Graft Options in Posterolateral and Posterior Interbody Lumbar Fusion

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Study Design. Review article, review of literature.

Objective. To review the bone graft options that exist for posterolateral and posterior interbody lumbar fusion.

Summary of Background Data. As the number of lumbar fusion surgeries has increased over the last decade, alternative methods of grafting have been developed. Iliac crest autograft bone has traditionally been used for lumbar fusion. The downside to this graft option, however, is donor site morbidity.

Methods. The current literature on alternatives to iliac crest autograft bone for obtaining lumbar fusion was reviewed.

Results. Platelet gels, demineralized bone matrix, synthetic bone graft, and bone morphogenetic protein are potential options for bone graft supplementation or substitution. In preclinical studies, platelet gels have been beneficial to bone growth when combined with autograft, but clinical studies do not support the use of platelet gel in posterolateral lumbar fusion. Preclinical studies of demineralized bone matrix have shown significant variability in the osteoinductive properties of the available products, and clinical data showing efficacy is limited. The use of synthetic bone graft material (ceramics) in lumbar fusion surgery is increasing. Calcium phosphate compounds (i.e., β-tricalcium phosphate and hydroxyapetite) are most commonly used and are often combined with type I collagen to form a matrix. These materials provide an osteoconductive scaffold for bony ingrowth and can be combined with bone marrow aspirate or used as a carrier for osteogenic factors. Bone morphogenetic protein (rh-BMP-2) has been shown to provide similar or even increased fusion rates over autograft iliac crest bone. There are, however, potential safety concerns associated with the use of bone morphogenetic protein that are not fully understood.

Conclusion. Several alternatives to iliac crest autograft bone provide promising early clinical results in achieving posterolateral and posterior interbody lumbar fusion.

Key words: lumbar fusion, platelet gel, demineralized bone matrix, DBM, bone morphogenetic protein, BMP. **Spine 2010;35:1629–1639**

Over the last decade, there has been a dramatic increase in the number of lumbar fusion surgeries performed, the percentage of total back surgery spending that spinal fusion surgery accounts for, and the number of new sur-

gical devices dedicated to lumbar spinal fusion.[1] Iliac crest autograft has been used for many years to achieve lumbar fusion.[2–5] It provides both the osteogenic factors and scaffold necessary for fusion. The associated morbidity of iliac crest graft harvesting, however, has led to the development of alternative bone graft options, including platelet gels, demineralized bone matrix (DBM), synthetic bone grafts (ceramics), and bone morphogenetic proteins (BMPs). These alternative methods avoid the problem of donor site morbidity. Questions remain, however, regarding their clinical efficacy and safety.

■ Iliac Crest Bone Graft

Iliac crest autograft has been used for many years to achieve lumbar fusion.[2–5] The most frequent complications following fusion surgery are pseudarthrosis and donor site morbidity. Pseudarthrosis has been reported to occur in up to 55% of patients undergoing posterolateral, uninstrumented fusion.[5,6] Despite the use of rigid instrumentation, the rate of pseudarthrosis remains significant with iliac crest autograft.[5,7–9] Dimar et al[9] recently published a retrospective review of prospectively collected data on 194 patients with degenerative lumbar disease who underwent single-level, instrumented lumbar fusion with iliac crest autograft. These patients represented the control arm of a Food and Drug Administration (FDA)-regulated, multicenter, prospective, randomized study comparing the use of recombinant human bone morphogenetic protein-2 (rhBMP-2)/ compression resistance matrix and iliac crest autograft in posterolateral lumbar fusion. Evidence of bridging bone was assessed using plain radiographs and fine-cut CT scan with CT reconstructions. At 2-year follow-up, 84% of the patients had evidence of fusion defined as the presence of bridging bone on CT scan.[9]

Morbidity associated with the harvesting of autologous iliac crest bone is unfortunately common. Donor site problems, including pain, paresthesias, hematoma, and infection, have been reported in up to 50% of patients in some series.[10–12] Up to 60% of patients experience long-term, persistent donor site pain and between 2% and 5% of patients develop wound complications that require reoperation.[10,12–18] The harvesting of posterior iliac crest autograft seems to be less morbid than that of anterior iliac crest graft.[19] Given the proximity of the posterior iliac crest donor site to the lumbosacral spine, however, it is questionable as to whether patients can accurately differentiate from harvest site and surgical site pain in the case of lumbar/lumbosacral fusion surgery. A recent study has shown that patients who un-

dergo thoracic fusion with iliac crest bone graft have less donor site pain than those who undergo lumbar fusion surgery, supporting the notion that it is difficult to differentiate lumbar surgical site pain from posterior iliac crest donor pain.[20] These findings suggest that the incidence of posterior iliac crest donor site morbidity may be over reported in the literature.

Due to the drawbacks of autograft iliac crest, the use of local autograft as an alternative in lumbar fusion surgery has been evaluated. Sengupta et al[21] performed a retrospective clinical and radiographic study comparing the use of iliac crest autograft (n = 36) to local autograft (n = 40) in posterolateral lumbar fusion. All of the patients underwent decompression and fusion with pedicle screw instrumentation. The levels of fusion varied between 1 level (67%), 2 levels (21%), 3 levels (7%), and 4 or more levels (5%). The fusion rate with autograft iliac crest was 75% compared to a fusion rate with local bone autograft of 65%. No statistically significant difference (P = 0.39) was seen. A similar fusion rate of 80% was seen for 1-level fusions among the iliac crest and the local bone autograft groups. In the multilevel fusion cases however, the local bone autograft groups had a significantly lower fusion rate of 20% compared to an autograft iliac crest fusion rate of 66% (P = 0.029). There were no clinical outcome differences between these 2 groups, and no correlation was found between the presence of a solid fusion and clinical outcome. These authors concluded that local bone autograft achieved a similar fusion rate to iliac crest in 1-level fusions, but a lower rate of fusion in multilevel surgery. Less morbidity was seen with the local bone autograft than with the iliac crest.[21]

■ Platelet Gels

Platelet gels containing platelet rich plasma are another grafting option for lumbar fusion surgery. Platelet gels are osteoinductive and contain platelets and growth factors. To prepare the platelet gel, blood is collected from the patient after positioning for surgery. This blood is then put through an autotransfusion machine. The buffy coat is collected and the red blood cells and platelet-poor plasma are returned to the patient. The buffy coat is concentrated into a platelet concentrate, and thrombin and calcium chloride are added to produce the platelet gel.[22] As a bone graft enhancer, the platelet gel can be used in combination with autograft iliac crest, local autograft, or allograft bone.

Preclinical studies have shown an osteoinductive effect related to the use of platelet gels. Walsh et al[23] compared autograft, platelet gel, and coralline hydroxyapetite in combinations in sheep with a L3–L4 posterolateral fusion model. They conducted a follow-up after 6 months. Of all of the combinations, they found that platelet gel was most beneficial when combined with autograft. Siebrecht et al[24] used a bone chamber rat model to examine the effect of platelet gel on bone ingrowth into porous hydroxyapetite. They concluded that the
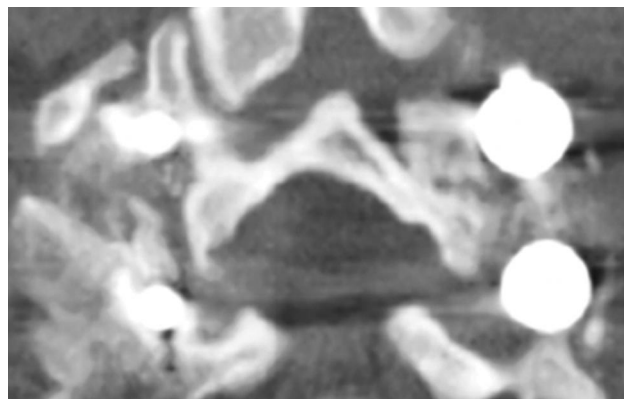

Figure 1. Coronal lumbar CT reconstruction showing a pseudarthrosis in a patient status post posterolateral fusion using a combination of platelet gel and autograft iliac crest bone. Reprinted with permission from Spine.[22] Copyright 2005, Lippincott Williams & Wilkins.

bone chambers with platelet gel showed increase bony ingrowth most likely due to an increased osteoinductive effect.

The clinical efficacy of platelet gels has not, however, been established, and current clinical studies do not support the use of platelet gel in posterolateral lumbar fusion surgery. Carreon et al[22] performed a retrospective study to determine if there was a difference between the use of iliac crest autograft combined with platelet gel and iliac crest autograft alone in achieving fusion. Seventy-six patients underwent either 1-level (74%), 2-level (20%), or 3-level (4%) posterolateral lumbar fusion surgery with iliac crest combined with platelet gel. Seventy-six age and sex matched controls underwent the surgery with iliac crest alone. At a minimum of 2-years of follow-up, there was a 25% nonunion rate in the platelet gel group versus a 17% nonunion rate in the iliac crest alone group (P = 0.18). The authors concluded that the platelet gel was not a reasonable bone graft enhancer, as the rate of fusion of platelet gel combined with iliac crest was not significantly better than the rate of iliac crest alone (Figure 1). Weiner and Walker[25] had similar results in a retrospective study comparing the rate of posterolateral lumbar fusion using iliac crest autograft alone with iliac crest autograft combined with platelet gel. The iliac crest fusion rate was 91% compared to 62% fusion rate of iliac crest combined with platelet gel. These authors concluded that the platelet gel did not enhance the fusion rate when it was combined with iliac crest autograft. Castro[26] studied the use of platelet gel in transforaminal lumbar interbody fusion surgery and noted a 19% decrease in the rate of fusion in the patients in whom platelet gel was used. Although this difference was not significant, the author concluded that there was not observed benefit to using platelet gel.

There are several potential reasons why platelet gels may not clinically enhance bone growth.[22] The platelet gel may dissolve relatively rapidly through fibrinolysis with subsequent diffusion of growth factors. The growth

Table 1. Concentrations of BMP-2 and BMP-7 Assayed From Extracts From Various DBM Formulations

	Lot Number 1 ng/g DBM	Lot Number 2 ng/g DBM	Lot Number 3 ng/g DBM	CV
ELISA analysis of BMP-2 ng/g DBM				
Allomatrix C bone graft putty	97.5	30.1	28.2	76.01%
DBX DBM putty	51.4	40.9	36.6	17.72%
DynaGraft II osteoinductive gel	49.2	38.8	25.4	31.56%
DynaGraft II osteoinductive putty	39.5	30.8	29.5	16.34%
Grafton gel	85.6	33.6	20.2	74.35%
Grafton putty	61.3	51.9	29.0	35.05%
Grafton crunch (written communication, February 2004)	40.8	30.5	29.0	19.21%
InterGro DBM putty (written communication, November 2003)	89.7	50.5	33.0	50.29%
Osteofil allograft paste	120.6	48.4	28.4	73.71%
BMP-2, lots: F = 15.12, $P < 0.0002$; products: F = 1.29, NS	70.6	39.5	28.8	
ELISA analysis of BMP-7 ng/g DBM				
Allomatrix C bone graft putty	118.8	67.8	66.3	35.45%
DBX DBM putty	179.7	94.1	90.9	41.43%
DynaGraft II osteo inductive gel	188.9	95.6	54.2	61.11%
DynaGraft II osteo inductive putty	226.8	67.9	55.0	82.08%
Grafton gel	70.5	69.9	60.3	8.56%
Grafton putty	84.7	80.0	78.6	3.95%
Grafton crunch (written communication, February 2004)	73.5	68.1	66.9	5.06%
InterGro DBM putty (written communication, November 2003)	77.5	72.7	72.7	3.71%
Osteofil allograft paste	81.6	68.1	66.5	11.51%
BMP-7, lots: F = 6.43, $P < 0.01$; products: F = 1.19 NS	122.4	76.0	67.9	

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BMP indicates bone morphogenetic protein; DBM, demineralized bone matrix; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; NS, not significant.

factors in the platelet gel may not be in a high enough concentration to have an osteogenic effect. Finally, there may be a possible presence of growth factors in the platelet gels that inhibit bone growth.[22] Little research is available on growth factors in platelet gel and the necessary concentration for an osteogenic effect.

■ Demineralized Bone Matrix

DBM is commonly used in spinal fusion procedures as a bone graft extender. DBM is produced by removing the mineral content of allograft bone through acid extraction, a process that isolates the remaining proteins (collagen, noncollagenous proteins, and growth factors). It contains variable amounts of osteogenic growth factors, including small amounts of BMPs. The production of DBM is loosely regulated by the Food and Drug Administration as a "minimally manipulated" human allograft tissue, with no mandated requirements for osteogenic growth factors concentration or for the demonstration of osteogenic efficacy.[27] As a result, DBM exists in various formulations produced by numerous manufacturers. Similar products from competing manufacturers and even those from the same manufacturer can differ in their biologic properties due to varying concentrations of osteogenic growth factors.[27,28] The carriers and fillers that make up the various DBM formulations exist in a range of forms, as both injectable and preformed sheets (*e.g.*, glycerol, hydrogel, and hyaluronic acid).

Studies have compared the content and osteogenic efficacy of some of the available DMB products.[27,28] Bae *et al*[27] evaluated the quantity of BMP in different DBM products as well as the variability of BMP in various lots from the same DBM manufacturer. Using enzyme-linked immunosorbent assay, they located bone BMP-2, BMP-4, and BMP-7. They found BMP-2 and BMP-7 in low concentrations (~20–200 ng/g) in all of the DBM products but BMP-4 could not be detected in all samples. It was also determined that greater variability of BMP exists between different lots of DBM from the same manufacturer than between different manufacturers (Table 1). This is likely the result of an FDA mandate that each lot must come from a single donor, with a significant amount of variability between donors.[27] BMP-2 and BMP-7 exist in nanogram concentrations in DBM, which is 1 million times less than the concentration of BMP that is required to produce a lumbar fusion clinically.[27,29,30]

Preclinical studies have shown significant differences in the osteoinductive properties of the various DBM products. Using a rabbit posterolateral intertransverse L5–L6 fusion model, Martin *et al*[31] compared fusion with Grafton DBM (Flex, Putty, Gel forms), iliac crest autograft, and a combination of Grafton and iliac crest autograft. At 6 weeks following surgery, the autograft alone group was greatly inferior to both the combined Flex DBM/iliac crest and Putty DBM/iliac crest groups, with a fusion rate of only 33%, compared to 100% fusion in both of the other groups. In the stand-alone groups, the Flex form had a fusion rate of 100%, compared to the Putty form fusion rate of 83% and Gel form fusion rate of 58%. They concluded that more mature fusions were achieved from all forms of DBM compared to iliac crest alone.

Peterson *et al*[32] examined an athymic rat L4–L5 posterolateral intertransverse fusion model. They compared Grafton Putty, DBX Putty, Allomatrix Putty, and con-

trols at 2, 4, and 8 weeks following surgery. It was found that Grafton Putty had the greatest osteoinductive potential with the greatest amount of radiologic and histologic evidence of fusion. Wang et al[33] also examined an athymic rat L4–L5 posterolateral intertransverse fusion model. They compared Grafton, Osteofil, Dynagraft, and autograft iliac crest at 2, 4, 6, and 8 weeks after surgery. Both Grafton and Osteofil had relatively high fusion rates (65% and 78%, respectively), while no fusions were seen in the Dynagraft or autograft groups. This study highlighted the between manufacturer variability in regards to osteogenic capacity.

There is limited clinical data on the efficacy of DBM. Recently, Kang et al[34] performed a multicenter prospective randomized study in which they compared Grafton and local bone (n = 18) to autograft iliac crest (n = 7) in single-level posterolateral lumbar fusion. The fusion rates were assessed with radiograph and CT. A fusion rate of 83% was achieved in the Grafton/local bone patients and an 85% fusion rate was seen in the iliac crest patients, with no statistical difference. At the 1-year follow-up, there were trends towards better patient-reported outcome measures in the Grafton group. This study is limited by the small number of patients in each group and by the relatively short follow-up.

■ Synthetic Bone Graft (Ceramics)

Numerous calcium-based synthetic products are used as bone graft extenders and/or substitutes in lumbar spine fusion. These products serve as osteoconductive scaffolds that support new bone ingrowth. Because it is reabsorbed only a few weeks after implantation, calcium sulfate is not sufficient for use of a scaffold in lumbar fusion surgery.[35] Calcium phosphate compounds, such as β-tricalcium phosphate and hydroxyapatite, are more commonly used. The porosity and pore size of these materials can be optimized for bony ingrowth during the manufacturing process. Ideally, the calcium phosphate compound provides a scaffold for bony ingrowth and the development of a fusion, but reabsorbs as the fusion develops. β-tricalcium phosphate (β-TCP) is absorbed over a period of several months, which makes it suitable for lumbar spine fusion. Hydroxyapatite is absorbed much slower,[35] on the order of years, and can obscure the evaluation of fusion mass on follow-up radiographs. Most of the products currently used in lumbar spine fusion consist of β-TCP and/or hydroxyapatite in combination with bovine collagen in varying ratios. Collagen affects the workability and reabsorption rate of the product and may also bind to and serve as a carrier for osteoinductive agents, including rhBMP-2.[36]

Preclinical data supporting the use of these products does exist. Healos (Depuy Spine, Inc., Raynham, MA) is a synthetic matrix that consists of 80% type I bovine collagen and 20% hydroxyapatite. Tay et al[37] performed a studied Healos using a rabbit, intertransverse fusion model. These authors compared autograft, Healos with bone marrow aspirate, and Healos alone in posterolat-

eral lumbar fusion. At 8 weeks, 75% of the autograft group, 100% of the Healos + bone marrow aspirate group, and 18% of the Healos alone group were noted to have radiographic evidence of fusion. The fusion obtained with the autograft group was biomechanically superior to that obtained with Healos. The authors concluded that Healos serves as an osteoconductive scaffold that must be combined with an osteogenic agent (e.g., bone marrow aspirate) to reliably provide a fusion.[37] β-TCP is a commonly used scaffold in lumbar spine fusion. Orii et al[38] studied β-TCP, using a macaque monkey posterior lumbar fusion model. These authors compared autograft, β-TCP + bone marrow stem cells, and β-TCP alone. They reported that 83% of the β-TCP/bone marrow group, 67% of the autograft group, and none of the β-TCP alone group developed fusion. These authors concluded that β-TCP and bone marrow stem cells can serve as a substitute to autograft bone for posterior lumbar fusion. An in vivo rabbit study that evaluated intervertebral body fusion, using a combination of bone marrow derived osteogenic cells and porous calcium phosphate showed similar results, i.e., that porous calcium phosphate, when combined with bone marrow derived cells, provides a potential alternative to autograft bone.[39]

Several clinical studies support the use of porous calcium phosphate and bone marrow aspirate in lumbar spine fusion. Vitoss (Orthovita Inc, Malvern, PA) is a synthetic matrix that consists of 80% β-tricalcium phosphate and 20% type I bovine collagen and has a porosity and pore size that is favorable for bony ingrowth.[40] Epstein[41] prospectively evaluated the efficacy of Vitoss/bone marrow aspirate combined with local autograft in performing instrumented 1-level (n = 27) and 2-level (n = 13) posterolateral lumbar fusion. Fusion was assessed on both radiograph and CT scan. By 6 months, 96% of the 1-level and 85% of the 2-level patients developed a solid fusion. Only one of the 3 patients with pseudarthrosis required reoperation. At 12 months follow-up, there was significant improvement compared to preoperative baseline in all measured patient-reported outcomes (i.e., SF-36 and Odom's Criteria).[41] Epstein[42] also studied the use of Vitoss/bone marrow aspirate combined with local autograft in noninstrumented 1- and 2-level posterolateral lumbar in the geriatric population (i.e., average age of 70 years old), with a reported fusion rate of 85% at 2-years follow-up. Dai and Jaing[43] recently published a prospective randomized study comparing the use of β-TCP combine with local autograft to iliac crest autograft in single-level instrumented posterolateral fusion. These authors found no difference in the fusion rate (i.e., 100% in both groups) or the clinical outcomes between groups at 3-years follow-up.

Healos and bone marrow aspirate has also been studied clinically. Neen et al[44] performed a prospective case-controlled study in which they compared Healos with bone marrow aspirate to iliac crest autograft in lumbar fusion surgery. Fusion procedures studied included pos-

terolateral lumbar fusion, posterior lumbar interbody fusion, and anterior/posterior lumbar fusion. These authors found that Healos with bone marrow aspirate and autograft had an equivalent fusion rate of approximately 93% and similar clinical outcomes in posterolateral lumbar fusion. Healos with bone marrow aspirate had a significantly lower fusion rate than autograft when used in interbody fusion. Other clinical studies have evaluated the use of Healos and bone marrow aspirate in transforaminal/posterior lumbar interbody fusion surgery and found interbody fusion rates of 91% to 92%, similar to that obtained with autograft.[45,46]

■ Bone Morphogenetic Protein

BMPs are soluble signaling molecules belonging to the transforming growth factor beta superfamily that bind to receptors and regulate the differentiation, maturation, and proliferation of mesenchymal precursor cells into osteogenic and/or chondrogenic cells.[47–50] Although the exact *in vivo* pathways of BMP are not fully understood, it is believed that the signaling pathway of osteoblastic differentiation and osteogenesis is a complex cascade of BMP expression, with different BMP's functioning synergistically at the various stages of the differentiation.[51,52] Of the more than 20 types of BMP have been described, only BMP 2,4,6,7, and 9 have been shown to have osteogenic properties.[48,53–56] At present, 2 commercial forms of recombinant BMP are available for clinical use: rhBMP-2 (infuse) and rhBMP-7 (OP-1), both of which have osteogenic properties. Of the 2 commercially available forms, only rhBMP-2 has been shown to induce osteoblastic differentiation from mesenchymal stem cells.[56]

The only FDA-approved indication for BMP use in the spine is for anterior lumbar interbody fusions (ALIF), using rhBMP-2 within a titanium tapered cage.[17] The use of BMP in ALIF surgery has yielded fusion rates of 95% to 100%.[17,29,57] The "off-label" uses for BMP includes its use in posterolateral fusion, posterior lumbar interbody fusion (PLIF), and transforaminal lumbar interbody fusion (TLIF).[7,30,36,58–61] FDA trials are underway for the approved use of rhBMP-7 in posterolateral lumbar fusion.[6,62–64]

Numerous carriers have been described that bind to BMP and maintain adequate BMP concentrations at the site of planned fusion. Carriers vary in their material and structural properties. The most common carrier currently used is an absorbable type I collagen sponge. This carrier is deformable and easily inserted for into a cage for interbody applications. A carrier, such as the absorbable collagen sponge, that lacks any structural properties, is not ideal for use in posterolateral applications. Studies suggest that a BMP carrier used for posterolateral fusion should have some structural integrity (*e.g.*, ceramic calcium phosphates, combined collagen/ceramic matrix), allowing it to resist compression from the surrounding paraspinal musculature and maintain a space where the posterolateral fusion can form.[30,36,58,65–67]

Figure 2. RhBMP-2 on an absorbable type I collagen sponge wrapped around local autograft bone for use in posterolateral spine fusion.

Alternatively, an absorbable type I collagen sponge carrier can be wrapped around a structural bulking agent (*e.g.*, local autograft bone, allograft cancellous bone chips, ceramic calcium phosphate) and used for posterolateral fusion (Figure 2).[68–70]

Preclinical Data

Preclinical studies have examined the safety and efficacy of rhBMP-2 and rhBMP-7 in lumbar fusion, with most studies reporting equal or superior fusion rates when compared to autograft iliac crest.[65,71–74] Cunningham *et al*[71] compared rhBMP-7 to autograft in a dog posterolateral spinal fusion model. Three treatment groups were used: autograft alone, rhBMP-7 alone, and autograft plus rhBMP-7. After 12 weeks, the fusion rate was highest in the combined autograft and rhBMP-7 group with a rate of 83%, followed by a 72% fusion rate in the rhBMP-7 group, and a 27% fusion rate in the autograft alone group. Biomechanical testing indicated that the fusions obtained with rhBMP-7 had decreased motion in flexion/extension and in axial rotation when compared with the autograft fusions. The rhBMP-7 bone formation occurred through intramembranous ossification, while

autograft bone alone produced fusion through enchondral bone formation.[71]

RhBMP-2 has been extensively studied as a bone graft alternative in multiple animal models. Schimandle et al[72] used a rabbit, intertransverse posterolateral fusion model. A fusion rate of 100% was obtained following the use of rhBMP-2 on a type I collagen sponge. A fusion rate of only 42% was seen with the use of autograft. Sandhu et al[75] used a dog, L4–L5 intertransverse process fusion model, treating the study animals with either rhBMP-2 or autograft. After 12 weeks, the animals treated with rhBMP-2 had a fusion rate of 100% compared to 0% fusion rate in the dogs treated with autograft alone. Several different doses of rhBMP-2, ranging from 58 to 920 μg, were studied in the treatment group. The cross-sectional area, stiffness, and histology of the fusion mass were not dose-dependent. These authors concluded that, above a certain threshold dose of rhBMP-2, increasing the quantity of protein does not necessarily improve the quality of the fusion mass. Martin et al[65] studied the use of rhBMP-2 for posterolateral fusion in nonhuman primates and found that this more evolved species required higher BMP doses to obtain fusion than other animal models (e.g., dog and rabbit) previously studied. The dose necessary to obtain posterolateral fusion in the nonhuman primate was found to be 3-fold less than originally reported when used with a structural bulking agent that is able to resist the compressive forces of the surrounding paraspinal muscles and maintain a space in which the fusion can form.[69,76]

Clinical Data

Numerous clinical studies have analyzed the use of BMP in ALIF, PLIF, and TLIF surgery. The use of rhBMP-2 was first studied clinically in ALIF surgery.[17,29,57] An FDA-regulated, multicenter prospective randomized study was performed with 279 patients who underwent ALIF using 2 tapered titanium threaded fusion cages.[17] RhBMP-2 on an absorbable collagen sponge was used in the cages in 143 patients, and iliac crest was used in the cages of 136 patients. The dose of rhBMP-2 ranged from 12 to 18 mg. A fusion rate of 94.5% was seen in the rhBMP-2 group compared to an 88.7% fusion rate in the iliac crest group, while the mean operative time and blood less were less in the rhBMP-2 group. Furthermore, 5.9% of the patients in the iliac crest group experienced an adverse event related to graft harvest, and at a 2-year follow-up, 32% of the patients reported graft site discomfort. Throughout the duration of the study, both groups had similar improvements in clinical outcome measures. Subsequent studies support the safety and efficacy of rhBMP-2 when used in ALIF surgery.[29,57]

The off-label use of rhBMP-2 in posterolateral fusion and TLIF is gaining popularity. Two prospective randomized multicenter FDA regulated studies are currently underway comparing rhBMP-2 and iliac crest in posterolateral lumbar fusion. The first study was a pilot study which compared posterolateral spine fusion in 3 groups:
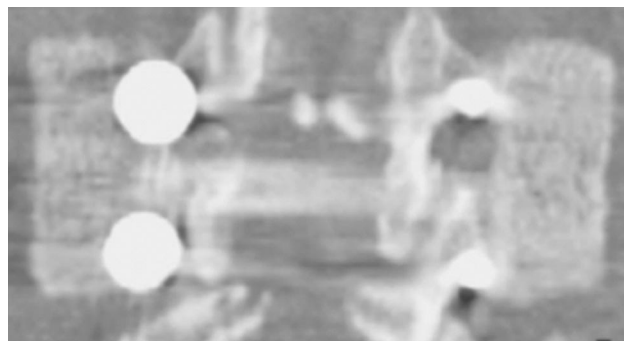

Figure 3.   Coronal lumbar CT reconstruction obtained immediately following posterolateral fusion using a compression resistance matrix as a carrier for rhBMP-2 Reprinted with permission from *Spine*.[36] Copyright 2005, Lippincott Williams & Wilkins.

autograft with pedical screw fixation (n = 5), rhBMP-2 with pedical screw fixation (n = 11), and rhBMP-2 without pedical screw fixation (n = 9).[30] All patients had single-level degenerative disc disease with no greater than Grade I spondylolisthesis. A dose of 20-mg rhBMP-2 on a calcium phosphate carrier was used on each side of the spine. At 17 months follow-up, the fusion rate in the autograft group was 40% compared to a 100% fusion rate in the patients whom received rhBMP-2. These authors demonstrated that rhBMP-2 at a dose of 20 mg per side can achieve posterolateral fusion at a higher rate than iliac crest autograft alone.

The second FDA-regulated prospective randomized study that evaluates the use of rhBMP-2 in posterolateral lumbar fusion used a dose of 20-mg per side of the spine carried on a compression resistant matrix that consisted of collagen, hydroxyapetite, and tricalcium phosphate.[8] This prospective randomized study compared the use of autograft iliac crest and rhBMP-2/compression resistant matrix (CRM) in single-level, instrumented posterolateral lumbar spinal fusion (Figure 3). Early results suggested that the rhBMP-2 group developed a fusion mass more rapidly than the autograft group.[36] Two-year data published from this study in 2006 on 98 study patients reported a fusion rate of 73% in the autograft (n = 45) and 91% in the rhBMP-2/CRM (n = 53) group (Figure 4).[8] Furthermore, compared to the autograft group, the rhBMP-2 group had less operative time and blood loss. No differences in the clinical outcome measures were noted between the 2 groups.[8] Most recently, data from this study was published on 463 study patients reporting an 89% fusion rate in the autograft group (n = 224) and a 96% fusion rate in the rhBMP-2/CRM group (n = 239) at 2-years follow-up (P = 0.014).[18] Operative time and intraoperative blood loss were significantly less in the rhBMP-2/CRM group (P < 0.001), but there was no difference between groups in length of hospital stay. Clinical outcomes measures were similar between the 2 groups. The rate reoperation was significantly higher in the autograft group (16% vs. 8%, P = 0.015). Of the patients in the autograft group, 60% reported donor site iliac crest pain at 2-years follow-up.[18]
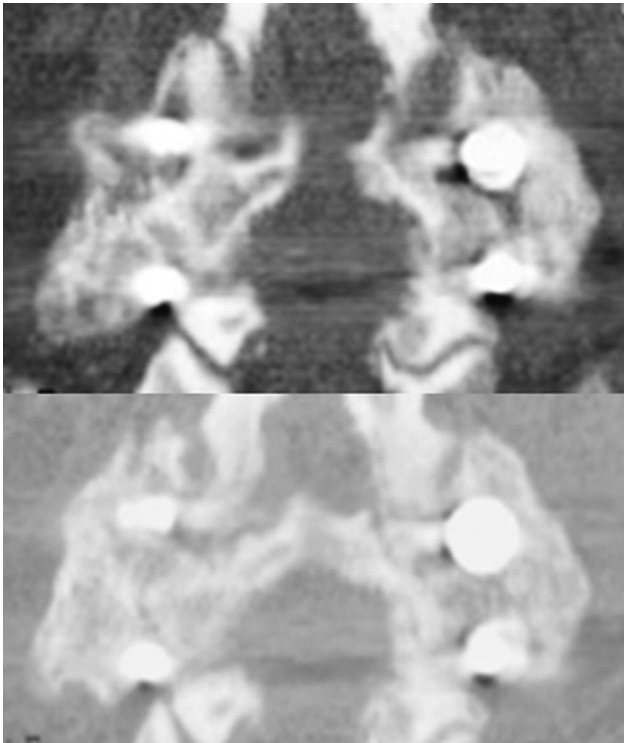
Figure 4. Coronal lumbar CT reconstructions obtained 6 months (top) and 12 months (bottom) following posterolateral fusion using rhBMP-2 on a compression resistance matrix, both demonstrating a solid fusion. Reprinted with permission from *Spine*.[36] Copyright 2005, Lippincott Williams & Wilkins.

A multicenter, prospective, randomized FDA approved clinical study examining the efficacy of rhBMP-7 (OP-1) in posterolateral uninstrumented lumbar fusion is also underway.[6,62,64] In this study, OP-1 putty was used as a replacement for iliac crest in single-level posterolateral lumbar fusion, with a dose of 3.5 mg used per side of the spine. Study patients had symptomatic lumbar stenosis and Grade I or II degenerative spondylolisthesis. At 1-year, 2-year, and 4-year follow-up, OP-1 provided similar fusion rates of approximately 50% and similar clinical outcomes compared to iliac crest. There were no adverse effects resulting from the OP-1.[6,62,64]

TLIF is a technique that provides both an anterior interbody and a posterolateral fusion through a single posterior approach. The interbody preparation and fusion is performed transforaminally to minimize medial retraction of the traversing nerve root and thecal sac. Although no prospective, randomized studies have been performed that evaluate the used of BMP in the TLIF procedure, some retrospective clinical data are available that supports its safety and efficacy (Figure 5A–D). Mummaneni et al[59] compared fusion rates of TLIF (both single and multi level) using rhBMP-2 combined with either autograft iliac crest or local autograft (n = 21) *versus* autograft iliac crest alone (n = 19). These represented preliminary results, with an average follow-up of 9 months. The mean time to fusion was 6 months in the autograft group, 4 months in the rhBMP-2/autograft

group, and 3 months in the rhBMP-2/local autograft bone group. No cases of pseudarthrosis were observed in the rhBMP-2/autograft group, whereas 1 patient in the autograft group and 1 patient in the rmBMP-2/local bone group were diagnosed with pseudarthrosis. No adverse events were related directly to the use of rhBMP-2 use and no cases of symptomatic ectopic bone formation were reported. The authors concluded that rhBMP-2 is a safe and effective when used in the TLIF procedure. Villavicencio et al[61] studied 74 patients who were treated with rhBMP-2 in single- and multilevel TLIF procedures. This analysis included patients who underwent minimally invasive and open procedures. The rhBMP-2 was applied on an absorbable collagen sponge and was combined with autologous local bone and/or allograft bone. Within 10 months of surgery, every patient developed a solid fusion. No complications or adverse reactions attributed specifically to the rhBMP-2 were reported, although 2 patients had persistent postoperative radiculitis. Patients in the minimally invasive group had slightly better patient reported clinical outcomes but the difference was not statistically significant. Both of these studies are limited by their retrospective design, small sample sizes, the absence of a group in which rhBMP-2 was used alone without some type of autograft (*i.e.*, local or iliac crest), and the lack of validated outcome measures. Certainly a controlled, prospective study is needed to further define the safety and efficacy of BMP used in the TLIF procedure.

Safety Concerns

Although adverse events attributed directly to the use of BMP in lumbar spine surgery are rare in the current reports, the issue of safety remains a concern. Certain complications and safety issues associated with BMP use in the lumbar spine have attracted a considerable amount of attention, including ectopic bone formation, postoperative radiculitis, vertebral osteolysis, and allergic/hyperinflammatory response.

Cases of ectopic bone formation in the anterior epidural space, lateral recess, and/or intervertebral foramen have been reported following the use of BMP in lumbar fusion surgery. An early study that evaluated the use of BMP in PLIF surgery demonstrated a relatively high rate of ectopic bone formation in the spinal canal.[60] Although, the ectopic bone did not result in clinical symptoms, it did raise concern regarding the use of BMP for this procedure.[60] The mechanism of ectopic bone formation remains unknown. It is felt to be related to the presence of a hematoma or a hemostatic agent (*e.g.*, Gelfoam) that can serve as a conduit through which BMP reaches the spinal canal and/or intervertebral foramen in sufficient amounts to stimulate ectopic bone formation.[59,61,77] The use of BMP in TLIF surgery has not been shown to be associated with clinically significant ectopic bone formation.[59,61,77]

The use of BMP in TLIF and PLIF surgery has been associated with severe postoperative radiculitis, most of-
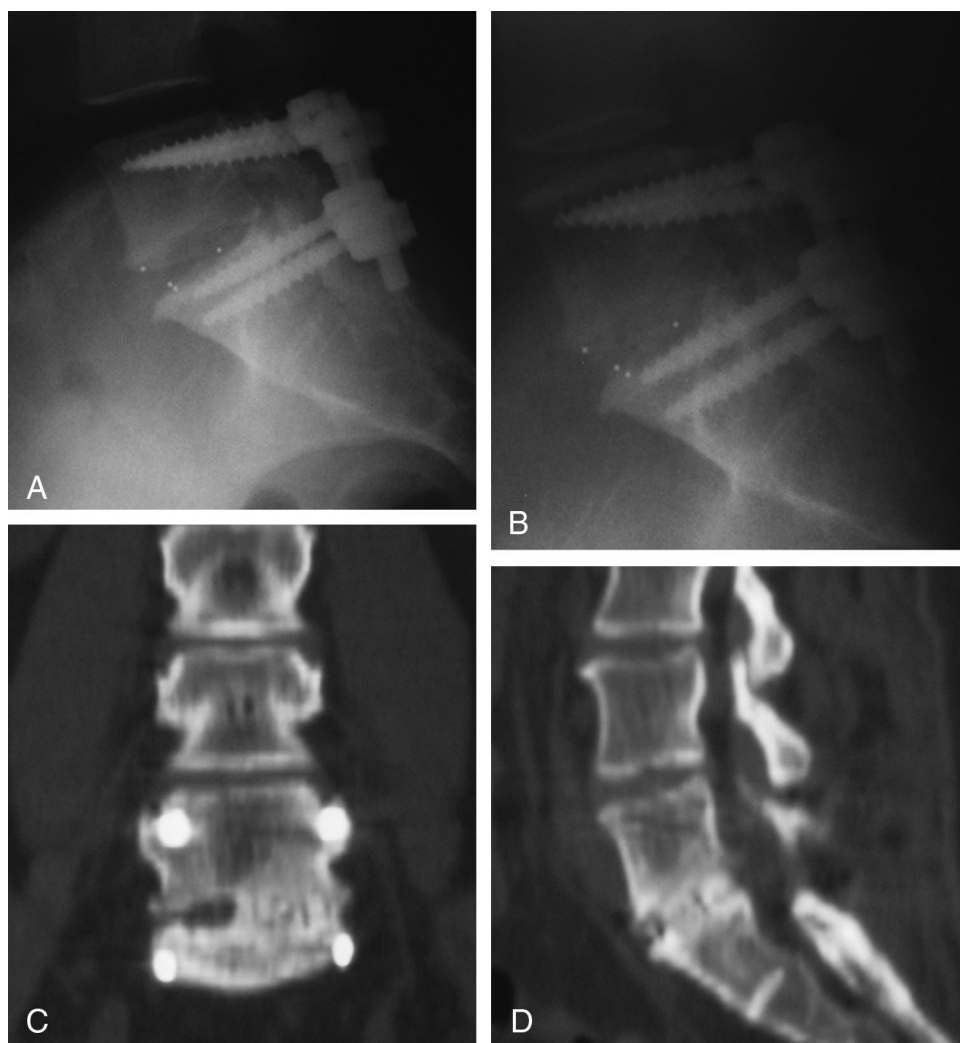
Figures 5. **A–D,** Initial postoperative lateral lumbar radiograph (**A**) and 12 month postoperative lateral lumbar radiograph (**B**), coronal lumbar CT reconstruction (**C**), and sagittal lumbar CT reconstruction (**D**) following a L5–S1 TLIF, using rhBMP-2 on an absorbable collagen sponge within an intervertebral cage (marked by metallic beads on radiographs). There is bone formation evident in the intervertebral space when comparing the initial and 12 month postoperative radiograph. Intervertebral fusion is confirmed on the 12 month coronal and sagittal CT reconstructions.

ten without any evidence of ectopic bone formation on imaging studies. Although the cause remains uncertain, it may result from a BMP-related hyper-inflammatory response. A retrospective study at our institution compared the rate of postoperative radiculitis in patients who underwent TLIF surgery using rhBMP-2 or autograft iliac crest.[78] We reported a significantly higher rate of postoperative radiculitis in the BMP group, affecting up to 20.4% of patients in the rhBMP-2 group and only 3% of the autograft group. The use of a hydrogel sealant over the annulotomy site (DuraSeal Xact Sealant System, Confluent Medical, Waltham, MA) significantly reduced the rate of postoperative radiculitis in patients undergoing TLIF surgery with rhBMP-2 from 20.4% to 5.4% (*P* = 0.047).[78] This sealant likely minimizes the amount of BMP that inadvertently seeps out of the intervertebral space (*i.e.*, is carried by blood) into the spinal canal and/or intervertebral foramen and forms a protective layer directly over the exposed dura and traversing nerve roots. DuraSeal has recently gained FDA approval for use in the spine specifically as an adjunct to suturing for intraoperative dural repair. The use of Du-

raSeal to minimize the risk of radiculitis following TLIF with rhBMP-2 remains "off-label."

Vertebral osteolysis has been observed after using BMP in an interbody fusion (Figure 6).[29,79] The pathophysiology and significance of the vertebral osteolysis remains unknown. It has been reported to occur in 8% to 18% of patients following the use of BMP for intervertebral body fusion.[29,79] Vertebral osteolysis is often associated with significant back and/or leg pain. Fortunately, it seems to be a self-limiting process with eventual resolution of the osteolysis and the symptoms and little, if any, effect on long-term clinical or radiographic outcomes.[29,79] Infection and nonunion must, however, be considered in the differential diagnosis of a patient with osteolysis and back pain following intervertebral body fusion, particularly when symptoms persist. Although the cause remains unknown, violation of the endplate(s) during disc space preparation may increase the risk of developing vertebral osteolysis.

Currently, there is no evidence to suggest that re-exposure to BMP causes a clinically significant hyper-inflammatory response, with no reported increase in lo-

Figure 6. Coronal lumbar CT reconstruction (left) and sagittal lumbar CT reconstruction (right) obtained 6 weeks following a L4–L5 TLIF using rhBMP-2 on an absorbable collagen sponge within an intervertebral cage. These images demonstrate vertebral osteolysis involving both the inferior aspect of the L4 vertebral body and the superior aspect of the L5 vertebral body.
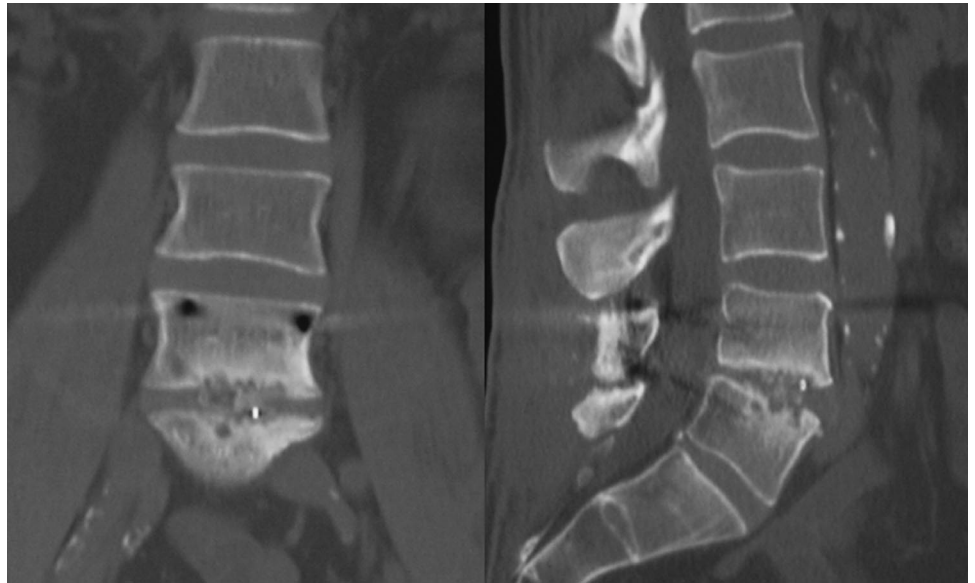
cal (*e.g.*, wound complications) or systemic (*e.g.*, anaphylaxis) consequences. A recent study evaluated 96 spine surgery patients who had at least 1 re-exposure to rhBMP-2.[80] There was no statistical difference in complications between patients during their first and second exposures to BMP and there were no documented allergic reactions.

■ Conclusion

The use of bone graft substitutes in lumbar fusion surgery continues to be a topic of research and debate. Although autograft iliac crest remains the "gold standard", its potential complications have led to the development of other bone graft options. Despite promising animal data, platelet gel and DBM continue to lack significant clinical data that supports their efficacy in lumbar fusion surgery. Several prospective randomized studies have been performed or are underway that suggest that BMP is at least as effective as iliac crest bone graft in obtaining a fusion in both ALIF and posterolateral lumbar surgery. The "off-label" use of BMP has increased in posterolateral and posterior interbody fusion surgery. Additional prospective randomized studies, particularly in the case of TLIF surgery, are needed to better define the safety and efficacy of BMP used for these "off-label" indications.

■ Key Points

- Morbidity associated with iliac crest harvest has led to bone graft alternatives or supplements.
- Platelet gels, demineralized bone matrix, and synthetic bone grafts (ceramics) have promising preclinical data but lack sufficient clinical data demonstrating efficacy in lumbar fusion.
- In preclinical and clinical studies, rhBMP-2 has shown equal to superior fusion rates compared to iliac crest autograft.

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