with diabetes, hypothyroidism, or a history of smoking have been shown to have reduced fusion rates [22]. The attractiveness of augmenting these risk factors brought

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**Table 1. Summary of Yale Open Access Study.**

1. No difference in fusion rates between rhBMP-2 and autograft iliac crest bone graft

2. Both rhBMP-2 and iliac crest bone graft are associated with similar rates of retrograde ejaculation and neurological complications when used in anterior interbody lumbar fusion or posterolateral fusion

3. There is clear evidence that rhBMP-2 usage leads to high rates of complication in anterior cervical procedures and high rates of ectopic bone formation in posterior lumbar interbody procedures

4. Although there is a slight increased relative risk of cancer with the use of BMP-2, the absolute risk remains very small and therefore most likely clinically insignificant
many surgeons onboard with BMP use. In the United States alone, BMP use in spinal fusions increased from 0.7 percent in 2002 to 25 percent in 2006, with Medtronic reporting nearly $400 million dollars in sales in 2012 [4,17].

**Anterior Lumbar Interbody Fusion**

In their 2002 landmark study, Burkus et al. showed that patients treated with rhBMP-2 with an LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, TN, USA) had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, median time to return to work, and fusion rates at 6, 12, and 24 months, as well as Oswestry Disability Index (OSI) scores and Physical Component and Pain Index scores at 3, 6, 12, and 42 months compared to patients treated with iliac crest bone graft (ICBG) [3]. Although this study was able to prove non-inferiority, it lacked sufficient statistical power to prove fusion superiority of rhBMP-2 versus autograft. In a follow-up study, combining datasets from two additional clinical trials, a 24-month fusion success rate of 94.4 percent (201/213) for rhBMP-2 and 89.4 percent (252/282) for autograft was found, showing statistical superiority of rhBMP-2 with respect to fusion [23]. At 6 years, 98 percent of the study group showed radiographic fusion and 79 percent had an improvement in the OSI score of > 15 points [24].

In two related, prospective FDA-approved Investigation Device Exemption (IDE) studies, Burkus et al. also evaluated the use of rhBMP-2 in ALIF with structural cortical allografts and the INTER FIX Threaded Fusion Device (Medtronic Sofamor Danek, Memphis, TN, USA) versus ICBG [23,25]. Patients treated with rhBMP-2 had superior clinical and radiographic outcomes compared with patients who had received ICBG. The study group was found to have significantly higher rates of radiographic fusion than the control group at all time-points with a difference of 99 percent and 76 percent, (p < 0.001) respectively at 2 years. Similarly, the authors also found that the INTER FIX device packed with rhBMP-2 led to improved ODI outcomes, improved radiographic fusion rate, and improved rate of return to work compared to ICBG controls.

In a non-industry sponsored, prospective cohort study in 2006, investigators evaluated the outcomes for patients undergoing ALIF with femoral ring allografts (FRAs) with ICBG and rhBMP-2. In contrast to Burkus et al. [25], the study found that rhBMP-2 paradoxically caused a trend toward higher rates of nonunion (56 percent) compared to ICBG (36 percent) as well as aggressive resorption of the FRAs [26]. One year later, an industry-sponsored trial using FRAs with pedicle screw fixation reported statistically superior clinical outcomes and fusion rates at all follow-up time points for patients with rhBMP-2 added to the FRAs (but no comparison to FRAs with ICBG) [27].

Although rhBMP-2 has been shown to significantly improve fusion rates in ALIF and early studies revealed no increased rate of rhBMP-2 related complications, more recent studies have revealed an array of complications. Multiple reports and trials have reported significant endplate resorption, osteolysis, and graft subsidence with rhBMP-2 used in ALIF [28-30]. Although many reports denied resultant clinical symptoms or effect of fusion, Carragee et al. reported a higher reoperation rate in patients treated with rhBMP-2, principally attributed to graft subsidence complications [4]. rhBMP-2 has also been implicated in increased rates of retrograde ejaculation (RE) following ALIF. Baseline rates of RE in ALIF without rhBMP-2 have been established to be less than 1 percent [31-33], but rates of RE with rhBMP-2 have been shown to be statistically significantly higher at 6 to 7 percent [34,35].

In spite of varying evidence, ALIF is the only FDA-approved application of rhBMP-2. Findings from YODA suggest no difference between rhBMP-2 and autograft iliac crest. However, iliac crest bone graft requires an additional surgical site operation. When autograft is not available or an additional procedure is not desired, rhBMP-2 is
a reliable alternate. YODA found retrograde ejaculation and neurological complications to be equal in both autograft and BMP augmented ALIF surgeries (Table 2) [16].

**Posterolateral Lumbar Fusion**

Two large, prospective randomized multicenter trials have evaluated the use of rhBMP-2 in posterolateral lumbar fusion (PLF). The first, conducted in 2002, compared three groups of patients with single-level degenerative disc disease undergoing PLF: autograft with pedical screw fixation, rhBMP-2 with pedical screw fixation, and rhBMP-2 without pedical screw fixation [36]. At 17 months follow-up, the fusion rate in the autograft group was 40 percent compared to a 100 percent fusion rate in the patients who received rhBMP-2 (with or without internal fixation). These authors demonstrated that rhBMP-2 at a dose of 20 mg per side can achieve PLF at a higher rate than iliac crest autograft alone.

The second study in 2009 compared the use of autograft and higher dose rhBMP-2 (AMPLIFY rhBMP-2 Matrix; Medtronic Sofamor Danek) in single-level, instrumented PLF. This study reported an 89 percent fusion rate in the autograft group (n = 224) and a 96 percent fusion rate in the rhBMP-2/CRM group (n = 239) at 2 years follow-up (p = 0.014). Clinical outcome measures were similar between the two groups, and the reoperation rate was significantly higher in the autograft group (16 percent vs. 8 percent, P = 0.015). Of the patients in the autograft group, 60 percent reported donor site iliac crest pain at 2 years follow-up [37]. Several smaller studies have found similar results of superior fusion rates with the use of rhBMP-2 in PLF compared to ICBG with minimal complications [22,38-41].

Concerns with the use of rhBMP-2 in PLF include risk for complications from heterotopic ossification and post-surgical edema and seroma formation. A study in 2008 reported a case of post-operative psoas ossification with subsequent development of pain along the iliac wing, groin, and greater trochanter 3 months after surgery [42]. In a 2010 retrospective review of 130 patients undergoing PLF with rhBMP-2, authors reported a 4.6 percent incidence of sterile seromas requiring surgical exploration (no data

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**Table 2. Recommendations for use of rhBMP-2.**

| Procedure                           | Recommendation                                                                 |
|-------------------------------------|--------------------------------------------------------------------------------|
| **Anterior Lumbar Interbody Fusion (ALIF)** | No difference between rhBMP-2 and ICBG. However, iliac crest bone graft requires additional surgical site operation. When autograft is not available or procedure is not desired, rhBMP-2 is a reliable alternate. Retrograde ejaculation and neurological complications are equal with both rhBMP-2 and ICBG. |
| **Anterior Cervical Fusion**         | An FDA warning has been issued to not use rhBMP-2 in the anterior cervical spine due to inflammation causing severe dysphagia and airway compromise. |
| **Posterolateral Fusion (PLF)**     | No difference between rhBMP-2 and ICBG. However, iliac crest bone graft requires additional surgical site operation. When autograft is not available or procedure is not desired, rhBMP-2 is a reliable alternate. |
| **Posterior Interbody Lumbar Fusion (PLIF)** | Use of rhBMP-2 has been associated with high rates of ectopic bone formation leading to neurological compromise. ICBG is preferred. |
| **Transforaminal Interbody Fusion (TLIF)** | Use of rhBMP-2 has been associated with seroma formation and neurological compromise. Further evidence is needed, but judicious use of rhBMP-2 is recommended due to complications. |
for seroma incidence in ICBG group for comparison) [43].

In accordance with the large body of positive study results and limited published reports of serious complications, Medtronic applied for FDA approval of higher dose rhBMP-2, AMPLIFY, for application in posterolateral spine fusion. In March 2011, the application for FDA was rejected due to concerns about potential increased risk of malignancy [4].

Recent YODA evidence shows that while there may be a small increased relative risk of malignancy with the use of rhBMP-2 in PLF, the absolute risk remains very low and therefore clinically insignificant. Findings show no difference between rhBMP-2 and ICBG in PLF and also show higher rates of ectopic bone formation in PLF procedures. Therefore, rhBMP-2 may be useful when autograft is not available in PLF surgery, and the benefits outweigh the risks of ectopic bone formation (Tables 1 and 2) [16].

**Posterior Lumbar Interbody Fusion**

Multiple clinical studies have shown positive fusion results using rhBMP-2 in posterior lumbar interbody fusion (PLIF), but have also identified a high propensity for the development of heterotopic bone formation. When comparing PLIF with rhBMP-2 in two INTER FIX cages (Medtronic Sofamor Danek, Memphis, TN) versus autograft, fusion rates were 92.3 percent for the rhBMP-2 group versus 77.8 percent for the control group, with no significant difference in clinical improvement between the two groups [5]. Although the findings show favorable results, ectopic bone formation away from the PLIF cages in preliminary CT imaging caused the investigators to suspend recruitment in the study. There was statistically significantly more extradiscal bone formation in the BMP group (75 percent; 24 of 32 patients) compared with the control group (13 percent; 4 of 31 patients). Despite the statistical significance, there was no relationship found between this bone formation and clinical symptoms.

Follow-up studies found a similar higher incidence of asymptomatic heterotopic bone formation in patients treated with rhBMP-2 [44,45]. A case report also showed the formation of ectopic bone following PLIF with rhBMP-2 that led to neurologic impairment and subsequent revision surgery [46]. However, some authors have shown high fusion rates with no incidence of heterotopic bone formation [46,47]. In addition to heterotopic bone formation, cage migration following PLIF with rhBMP-2 has been described [29]. Meta-analysis data from YODA suggests clinicians should avoid rhBMP-2 use in PLIF procedures due to concern about ectopic bone formation and neurological compromise (Table 2) [16].

**Transforaminal Lumbar Interbody Fusion**

The off-label use of rhBMP-2 in transforaminal lumbar interbody fusion (TLIF) is becoming increasingly common. Although there are no prospective, randomized studies evaluating the use of rhBMP-2 in TLIF, results from several retrospective studies support its clinical efficacy. In a series of 74 patients who underwent single and multiple-level TLIF with rhBMP-2 applied on an ACS and combined with allograft or autograft, all patients had developed radiographic fusion at 10 months follow-up [48]. No complications or adverse reactions attributed specifically to the rhBMP-2 were reported, although two patients had persistent postoperative radiculitis. A similar study retrospectively reviewed clinical and radiographic outcomes in 48 patients who underwent single-level TLIF using rhBMP-2 [49]. Radiographic fusion was achieved in 95.8 percent of patients, improvement in symptoms was reported in 83 percent of patients, and satisfaction with surgical outcome was reported in 84 percent of patients. However, 27.1 percent of patients had one or more complications, including transient postoperative radiculitis (8/48), vertebral osteolysis (3/48), nonunion (2/48), and symptomatic ectopic bone formation (1/48).

Complications with rhBMP-2 used in TLIF have been reported in several case series and reports. Postoperative radiculitis has been a complication of TLIF surgery with rhBMP-2, with rates as high as 20 percent
being reported [50]. Also, ectopic bone formation following TLIF using rhBMP-2 has been reported in many case reports, with cases of symptomatic, delayed neural compression in patients following TLIF using rhBMP-2 [51]. Finally, vertebral osteolysis has been reported to occur in 5.8 to 7.4 percent [50,52]. Although the osteolytic defects filled spontaneously in most of these patients, a small subset of these patients were later found to have osteomyelitis that required revision debridement and reconstruction.

Given the variety and frequency of complications associated with rhBMP-2 use in TLIF, additional caution should be exercised in implementing BMP use in TLIF procedures. Further evidence is needed in order to make practice guidelines, and in the meantime, judicious use of rhBMP-2 in TLIF procedures is recommended due to complications (Table 2) [16].

**Anterior Cervical Fusion**

The efficacy of rhBMP-2 to promote fusion in the cervical spine has been well documented in numerous clinical studies. In their prospective, randomized, FDA-approved pilot trial, Baskin showed a 100 percent fusion rate and no increase in complications when using rhBMP-2 versus autograft within an allograft ring [53]. In subsequent studies with larger sample sizes and less contained doses of rhBMP-2, the efficacy of achieving solid fusion was further supported with 100 percent fusion rates when rhBMP-2 was added to absorbable collagen sponges, PEEK cages, bioabsorbable spacers, and allograft rings. Despite the common finding that rhBMP-2 was equivalent or superior to autograft in promoting fusion, there emerged a clear increase in the incidence of soft-tissue related complications.

In 2006, authors reported high complication rates in 151 patients who underwent anterior cervical fusion using high-dose rhBMP-2 (2.1mg/level) [54]. Overall, 23.2 percent (35/151) experienced complications, including 15 patients diagnosed with a hematoma (of whom eight were surgically evacuated) and 13 patients with either a prolonged hospital stay or hospital readmission because of swallowing/breathing difficulties or dramatic swelling without hematoma. Although there was no study group for comparison, the authors concluded that rate of complications differed from their significant surgical experience in anterior cervical fusion without rhBMP-2. Two years later, another report of soft tissue swelling emerged in a series of 200 patients who underwent single- or multilevel anterior cervical fusion with PEEK spacers filled with an ACS impregnated with varying doses of rhBMP-2 [55]. During the study, they decreased the dose of rhBMP-2 twice. The first reduction from 2.1mg to 1.05mg/level was due to an observation of asymptomatic excess bony formation. The second reduction from 1.05mg to 0.7mg/level was due to the authors noting anecdotal reports of dysphagia with higher concentration. The authors did not find a significant difference in dysphagia or swelling between the study group and historical controls, and there were not a sufficient number of patients to compare complications between patients receiving the different doses of rhBMP-2. However, the authors of this study agreed with the conclusions of other studies suggesting a relationship between complication rates and increased rhBMP-2 concentration.

Although there is a breadth of literature documenting high complication rates with rhBMP-2 usage in anterior cervical surgery, it is difficult to assess true risk given the design of most of the published studies. Specifically, surgical technique, instrumentation, concentration of rhBMP-2, and number of levels fused are not controlled between studies. Furthermore, in multiple instances, authors cite that their use of rhBMP-2 was due to their patients having known risk factors for pseudarthrosis. Most importantly, the only prospective, randomized trial evaluating rhBMP-2 in anterior cervical fusion found that there was no increased rate of complication. However, in light of the serious adverse events reported in the literature, the FDA released a public health notification warning of the life-threat-
ening risks associated with rhBMP-2 in anterior cervical fusion and recommended that "practitioners either use approved treatments or consider enrolling as investigators in approved clinical studies" [17]. Currently, clinical recommendations are to avoid the use of rhBMP-2 in anterior cervical fusion (Table 2) [16].

**OP-1**

OP-1, also known as BMP-7, is another member of the TGF-β family that has received significant investigation for clinical use in the spine. Initial animal studies of spinal fusion rates suggested OP-1 was a promising new BMP. In 2000, a study in a New Zealand White Rabbit model showed a 100 percent intertransverse process lumbar fusion rate with OP-1 versus a 63 percent fusion rate for autograft alone [56]. Two years later, additional authors showed a superior bone formation rate with OP-1 versus autograft alone in a Canine model of posterolateral arthrodesis [57].

These early animal studies led Vaccaro et al. to perform safety and efficacy trials of OP-1 in patients with grade I or II spondylolisthesis. The safety and efficacy of OP-1 was first assessed in 2003 in a 12-patient study in which the authors showed a 70 percent rate of bridging bone formation and an 89 percent clinical success rate at 1-year follow-up when OP-1 was used in conjunction with autograft alone [58,59]. The authors then examined the efficacy of OP-1 versus autograft alone in a study examining 36 patients with neurogenic claudication and spondylolisthesis who underwent decompression laminectomy and one-level uninstrumented PLF [60]. Successful radiographical fusion was found in 74 percent of OP-1 patients versus 60 percent of patients with autograft alone. These two studies led to an FDA Humanitarian Device Exemption approval in 2004 to allow up to 4,000 patients a year to receive OP-1 for revision PLF in patients who suffer from factors that complicate healing or for whom autograft harvest is not feasible.

Based on the success of the early pilot studies, Vaccaro et al. undertook a large, prospective, randomized, controlled multicenter clinical trial of 295 patients to demonstrate the noninferiority of OP-1 versus autograft in patients with spondylolisthesis undergoing one-level posterior decompression and uninstrumented posterolateral intratransverse process arthrodesis [61]. The investigators hypothesized that OP-1 would prove as efficacious as autograft alone, and therefore serve as a potential replacement, circumventing the morbidity of an autograft procedure. However, the study results showed superior results for autograft versus OP-1, with bone formation in 51.9 percent of OP-1 patients compared to 73.5 percent of autograft patients on plain films at 2-year follow-up. The authors questioned if the result was due to the insensitivity of plain films to assess for bridging bone formation and decided to add an additional 3-year follow-up with a CT scan for 257 of the original 295 patients. CT results at 3 years again suggested the superiority of autograft, with 36 percent of autograft patients showing evidence of bridging bone formation versus 26 percent of OP-1 patients [62].

The findings of the large Vaccaro et al. study ultimately lead to the FDA rejection of Pre-Market Approval of OP-1 in April 2009. While this has been a significant setback in the clinical use of OP-1, studies are ongoing to find an optimal dosage and delivery system for OP-1 in the future.

**GDF-5**

GDF-5, also known as cartilage-derived morphogenetic protein-1 or BMP-14, is under development in combination with a specific collagen carrier called Healos (DePuy Spine, Inc., Raynham, MA), a cross-linked type I collagen with hydroxyapatite coating that serves as a vehicle for cellular attachment and vascular ingrowth. The collagen carrier is further soaked in bone marrow aspirate during preparation to provide adequate stem cells for bone growth. When used together with bone marrow aspirate, Healos has shown promising results in terms of fusion in both animal and human studies. Animal studies have shown that Healos has strong potential for clinical benefit. A
A pre-clinical study using GDF-5 0.5 and 1.0 mg/cc Healos doses showed abundant bone formation and 100 percent fusion in a New Zealand Rabbit model [63]. A similar study compared Healos and autograft in a posterolateral instrumented spinal fusion in sheep and found 100 percent fusion in both the Healos and autograft groups [64]. These early animal study results, combined with many others, propelled Healos into clinical testing.

Clinical testing of Healos and bone marrow aspirate are ongoing. However, a few successful clinical studies have been promising. A trial of Healos was conducted in 2006, in which the authors compared 50 spinal fusion operations using Healos to 50 matched controls using autograft alone [65]. For posterolateral lumbar fusions, there were equivalent radiologic fusion rates for the two groups with no significant difference in the subjective and objective clinical outcomes. There were no lasting complications associated with Healos use compared with a 14 percent persisting donor site complication rate in the autograft patients. Similar positive results have been shown with Healos in ACDF [62], TLIF [63], and PLF [64] procedures [19,66,67].

These early clinical trials suggest Healos has potential to have great clinical benefit in spinal fusion procedures. However, it remains to be seen if Healos will have the same effect as other BMPs. In a study comparing Healos and INFUSE (BMP-2), Krawattanapong et al. showed that INFUSE was far superior to Healos in their posterolateral lumbar spine fusion model in New Zealand White Rabbits [10]. In the study, 100 percent (12/12) of rabbits had successful fusion with INFUSE, while 0 percent (0/12) had successful fusion with Healos. The data on Healos should be questioned, as the fusion rates for Healos are not similar to other reported fusion rates in rabbits, but the study highlights the need to compare Healos with other BMPs.

The animal and clinical studies on Healos suggest it has great clinical potential in spinal fusion; however, the data is limited and more research must be undertaken to identify the risks and benefits of using Healos in spinal fusion techniques. Additionally, studies have not been undertaken to compare Healos to other BMPs, which will be essential in determining the clinical efficacy of Healos.

**SUMMARY AND FUTURE DIRECTIONS**

Recent research calls into question the ultimate fate of rhBMP-2 in its superiority to autograft from the iliac crest. The Yale University Open Access Project’s published studies offer important insight for clinicians in their determination to use BMPs in spinal surgery. The authors of this study suggest judicious use of rhBMP-2 in spinal surgery. rhBMP-2 will likely hold an important role in future spinal surgery, as it offers augmentation options when autograft from the iliac crest is either unavailable or the side effects of the procedure are unwanted by the patients (Table 2). However, it is most likely that recent findings will temper the widespread use of BMP in a majority of spinal fusions where iliac bone graft is a reliable option.

In addition, ongoing research in spinal fusion augmentation offers many alternates to BMP-2 usage. Most promising is the ever-increasing use of bone marrow aspirate to augment spinal fusion. Recent studies have described the use of bone marrow aspirate derived from the vertebral body, which is already accessed during spinal fusion procedures with instrumentation, resulting in augmented fusion rates and no donor site morbidity [68-70]. Additionally, further studies with GDF-5 may provide safer, more efficacious osteobiologics for certain spinal surgeries.

In conclusion, surgeons should be aware that aggregate data analysis from the Yale University Open Access Project does not suggest that rhBMP-2 is superior to autograft iliac bone graft. Additionally, surgeons should be wary of use of rhBMP-2 in the cervical spine, aware of complications of ectopic bone growth in posterolateral fusion, and judicious when using BMP in transforaminal interbody fusion due to
seroma formation. Overall, rhBMP-2 remains a viable option for complex cases when autograft iliac bone graft is not desirable or available. Further research and evaluation of the clinical data is ongoing and will likely further provide evidence for the use of BMPs in spinal fusion. Spinal surgeons should remain aware of current research in order to practice current evidence-based medicine.

REFERENCES

1. Resnick DK. Evidence-based spine surgery. Spine (Phila Pa 1976). 2007;32(11):S15-9.
2. Hsu WK, Wang JC. The use of bone morphogenetic protein in spine fusion. Spine J. 2008;8(3):419-25.
3. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech. 2002;15(5):337-49.
4. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011;11(6):471-91.
5. Haid RW Jr, Branch CL Jr, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. Spine J. 2004;4(5):527-38; discussion 38-9.
6. Mroz TE, Wang JC, Hashimoto R, Norvell DC. Complications Related to Osteobiologics Use in Spine Surgery A Systematic Review. Spine. 2010;35(9):S86-104.
7. Smoljanovic T, Bojanic I, Pecina M. The Use of Bone Morphogenetic Protein in Lumbar Spine Surgery. J Bone Joint Surg Am. 2009;91A(8):2045-6.
8. Agarwal R, Williams K, Umscheid CA, Welch WC. Osteoinductive bone graft substitutes for lumbar fusion: a systematic review Clinical article. J Neurosurg Spine. 2009;11(6):729-40.
9. Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG, et al. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes. J Neurosurg Spine. 2005;2(6):733-6.
10. Krawiwanntanon C, Boden SD, Louis-Ugbo J, Attallah E, Barnes B, Hutton WC. Comparison of Heelas/bone marrow to INFUSE(rhBMP-2/ACS) with a collagen-ceramic sponge bulking agent as graft substitutes for lumbar spine fusion. Spine. 2005;30(9):1001-7.
11. Zlotolow DA, Vaccaro AR, Salamon ML, Albert TJ. The role of human bone morphogenetic proteins in spinal fusion. J Am Acad Orthop Surg. 2000;8(1):3-9.
12. Carlisle E, Fischgrund JS. Bone morphogenetic proteins for spinal fusion. Spine J. 2005;5(6 Suppl):240S-9S.
13. Axelrad TW, Einhorn TA. Bone morphogenetic proteins in orthopaedic surgery. Cytokine Growth Factor Rev. 2009;20(5-6):481-8.
14. Cahill KS, Chi JH, Day A, Claus EB. Prevalence, Complications, and Hospital Charges Associated With Use of Bone-Morphogenetic Proteins in Spinal Fusion Procedures. JAMA. 2009;302(1):58-66.
15. Fu R, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. Ann Intern Med. 2013;158(12):890-902.
16. Simmonds MC, Brown JV, Heirs MK, Higgins JP, Mannion RJ, Rodgers MA, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. Ann Intern Med. 2013;158(12):877-89.
17. Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. US Food and Drug Administration [Internet]. 2008. [cited 25 Jul 2013]. Available from: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm.
18. Carrey-Rou J, McGinty T. Medtronic Surgeons Held Back, Study Says. Wall Street Journal. June 29, 2011.
19. Carter JD, Swearingen AB, Chaput CD, Rahm MD. Clinical and radiographic assessment of transforaminal lumbar interbody fusion using HEALOS collagen-hydroxyapatite sponge with autologous bone marrow aspirate. Spine J. 2009;9(6):434-8.
20. Armstrong D. Medtronic paid the surgeon accused of falsifying study nearly $800,000. Wall Street Journal. June 18, 2009.
21. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages - Definitive evidence of osteoinduction in humans: A preliminary report. Spine. 2000;25(3):376-81.
22. Glassman SD, Dimar JR, Burkus K, Hardacker JW, Pryor PW, Boden SD, et al. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. Spine. 2007;32(15):1693-8.
23. Burkus JK, Heim TE, Gornet MF, Zdeblick TA. Is INFUSE bone graft superior to autograft bone? An integrated analysis of clinical trials using the LT-ÇAGE lumbar tapered fusion device. J Spinal Disord Tech. 2003;16(2):113-22.
24. Burkus JK, Gornet MF, Shuler TC, Kleeman TJ, Zdeblick TA. Six-Year Outcomes of Anterior Lumbar Interbody Arthrodesis with Use of Interbody Fusion Cages and Recombinant Human Bone Morphogenetic Protein-2. J Bone Joint Surg Am. 2009;91(5):1181-9.
25. Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of rhBMP-2 in combination with structural cortical allografts: Clinical and radiographic outcomes in anterior lumbar spinal surgery. J Bone Joint Surg Am. 2005;87(6):1205-12.

26. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. graft resorption with the use of bone morphogenetic protein: Lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. Spine. 2006;31(10):E277-84.

27. Slosar PJ, Josey R, Reynolds J. Accelerating lumbar fusions by combining rhBMP-2 with allograft bone: a prospective analysis of intervertebral fusion rates and clinical outcomes. Spine J. 2007;7(3):301-7.

28. Hansen SM, Sasso RC. Resorptive response of rhBMP2 simulating infection in an anterior lumbar interbody fusion with a femoral ring. J Spinal Disord Tech. 2006;19(2):130-4.

29. Vaidya R, Sethi A, Bartol S, Jacobson M, Coe C, Craig JG. Complications in the Use of rhBMP-2 in PEEK Cages for Intervertebral Spinal Fusions. J Spinal Disord Tech. 2008;21(8):557-62.

30. Vaidya R, Weir R, Sethi A, Meisterling S, Hakeos W, Wybo CD. Intervertebral fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence. J Bone Joint Surg Am. 2007;89(3):342-5.

31. Kang B-U, Choi W-C, Lee S-H, Jeon SH, Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: Lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. Spine. 2006;31(10):E277-84.

32. Sasso RC, Best NM, Mummaneni PV, Reilly J, Burkus JK, Sandhu HS, Gornet MF, Longley MC. Use of bone morphogenetic protein: Lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. Spine. 2006;87(6):1205-12.

33. Pradhan BB, Bae HW, Dawson EG, Patel VV, Delamarter RB. Graft resorption with the use of bone morphogenetic protein: Lessons from anterior lumbar interbody fusion using femoral ring allografts and recombinant human bone morphogenetic protein-2. Spine. 2006;31(10):E277-84.

34. Carragee EJ, Mitsunaga KA, Hurwitz EL, Scuderl GI. Retrograde ejaculation after anterior lumbar interbody fusion using a titanium cylindrical threaded fusion device. Spine. 2004;29(2):113-21.

35. Jarrett CD, Heller JG, Tsai L. Anterior Exposure of the Lumbar Spine With and Without an “Access Surgeon” Morbidity Analysis of 265 Consecutive Cases. J Spinal Disord Tech. 2009;22(8):559-64.

36. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenic protein-2 to achieve posteroilateral lumbar spine fusion in humans - A prospective, randomized clinical pilot trial - 2002 Volvo Award in clinical studies. Spine. 2002;27(23):2662-73.

37. Carreon LY, Glassman SD, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, et al. RhBMP-2 Versus Iliac Crest Bone Graft for Lumbar Spine Fusion in Patients Over 60 Years of Age A Cost-Utility Study. Spine. 2009;34(3):238-43.

38. Dawson E, Bae HW, Burkus JK, Stambough JL, Glassman SD. Recombinant Human Bone Morphogenetic Protein-2 on an Absorbable Collagen Sponge with an Osteoconductive Bulking Agent in Posteroilateral Arthrodesis with Instrumentation A Prospective Randomized Trial. J Bone Joint Surg Am. 2009;91(7):1604-13.

39. Glassman SD, Carreon LY, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, et al. RhBMP-2 Versus Iliac Crest Bone Graft for Lumbar Spine Fusion. Spine. 2008;33(26):2843-9.

40. Hamilton DK, Smith JS, Reames DL, Williams BJ, Shaffrey CI. Use of recombinant human bone morphogenetic protein-2 as an adjunct for instrumented posterior arthrodesis in the occipital cervical region: An analysis of safety, efficacy, and dosing. J Craniovertebr Junction Spine. 2010;1(2):107-12.

41. Lee KB, Taghavi CE, Hsu MS, Song KJ, Yoo JH, Keorochana G, et al. The efficacy of rhBMP-2 versus autograft for posteroilateral lumbar spine fusion in elderly patients. Eur Spine J. 2010;19(6):924-30.

42. Brower RS, Vickroy NM. A case of psoas ossification from the use of BMP-2 for posteroilateral fusion at L4-L5. Spine. 2008;33(18):E653-5.

43. Garrett MP, Kakarla UK, Porter RW, Sonntag VKH. Formation of Painful Seroma and Edema After the Use of Recombinant Human Bone Morphogenetic Protein-2 in Posteroilateral Lumbar Spine Fusions. Neurosurgery. 2010;66(6):1044-9.

44. Joseph V, Rampersaud YR. Heterotopic bone formation with the use of rhBMP2 in posterominimal access interbody fusion - A CT analysis. Spine. 2007;32(25):2885-90.

45. Meisel HJ, Schnoring M, Hohaus C, Minkus Y, Beier A, Ganey T, et al. Posterior lumbar interbody fusion using rhBMP-2. Eur Spine J. 2008;17(12):1735-44.

46. Wong DA, Kumar A, Jatana S, Ghiselli G, Wong K. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). Spine J. 2008;8(6):1011-8.

47. Geibet PT, Boyd DL, Slabisak V. The Use of Recombinant Human Bone Morphogenetic Protein in Posterior Interbody Fusions of the Lumbar Spine A Clinical Series. J Spinal Disord Tech. 2009;22(5):315-20.

48. Villavicencio AT, Burneikeyi S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. Spine. 2009;34(3):238-43.
morphogenetic protein-2. J Neurosurg Spine. 2005;3(6):436-43.

49. Rihn JA, Makda J, Hong J, Patel R, Hilibrand AS, Anderson DG, et al. The use of rhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis. Eur Spine J. 2009;18(11):1629-36.

50. Rihn JA, Patel R, Makda J, Hong J, Anderson DG, Vaccaro AR, et al. Complications associated with single-level transforaminal lumbar interbody fusion. Spine J. 2009;9(8):623-9.

51. Chen NF, Smith ZA, Stiner E, Armin S, Balseiro S, Nottmeier EW. Vertebral osteolysis originating from subchondral cyst end plate defects in transformaminal lumbar interbody fusion using rhBMP-2. Report of two cases. Spine J. 2010;10(7):e6-10.

52. Balseiro S, Nottmeier EW. Vertebral osteolysis originating from subchondral cyst end plate defects in transformaminal lumbar interbody fusion using rhBMP-2. Report of two cases. Spine J. 2010;10(7):e6-10.

53. Baskin DS, Ryan P, Sonntag V, Westmark R, Chen NF, Smith ZA, Stiner E, Armin S, Balseiro S, Nottmeier EW. Vertebral osteolysis originating from subchondral cyst end plate defects in transformaminal lumbar interbody fusion using rhBMP-2. Report of two cases. Spine J. 2010;10(7):e6-10.

54. Shields LBE, Raque GH, Glassman SD, Campbell M, Vitz T, Harpring J, et al. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 in anterior cervical spine fusion. Spine. 2006;31(5):542-7.

55. Timualan LM, Pan J, Rodts GE, Mummneni PV. The safety and efficacy of anterior cervical disectomy and fusion with polyetheretherketone spacer and recombinant human bone morphogenetic protein-2: a review of 200 patients. J Neurosurg Spine. 2008;6(8):529-35.

56. Grauer J, Patel T, Erulkar J, Troiano N, Panjabi M, Friedlaender G. 2000 Young Investigator Research Award winner. Evaluation of OP-1 as a graft substitute for intertransverse process lumbar fusion. Spine (Phila Pa 1976). 2001;26(2):127-33.

57. Cunningham BW, Shimamoto N, Sefter JC, Dmitriev AE, Orbegoso CM, McCarthy EF, et al. Osseointegration of autograft versus osteoinductive bone graft for instrumented lumbar intertransverse process fusion. Spine (Phila Pa 1976). 2001;26(2):127-33.

58. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz H, et al. The safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. Eur Spine J. 2003;12(5):495-500.

59. Vaccaro AR, Anderson DG, Patel T, Fischgrund J, Truumees E, Herkowitz HN, et al. Comparison of OP-1 Putty (rhBMP-7) to iliac crest autograft for posterolateral lumbar arthrodesis: a minimum 2-year follow-up pilot study. Spine. 2005;30(24):2709-16.

60. Vaccaro AR, Patel T, Fischgrund J, Anderson DG, Truumees E, Herkowitz HN, et al. A pilot study evaluating the safety and efficacy of OP-1 putty (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis for degenerative spondylosis. Spine. 2004;29(17):1885-92.

61. Vaccaro AR, Whang PG, Patel T, Phillips FM, Anderson DG, Albert TJ, et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. Spine J. 2008;8(3):457-65.

62. Munns J, Park D, Singh K. Role of osteoinductive bone graft for instrumented lumbar intertransverse process fusion in sheep. Spine. 2004;29(24):2800-8.

63. Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, Birch N. Healon/recombinant human growth and differentiation factor-5 induces posterolateral lumbar fusion in a New Zealand white rabbit model. Spine. 2006;31(19):2180-8.

64. Kim DH, Jahng TA, Fu TS, Zhang HY, Novak SA. Evaluation of HealonMP52 osteoinductive bone graft for instrumented lumbar intertransverse process fusion in sheep. Spine. 2004;29(24):2800-8.

65. Garcia-Ramos J, Blaich M, Roemer K, Hulten P, Söderlund S, Söderlund S, et al. HealonMP52 osteoinductive bone graft for instrumented lumbar intertransverse process fusion in sheep. Spine. 2004;29(24):2800-8.

66. Khoueir P, Oh BC, DiRisio DJ, Wang MY. Multilevel anterior cervical fusion using a collagen-hydroxyapatite matrix with iliac crest bone marrow aspirate: An 18-month follow-up study. Neurosurgery. 2006;51(5):963-70.

67. Ploumis A, Albert TJ, Brown Z, Mehbood AA, Transfeldt EE. Healon graft carrier with bone marrow aspirate instead of allograft as adjunct to local autograft for posterolateral fusion in degenerative lumbar scoliosis: a minimum 2-year follow-up study. J Neurosurg Spine. 2010;13(2):211-5.

68. Badrinarth R, Bohi DD, Hustedt JW, Webb ML, Grauer JN. Only prolonged time from abstraction found to affect viable nucleated cell concentrations in vertebral body bone marrow aspirate. Spine J. 2014;14(6):990-5.

69. Hustedt JW, Jegede KA, Badrinarth R, Bohi DD, Blizzard DJ, Grauer JN. Optimal aspiration volume of vertebral bone marrow for use in spinal fusion. Spine J. 2013;13(10):1217-22.

70. Risbud MV, Shapiro IM, Guttagalli A, Di Martino A, Danielson KG, Beiner JM, et al. Osteogenic potential of adult human stem cells of the lumbar vertebral body and the iliac crest. Spine (Phila Pa 1976). 2006;31(1):83-9.