A Review Paper

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Bone Graft Extenders and Substitutes in the Thoracolumbar Spine

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Abstract

Autologous iliac crest bone graft remains the gold standard for lumbar fusion. The potential for complications has led to the development of alternative bone graft materials and enhancers, including autologous growth factors, demineralized bone matrix products, osteoinductive agents, and ceramic products. The current literature centers mainly on preclinical studies, which, further complicating the situation, evaluate these products in different clinical scenarios or surgical techniques. Autologous growth factors and demineralized bone matrix products have had promising results in preclinical studies, but few strong clinical studies have been conducted. Ceramic extenders were evaluated with other substances and had good but often inconsistent results. Bone morphogenetic proteins have been extensively studied and may have benefits as osteoinductive agents. Category comparisons are difficult to make, and there are differences even between products within the same category. The surgeon must be knowledgeable about products and their advantages, disadvantages, indications, contraindications, and possible applications so that they can make the best choice for each patient.

As the only bone graft substance with osteoinductive, osteoconductive, and osteogenic properties, autologous iliac crest bone graft (AICBG) remains the gold standard for lumbar fusion. Reported rates of posterolateral fusion with autograft are excellent, though up to 30% of patients may have complications related to bone graft harvest.[1] Hence, several bone graft alternatives and extenders have been developed. These include allograft, demineralized bone matrix (DBM), osteopromotive growth factors, autologous growth factor (AGF) concentrates, and ceramics. As these products have different osteoconductive or osteoinductive properties, they are usually applied in combination. Despite their growing popularity, there is little level 1 evidence supporting their use. In this review, we summarize use of these substances in thoracolumbar spine surgery.

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Autologous Growth Factors

Given their role in initiating bone healing, platelet concentrates have been examined as potential adjuncts to lumbar fusion. AGF concentrate is prepared by separating and concentrating platelets from whole blood drawn from the patient at time of surgery. The concentrate is then mixed with a carrier, such as thrombin, to form a usable gel.[2] The gel must be combined with an osteoconductive matrix (eg, allograft, ceramic) before being implanted. Although some investigators have reported good results or near equivalency, others have reported lower fusion rates with use of AGF as an adjunct to AICBG, compared with AICBG alone.[3] One recent meta-analysis found no significant difference between AGF and AICBG with respect to radiographic nonunion.[4]

Jenis and colleagues[5] compared 15 patients (25 levels) treated with AGF combined with allograft in 1- or 2-level anteroposterior lumbar interbody fusion with 22 patients treated with AICBG. At 6 months, both the experimental group and the control group had 56% fusion. At 24 months, computed tomography showed 85% arthrodesis with autograft and 89% with AGF; there was no significant difference between groups in regard to pain or function. The authors concluded that AGF combined with an appropriate carrier may be a realistic alternative to AICBG.

Autologous bone marrow aspirate (BMA) is another option in this category. The well-known osteogenic properties of mesenchymal stem cells, in combination with osteoconductive and osteoinductive properties, make autologous bone graft the gold standard for fusion. As these osteogenic factors are percutaneously aspirated and concentrated in BMA, and mixed with an osteoconductive matrix such as allograft, BMA is a potential alternative to autologous bone graft harvest.[6] Animal studies have shown that BMA has osteopromotive properties in multiple orthopedic applications, including spinal fusion.[7,8]

One prospective study of 1-level posterolateral fusion evaluated 3 graft combinations: AICBG alone, BMA with autogenous laminectomy bone chips, and BMA with calcium sulfate (CS) pellets.[6] Computed tomography evaluation showed equivalent fusion rates for

AICBG and BMA plus local bone, but poorer fusion rates for BMA plus CS. It is unclear if BMA played a role in fusion rates or if local bone alone was sufficient, as they were used in combination.

Carreon and colleagues[3] assessed the addition of platelet gel, AGF, to AICBG in posterolateral lumbar fusion. They found no statistically significant difference in nonunion and, given the added expense, recommended against supplementing AICBG with AGF. In a similar study, Castro[9] evaluated 22 patients with 1- or 2-level transforaminal lumbar interbody fusion (TLIF). At 34-month follow-up, there was a 19% decrease in arthrodesis with the addition of AGF; however, this was not statistically significant. Similarly, Rihn and colleagues[10] conducted a review and concluded that preclinical studies show a benefit in using AGF with autograft but that clinical studies do not show the same benefit in posterolateral lumbar fusion.

Bansal and colleagues[11] combined BMA with ceramic scaffolds in instrumented posterior fusion and found successful fusion in 29 of 30 patients. Carter and colleagues[12] evaluated use of a collagen hydroxyapatite (HA) sponge with BMA and found 95% fusion in TLIF/posterior lumbar fusion (PLF). Neen and colleagues[13] conducted a similar study with 50 patients and found that ceramic with BMA is equivalent to AICBG in posterolateral lumbar fusion but not in interbody fusion. Although AGFs have had some promising research results, they are expensive, and more investigation is needed to evaluate their efficacy.

Osteoinductive Agents

Bone morphogenetic proteins (BMPs) are a family of osteoinductive growth factors that stimulate stem cells to differentiate into osteoblasts. The only BMP application approved by the US Food and Drug Administration (FDA) in spine surgery involves the lumbar spine. Infuse rhBMP-2 (Medtronic Sofamor Danek, Memphis, Tennessee) is FDA-approved for 1-level anterior lumbar interbody fusion (ALIF) with LT-CAGE (Medtronic Sofamor Danek). OP-1 (Stryker Biotech, Hopkinton, Massachusetts) or rhBMP-7 was granted FDA approval only with a humanitarian device exemption for use in compromised patients who require revision posterolateral lumbar fusion. All other uses of these products are off-label and not FDA-approved. There is increasing evidence that rhBMP-2 is a possible replacement for AICBG for posterolateral lumbar fusion.[14] In addition, rhBMP-7 is under FDA study for uninstrumented posterolateral lumbar fusion.[15] One advantage of rhBMP-7 is that it is available as a putty, which can be molded to fit into the spine. Clinical trials with these materials have shown promise, but the high cost of these materials is a concern.[4,15]

Typically, BMPs are mixed with a carrier matrix. For example, rhBMP-2 dry powder is mixed with saline and allowed to soak into an absorbable collagen sponge. This sponge can then be packed inside an interbody cage and impacted into the disk space. Whenever the surgeon intends to use this combination for posterolateral fusion, the sponge should be combined with a bulking agent to prevent it from being crushed by the paraspinal muscles and to allow space for new bone growth.[16,17] This is typically done with use of allograft, autograft, or a ceramic artificial bone expander, which acts as an osteoconductive agent.

Numerous preclinical studies in lower species have concluded that BMP is a possible alternative to AICBG in terms of efficacy and safety.[17] When primates were tested, the concentration ratio that had yielded fusion in lower animals did not have the same success.[18] One study that evaluated PLF in osteoporotic rats using rhBMP-7 on a collagen carrier found a dose-dependent relationship with fusion.[19] The collagen carrier alone did not show fusion, rhBMP-7 30 μg showed some new bone formation, and rhBMP-7 90 μg showed mature trabeculated bone at 21 days.[19]

Multiple clinical studies have described both on- and off-label BMP applications for spine fusion, but these studies were heterogeneous, using different experimental methodologies, surgical techniques, outcome measures, and BMP–expander combinations, making it difficult to generalize results to all applications. A recent meta-analysis identified 12 studies of BMPs.[4] Of these 12 studies comparing rhBMP-2 with AICBG, 10 found decreased radiographic nonunion at 12 to 24 months, and 2 found no difference. The studies examined BMP use in ALIF, PLF, and posterior lumbar interbody fusion (PLIF). In 11 of the 12 studies, BMP use, compared with AICBG use, was associated with statistically significantly lower or equivalent rates of nonunion. The meta-analysis of studies comparing rhBMP-7 with AICBG and local graft in PLF found no significant difference in fusion rates. Differences in operative time, blood loss, length of stay, complications, and outcomes measures were inconclusive. The authors suggested that radiographic outcomes of rhBMP-2 and rhBMP-7 may differ, though the available data for rhBMP-7 was somewhat limited by low numbers of patients. They reported that rhBMP-7 was not effective, but they also estimated that, for every 8 patients treated with rhBMP-2, 1 would avoid nonunion.

Delawi and colleagues[20] reported that rhBMP-7 used with local autograft was a safe and effective alternative to AICBG in 1-level posterolateral lumbar fusion. The authors recommended against substituting rhBMP-7 for AICBG in multilevel fusions. Taghavi and colleagues[21] evaluated use of rhBMP-2 and BMA with autograft in revision PLF (N = 62 patients; 125 levels) and found a multilevel fusion rate of 93.5% and a 1-level fusion rate of 100%. Multilevel rhBMP-2 and autograft had a 100% fusion rate as well, while BMA alone had a 63.5% fusion rate. Fusion occurred earlier in the rhBMP-2 groups (1-level, multilevel) than in the other groups, leading the authors to conclude that rhBMP-2 is more

effective than BMA alone. These retrospective data suggest that use of rhBMP-2 and BMA with autograft results in clinically acceptable fusion, as does rhBMP-2 alone and autograft alone. Given the cost of rhBMP-2, the authors determined that BMA may be a reasonable alternative to rhBMP-2 for 1-level, but not multilevel, revision PLF.

In a prospective study evaluating rhBMP-2 in 98 patients who underwent multilevel anterior or posterior spinal fusion (308 levels), 3 groups were followed up over 2 years.[22] One group (98 patients) had BMP-2 (1.5 mg/mL or 10 mg/level) and a collagen sponge in a titanium cage in anterior spinal fusion. A second group (43 patients) had rhBMP-2 (1.5 mg/mL or 20 mg/level), a collagen sponge, tricalcium phosphate/HA (TCP-HA), and local bone graft in posterior spinal fusion. The third group (8 patients) had rhBMP-2 (1.5 mg/mL or 40 mg/level) and TCP-HA without local bone in posterior spinal fusion. The overall fusion rate was 95%. There was no statistically significant difference between groups. The authors noted that rhBMP-2 "eliminated the necessity of AICBG and yielded excellent fusion rates." Other investigators[23] reported that rhBMP-2 was more effective than AICBG at a high dose (2.0 mg/mL or 40 mg/level) when used with a TCP-HA carrier. Boden and colleagues[24] used a lower dose of rhBMP-2 (20 mg/level) on TCP-HA for PLF in 25 patients, and the fusion rate was 100%. Another study using an even lower dose (12 mg/mL) on a collagen carrier for 1- and 2-level fusion in 91 patients, reported results equivalent to those of AICBG.[25]

In a prospective study evaluating the costs and benefits of using rhBMP-2 in lumbar fusion, the potential advantages of BMPs included less pain, shorter operative time, and lower surgical fee—all attributed to elimination of AICBG harvesting, quicker rehabilitation, fewer complications, and more rapid healing. Compared with AICBG use, rhBMP-2 use led to a $3367 decrease in lower total payer expenditure.[26] Polly and colleagues[27] recognized the high price of rhBMP-2 in 1-level ALIF and determined that the upfront price was $3380, but wrote that the "cost is likely to be offset to a significant extent by reductions in the use of other medical resources." Another study, following almost 700 patients who underwent ALIF, concluded that rhBMP-2 was financially worthwhile for similar reasons.[28]

A major concern about BMP is possible complications. In the lumbar spine, these include heterotopic bone formation (8%), resorption or osteolysis (44%), subsidence (25%) or migration (27%) of graft/cage, seromas/hematomas (2%), wound complications (3%), antibody formation (0-5% for rhBMP-2; 26-29% for rhBMP-7), and inflammatory reaction to carrier substance (16%).[29] There are also safety concerns related to the effect of BMP on neural elements and the dura. Investigators have reported ectopic bone formation and other rare complications, including radiculitis, vertebral osteolysis, and inflammation.[29] One study showed substantial ectopic bone formation in PLIF with BMP use, though clinical symptoms were not apparent.[30] No study has clearly shown clinically significant ectopic bone formation caused by BMPs in TLIF.[10]

Some clinicians have hypothesized that BMP-associated complications may be dose-dependent, with higher doses or concentrations leading to increased reactions.[29] A prospective study found no additional complications related to rhBMP-7 use and concluded that rhBMP-7 was at least comparable to AICBG in uninstrumented lumbar fusion for degenerative spondylolisthesis.[31] Another hypothesized concern is risk for anaphylactic reactions when BMPs are used for a second time in a patient, though Carreon and colleagues[32] found this was not the case with rhBMP-2, regardless of procedure. Mroz and colleagues[29] also suggested that, though the dosage and complication profile of rhBMP-2 as used in the FDA-approved manner are well known, the optimal dosing for off-label use (eg, posterolateral fusion) and for multilevel use has yet to be defined. Given the high rate of "off-label" BMP use, more well-designed research must be conducted on BMP use in posterolateral fusion, posterior interbody fusion, and TLIF before definitive statements can be made about these alternative uses.

Demineralized Bone Matrix

DBM is an allograft product created by acid extraction of bone, which removes the mineralized components and leaves behind proteins, collagen, and osteoinductive growth factors, including BMPs. For almost 20 years, these products have been available in a variety of formulations from several manufacturers. The most significant differences between products are in bone type, processing, and carrier type. The result of these differences is a wide range of forms of DBM, including extruded paste and moldable putty, and DBM mixed with ceramic pellets. Some forms are supplied in heat-sensitive carriers that firm up at body temperature.

DBMs are inconsistent in their ability to induce bone formation.[33] One reason for this is that the sterilization process, gamma irradiation, can denature growth factors and decrease graft viability.[34] In an animal study, Alanay and colleagues[34] found that, when the Clearent procedure (radioprotectants and cold temperature) was performed before high-dose gamma irradiation, free radicals were minimized, and therefore, the viability of DBM was salvaged. Although not statistically significant, soaking the allograft in hydrogen peroxide for less than 1 hour before performing the Clearant and irradiation procedures led to the best outcomes with human DBM in 1-level posterior fusion in rats.[34]

The literature on the clinical efficacy of DBMs is sparse and, given the variety of products, difficult to generalize. Most products have demonstrated some evidence of osteoinductivity in either in vitro or in vivo laboratory studies. Few products, however, have been evaluated in

higher animal models or in prospective human clinical studies. A recent meta-analysis evaluated 3 premarket approval studies comparing DBM products with AICBG in PLF or PLIF.[4] These studies, which included a total of 298 patients, suggested no added benefit with DBM, compared with AICBG. Several other studies have found equivalency or noninferiority for DBM–autograft combinations, compared with AICBG.[35-38] Becker and colleagues[39] reported overall posterolateral fusion rates of 63% for DBM combined with BMA and 70% for DBM combined with AICBG, which suggests equivalent results. Another study evaluated DBM with local autologous bone and found a fusion rate (60%) similar to that of AICBG (56%).[36] In a prospective, randomized, multicenter study, Kang and colleagues[40] evaluated the efficacy of DBM in 1-level lumbar fusions and reported similar fusion rates for DBM plus local bone (83%) and AICBG (86%). Cammisa and colleagues[38] reported similar results in a study of 120 patients who underwent instrumented posterolateral fusion with AICBG on one side and DBM–autograft composite on the other. At 24-month follow-up, 52% of the DBM side and 54% of the autograft side showed fusion. Caution must be applied here, though, as one study found significant variability in the composition and osteoinductivity of different brands of DBM products,[33] and another found substantial variability in osteoinduction and BMP content across multiple lots of the same DBM product.[41]

Ceramic Bone Graft Extenders

Several natural and synthetic ceramic bone graft extenders act as osteoconductive agents. The major advantages of ceramics are minimal local inflammatory response to implantation and sterilization without elimination of bioactive components or structure weakening. Ceramics can be molded or manufactured into specific shapes. A relative disadvantage is their tensile strength, which is lower than that of bone. These products include CS, natural coralline ceramics, calcium phosphate/HA, and TCP. Ceramics are porous and mimic the porosity and scaffold structure of bone, allowing cell migration and adhesion. Ceramics alone are not sufficient in spinal fusion; an osteoinductive material must also be incorporated with this scaffold. It has been reported that, when TCP, HA, and hydroxyceramics are combined with BMA in animal models, osteogenesis is improved.[42-44]

TCP and HA are the most common clinically used ceramics, as they provide a scaffold for bone ingrowth but resorb as fusion occurs. When used in lumbar spinal fusion, TCP resorbs within 6 weeks.[45] Alternatively, CS resorbs within the first few weeks, which may be too early to facilitate lumbar fusion.[46] Several preclinical and clinical studies support the efficacy of ceramics. Specifically, BMA and TCP have had favorable results.[47] Local bone added to TCP or HA also has shown promise, according to a few clinical studies. Investigators have concluded that BMA combined with TCP and HA was equivalent to autograft in posterolateral fusion, but study results conflict with respect to interbody fusion.[48,49]

Numerous animal studies have favorably evaluated the efficacy of ceramics.[39,47,48,50,51] As with other bone graft extenders and substitutes, the clinical data on ceramics are limited. A prospective clinical study found that BMA plus local bone is an effective alternative to AICBG, yet BMA plus CS pellets is significantly less effective.[6] These outcomes may derive from the initial resorption of the CS scaffold, which leaves BMA without any osteoconductive material, and from the nonporous nature of the pellets.[6,49] The authors felt that porous and granular preparations of ceramics, including CS, may lead to better outcomes and should undergo further research.[6] Muschik and colleagues[52] evaluated a granular form of TCP mixed with autograft, and autograft mixed with allograft, in 28 patients with adolescent idiopathic scoliosis (AIS).[52] Both groups showed radiographic fusion and complete resorption of TCP at approximately 8 months. The authors concluded that TCP is a valid alternative even in AIS, in which large amounts of bone are required.[52]

In a recent technology overview of synthetic bone void fillers, the American Academy of Orthopaedic Surgeons identified 2 studies comparing ceramics with AICBG for posterior spinal fusion.[53] In a study of patients who underwent posterior fusion for AIS, those who received TCP had fewer intraoperative complications, significantly lower visual analog scale pain scores at discharge, and, not surprisingly, no donor-site pain in comparison with the AICBG group.[54] In the other study of adults who underwent posterior fusion for spondylolisthesis and stenosis, investigators compared a biphasic calcium phosphate ceramic and AICBG and found that the ceramics group had shorter operations and less blood loss.[55] Other studies have found similar fusion rates for autograft plus TCP and autograft plus allograft or autograft alone.[56,57] Another study evaluated coralline HA in instrumented posterolateral lumbar fusion and found fusion rates of 92.5% for coralline HA used alone and 89.3% for coralline HA used with DBM.[37] In a study of 42 patients, a silicate-substituted calcium phosphate had a 76.5% fusion rate in 1- or 2-level posterolateral lumbar fusion, and pain scores were improved; the results are consistent with those of other bone graft alternatives.[58] Ceramics have potential as osteoconductive bone graft extenders but lack the theoretical risks or complications associated with allograft or AICBG. Although there is promising preclinical and clinical evidence, further prospective, randomized clinical trials are required.

Conclusion

There are multiple options for bone graft extension and augmentation in lumbar spine surgery. Purely osteoinductive agents should be augmented with an osteoconductive substance (allograft or ceramic), local autologous

bone, or autologous iliac crest graft as a bulking agent to allow intergrowth of new bone. Given the numerous agents available, the surgeon must be cautious using them. The literature offers little strong evidence favoring one substance over another, and many studies are sponsored by the industry. When considering bone graft extenders, one must be aware of their FDA status, indications, contraindications, potential complications, and preclinical and clinical data. The surgeon must be careful not to generalize findings from one application, such as ALIF, to another, PLF. Likewise, the results of using one brand or preparation of a substance cannot be generalized to all substances in that category or across other categories of substitutes. Ultimately, the surgeon must choose the substance that offers the best option for the particular patient being treated.

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