The Use of Bone Morphogenetic Protein in Lumbar Spine Surgery

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Lumbar spinal fusion is an integral component of the surgical management of degenerative disease, trauma, deformity, tumor, and infection of the spine. Pseudarthrosis can, in turn, lead to persistent pain, failure of the instrumentation, and the need for revision surgery. It is a challenge to obtain a solid osseous fusion; therefore, both mechanical and biological variables should be optimized. Mechanical stability is optimized by using pedicle screws and rods for rigid fixation until there is osseous fusion. Internal fixation improves the fusion rates compared with those associated with lumbar fusion without instrumentation, but it does not ensure a 100% fusion rate.

Autogenous bone graft has been used to optimize the biological environment and is considered the “gold standard” for fusion in lumbar spine surgery; however, pseudarthrosis rates of up to 55% have been reported even with use of autogenous bone graft10. In addition, up to 25% of patients have reported substantial and persistent morbidity associated with the harvesting of autogenous iliac crest bone11-12. There is a limited supply of autogenous iliac crest, and it may not be available for a patient requiring revision surgery.

Biologics have been used as alternatives to, or enhancements of, autograft in lumbar fusion surgery over the last decade. One of the most studied and frequently used biological alternatives to autograft is bone morphogenetic protein (BMP). In this paper, we review the types of BMP used in lumbar spine surgery, the clinical results and complications associated with BMP use, and their economic impact.

What is BMP?
BMP was discovered by Marshall Urist in 19659. It is a group of growth factor proteins within the transforming growth factor-β (TGF-β) superfamily of growth factors10. Through molecular cloning techniques and recombinant expression, osteoinductive BMP molecules have been identified and have been produced in mass quantities in their pure form11-12. More than twenty types of BMP have been recognized, but only BMP-2, 4, 6, 7, and 9 have been shown to have significant osteogenic properties13-17.

BMP molecules seem to induce bone formation in a stepwise fashion, with individual BMP molecules functioning at different stages of osteoblastic differentiation and osteogenesis. There is probably a synergistic relationship between the different BMP molecules15. The BMP molecules combine in vivo to form heterodimers that are much more potent osteoinductive agents than the individual BMP molecules alone19. Receptors for these heterodimers have also been discovered20. It has been postulated that the signaling pathway of osteoblastic differentiation and osteogenesis is a complex cascade of BMP expression that consists of substantial interaction between the different types of BMP and other signaling molecules and receptors20.

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Two commercial forms of recombinant BMP have demonstrated success in preclinical and clinical trials and are available for clinical use. One is rhBMP-2 (Infuse; Medtronic Sofamor Danek, Memphis, Tennessee) and the other is rhBMP-7 (OP-1; Stryker Biotech, Hopkinton, Massachusetts). Although both of these types of BMP have osteogenic properties, only rhBMP-2 has been shown to induce osteoblastic differentiation of mesenchymal stem cells. Currently, the only United States Food and Drug Administration (FDA)-approved indication for use of any BMP in the spine is anterior lumbar interbody fusion with use of rhBMP-2 within a titanium tapered cage. All other uses in the spine are “off-label”.

**BMP Carriers**

To be effective, the BMP must be maintained at the planned site of fusion until the cascade of osteoblastic differentiation and osteogenesis is under way. Because BMP molecules are relatively soluble, less soluble carriers are used to maintain the BMP at the planned site of fusion. Carriers can either have structural, space-occupying properties (synthetic polymers and calcium phosphate ceramics) or provide little structure or space maintenance (type-I collagen sponge). Some of these structural carriers are porous and are composed of calcium compounds, making them osteoconductive (e.g., coral). Carriers with structural integrity are more desirable in posterolateral lumbar fusion because they maintain a space around the transverse processes in which the fusion mass can form. Carriers that are deformable, such as the type-I collagen sponge, are more suitable for use within interbody cages.

Types of BMP carriers include synthetic polymers, calcium phosphate ceramics, and type-I collagen. Synthetic polymers are advantageous because they are bioinert and can be manufactured with complete control over their architecture and rate of reabsorption. The most common synthetic polymers are polyactic acid and polyglycolic acid. These polymers are also used to make bioabsorbable implants and suture. When used as a BMP carrier, they are a porous, structural scaffold, which promotes osseous in-growth and then is absorbed after the fusion mass is established.

Calcium phosphate ceramics are highly crystalline, bioinert materials that, like synthetic polymers, are reabsorbed over time. The most commonly used are hydroxyapatite and tricalcium phosphate. Tricalcium phosphate is reabsorbed over about six weeks, which is probably not sufficient time for a bone fusion mass to develop. The resorption rate of hydroxyapatite, on the other hand, is years. Natural coral has an interconnecting porosity that is similar to that of bone. It can either be used in its calcium carbonate form or be processed (i.e., the carbonate can be replaced with phosphate) into a form that contains varying amounts of hydroxyapatite. The thickness of the hydroxyapatite determines its rate of dissolution.

Type-I collagen, the most abundant protein in bone, binds to non-collagenous protein and has a structure that promotes bone formation. These properties make it an attractive BMP carrier. As a BMP carrier, it is usually manufactured as an absorbable sheet or sponge from either porcine or bovine skin or bone. These type-I-collagen carriers do not provide structural support or maintain space. They can be combined with calcium phosphate ceramics to form structural scaffolds (e.g., Healon [DePuy, Raynham, Massachusetts] and Mastergraft Matrix [Medtronic Sofamor Danek]). The structural support of an interbody fusion is provided by the interbody cage, into which BMP carrier is placed over the transverse processes. A posterolateral lumbar fusion requires a BMP carrier with a structural capacity to withstand collapse under the forces of the surrounding paraspinal muscles and provide a space in which the fusion mass can form. Calcium phosphate ceramic has been shown to be an effective structural carrier in this setting. Alternatively, BMP can be carried on an absorbable type-I collagen sponge that is combined with a bulking agent (e.g., ceramic, allograft cancellous chips, or local autograft bone). This combination provides structural integrity and resists compression after placement over the transverse processes.

**Preclinical Results of BMP Use in Lumbar Fusion Surgery**

Before the use of BMP, a posterior spinal fusion was done by decorticating the osseous surfaces of the posterior vertebral elements and then applying an onlay graft of autogenous or allogenic bone. Most preclinical studies evaluating the safety and efficacy of rhBMP-7 and rhBMP-2 as substitutes for bone graft have shown them to be equal or superior to autogenous iliac crest bone graft in lumbar fusion surgery. RhBMP-7 and autograft were compared with regard to their effect on the maturation processes of lumbar posterolateral fusions in a canine model. Three treatment groups were compared: autograft alone, autograft plus rhBMP-7, and rhBMP-7 alone. The time to fusion, the resistance of the fusion to motion, and the pathway of bone formation producing the fusion were measured. At twelve weeks, fusion had been achieved at 83% of the posterolateral sites in which autograft plus rhBMP-7 had been implanted and 72% of the sites at which rhBMP-7 alone had been implanted, but only 27% of the sites treated with autograft alone. Biochemical testing indicated that the fusions obtained in both rhBMP-7 treatment groups had substantially preserved motion in flexion-extension and in axial rotation than did those obtained with the autograft bone alone. Plain and polarized light microscopic studies indicated that, in both of the rhBMP-7 treatment groups, bone formation had occurred by means of intramembranous ossification whereas, in the group treated with autograft bone alone, bone had been produced by means of endochondral bone formation. This may partly explain the increased prevalence, speed, and stability of the rhBMP-7-induced fusions.
One potential complication of using BMP is leakage of the BMP resulting in bone formation at remote sites. The effect of rhBMP-7 intentionally placed into the subarachnoid space after thecal sac decompression was studied in a canine model\(^3\). An opening was created in the dura and arachnoid membranes, and rhBMP-7 was placed into the subarachnoid space in thirty dogs. At sixteen weeks, new bone had developed in the subarachnoid space of all animals, with spinal stenosis and compression of the spinal cord. No neurotoxicity was noted. This result suggests that bone growth can occur over exposed dura and that the delivery and containment of rhBMP-7 are important to minimize this potential iatrogenic problem.

rhBMP-2 has also been studied as a bone graft substitute. In a rabbit model, the posterolateral lumbar fusion rate was 100% after use of rhBMP-2 on a type-I fibrillar collagen sponge whereas only 42% of the spines fused after use of autogenous iliac crest bone graft\(^4\). In a study of beagle dogs evaluated twelve weeks after L4-L5 intertransverse process fusion with either rhBMP-2 or autograft bone alone, all dogs treated with rhBMP-2 had a fusion whereas none of the dogs treated with autograft bone alone had a fusion\(^5\). In that study, several doses of rhBMP-2 were used, with a fortyfold variation between the highest and lowest doses. There were no mechanical, radiographic, or histological differences in the quality of the fusion masses obtained with the different doses\(^6\). This finding suggests that, above a threshold dose, the quality of spinal fusion produced with rhBMP-2 does not change with the dose.

Primates are thought to require higher doses of BMP to effect similar outcomes, and in one study concentrations of rhBMP-2 that produced fusions in canines and rabbits failed to do so in rhesus monkeys\(^7\). One reason for this finding is that primates are believed to have lower concentrations of BMP-responsive cells\(^8\).

Another problem encountered in nonhuman primates that was not seen in rabbits and dogs was compression of the collagen sponge carrier by the large paraspinal muscles\(^9\). It is possible that this excessive compression squeezed the protein out of the carrier sponge and prevented the development of an adequate fusion mass\(^10\). A subsequent study showed that a structural ceramic BMP carrier that is able to resist compression may be more suitable for posterolateral fusion in primates: all of fifteen rhesus monkeys treated with rhBMP-2 in this structural ceramic carrier had a successful posterolateral fusion\(^10\).

The safety of direct contact of rhBMP-2 with neural tissue was tested in twenty beagles that underwent an L5 laminectomy\(^11\). Half of the dogs had a puncture wound created in the dura, and either autogenous bone graft or rhBMP-2 was randomly applied to the exposed dura. At twelve weeks, there was no clinical, radiographic, or histological evidence of neurological abnormalities. The rhBMP-2 had stimulated bone growth in the laminectomy defect that was in direct contact with the dural membrane, and there was no evidence of abnormal mineralization within the thecal sac or in the spinal cord itself.

**Clinical Results of BMP Use in Lumbar Fusion Surgery**

**Anterior Lumbar Interbody Fusion**

The use of rhBMP-2 in spinal surgery was first studied in anterior lumbar interbody fusion, and this is the only FDA-approved indication for its use. In a multicenter, prospective, randomized study, 279 patients with single-level degenerative lumbar disc disease underwent anterior lumbar interbody fusion with use of two tapered titanium threaded fusion cages\(^12\). RhBMP-2 on an absorbable collagen sponge was used in the cages in 143 patients, and autograft iliac crest was used in the cages in 136 patients. The dose of rhBMP-2 ranged from 12 to 18 mg (in the form of a 1.5-mg/mL solution), depending on the size of the cage that was used. The mean operative time and blood loss were less in the rhBMP-2 group. The autograft group had substantial morbidity at the iliac crest donor site, with 5.9% of the patients experiencing an adverse event related to graft harvest and 32% of the patients reporting discomfort at the graft site after two years. Two years after the surgery, plain radiographs and computed tomography scans were used to evaluate the osseous fusion. The rhBMP-2 group was reported to have a 94.5% fusion rate compared with an 88.7% fusion rate in the autograft group. Both groups had similar improvements in clinical outcome measures through the duration of the study.

Two different prospective multicenter studies were performed to compare rhBMP-2 and autogenous iliac crest used in threaded allograft cortical dowels for single-level anterior lumbar interbody fusion\(^12\). Plain radiographs and computed tomography scans were used to evaluate the fusion. In the first study, all twenty-four patients in the rhBMP-2 group and only 68% of the twenty-two in the autograft group had a solid osseous fusion at two years after the surgery\(^12\). At the time of final follow-up, the patients in the rhBMP-2 group had a better neurological status and less back and lower-limb pain than the patients in the autograft group. No adverse events were associated with the use of rhBMP-2. In the second study, 131 patients had a single-level anterior lumbar interbody fusion with threaded allograft dowels; seventy-nine received rhBMP-2, and fifty-two received autograft\(^13\). The authors reported a 100% fusion rate in the rhBMP-2 group at one and two years and an 89% fusion rate at one year and an 81.5% fusion rate at two years in the autograft group. Eighteen percent of the patients in the rhBMP-2 group had transient vertebral osteolysis; all of these cases resolved by two years and had no effect on the clinical outcome.

**Posterolateral Lumbar Fusion**

The use of rhBMP-2 was compared with the use of autograft iliac crest bone in posterolateral lumbar fusion in two prospective, randomized, multicenter, FDA-regulated investigational device exemption clinical studies. Part of the first FDA-regulated study was a prospective, randomized clinical pilot study...
comparing posterolateral lumbar spine fusion in three groups of patients\textsuperscript{32}. Five patients were treated with autograft with pedicle screw fixation; eleven patients, with rhBMP-2 with pedicle screw fixation; and nine patients, with rhBMP-2 without pedicle screw fixation. All patients had single-level degenerative disc disease with no greater than Grade-I spondylolisthesis. The dose of rhBMP-2 was 20 mg per side of the spine (in a 2-mg/mL solution), which was larger than the dose used in the anterior lumbar interbody fusion procedures\textsuperscript{21-23}, carried on calcium phosphate ceramic granules. At an average of seventeen months postoperatively, only 40\% of the spines in the autograft group were fused whereas 100\% of those in the groups that had received rhBMP-2 (both with and without pedicle screw fixation) were fused; also, clinical improvement was seen earlier in the rhBMP-2 groups. The patients treated with rhBMP-2 without pedicle screws had the greatest improvement in the Oswestry Disability Index at the time of final follow-up.

In the second ongoing prospective, randomized, FDA-regulated study, rhBMP-2 at a dose of 20 mg per side (in a 2-mg/mL solution) on a compression-resistant matrix (hydroxyapatite and tricalcium phosphate/collagen) carrier was compared with autograft iliac crest for use in a single-level posterolateral lumbar fusion\textsuperscript{32}. The patients in the study had degenerative lumbar disc disease with no greater than Grade-I spondylolisthesis and a failure of at least six months of conservative treatment. The rhBMP-2 group had a significantly higher mean fusion grade than the autograft group at both six months (p < 0.0001) and twelve months (p < 0.0023) (Fig. 1). In a later report of the two-year results of this study\textsuperscript{43}, which included forty-five patients in the autograft group and fifty-three in the rhBMP-2 group, there was a shorter operative time and less blood loss in the rhBMP-2 group. There were no differences in clinical outcomes. The fusion rates were 73\% in the autograft group and 91\% in the rhBMP-2 group (p = 0.051). Complication rates were similar, and most complications were secondary to gastrointestinal, traumatic, or cardiac events.

A separate publication involving the same data presented a comparison of patients who smoked and those who did not\textsuperscript{44}. At two years after the surgery, solid lumbar fusion was obtained in 100\% of the fifty-five nonsmokers and 95\% of the twenty-one smokers in the rhBMP-2 group. In the autograft group, solid fusion was achieved in 94\% of the fifty-one nonsmokers and 76\% of the twenty-one smokers. Despite the improved rate of solid fusion in the smokers who had received rhBMP-2, the values for the clinical outcome measures for the smokers were decreased compared with the values for the nonsmokers. The authors concluded that rhBMP-2 can enhance the fusion rate in smokers who undergo single-level posterolateral lumbar fusion.

In another study, a group of forty-one patients who had had a posterolateral lumbar fusion with rhBMP-2 (12 mg in the form of a 1.5-mg/mL solution) on a collagen sponge placed along with autograft iliac crest was compared with a group of eleven age and sex-matched patients who had been treated with autograft iliac crest alone\textsuperscript{45}. The rhBMP-2/autograft group had an increased rate of fusion of 97\% (sixty-eight of seventy operatively treated levels) compared with the autograft group, which had a fusion rate of 77\% (seventeen of twenty-two operatively treated levels) (p < 0.05). Although the combination of rhBMP-2 and autograft iliac crest pro-
provided the highest reported fusion rate following posterolateral lumbar arthrodesis, to our knowledge, it does not eliminate the substantial potential for morbidity at the iliac crest harvest site.

In a retrospective study, ninety-one patients who had been treated, at a single institution, with a posterolateral lumbar spine fusion with use of rhBMP-2 (12 mg in the form of a 1.5-mg/mL solution) on a collagen sponge that was wrapped around local bone and bone-graft extender were compared with a group of thirty-five patients who had undergone single-level posterolateral lumbar fusion with use of autogenous iliac bone graft. In the rhBMP-2 group, forty-eight patients had a primary single-level fusion, twenty-seven had a primary multilevel fusion, and sixteen patients had revision fusion surgery because of nonunion. At the time of follow-up, at a minimum of two years, the nonunion rates in these three groups were 4.2%, 0%, and 25%, respectively. The autograft group had a nonunion rate of 11.4%. Within the rhBMP-2 group, a subgroup of patients who were identified as smokers had no nonunions. The men in the rhBMP-2 group had a significantly higher nonunion rate than the women (11.1% and 3.4%, respectively; p = 0.036). The authors of the study concluded that use of the lower dose of rhBMP-2 (compared with that used in prior studies), applied with local bone and bone graft extender, results in a fusion rate similar to that following use of autograft iliac crest in posterolateral lumbar fusion. It also appeared that rhBMP-2 may increase fusion rates in smokers.

Several investigators have evaluated the clinical efficacy of rhBMP-7 (OP-1), particularly in posterolateral lumbar fusion. These early studies did not show the fusion rate following use of OP-1 combined with autograft to be superior to that achieved with autograft alone, but there were no documented complications related to the use of OP-1. A larger multicenter, prospective, randomized, FDA-approved investigational device exemption clinical study was performed to evaluate the use of OP-1 putty as a replacement for iliac crest autograft in single-level posterolateral lumbar fusion in patients with symptomatic lumbar stenosis and Grade-I or II degenerative spondylolisthesis. Twenty-four patients were randomized to receive OP-1 putty and twelve, to receive iliac crest autograft. The OP-1 putty (3.5 mg per side of the spine) was placed between the transverse processes at the level of interest. No local autograft bone or instrumentation was used. At one year, two years, and four years postoperatively, the OP-1 and iliac crest autograft groups had similar fusion rates (approximately 50%) and clinical outcomes. No adverse effects had resulted from the use of the OP-1.
In a prospective randomized study, OP-1 putty (3.5 mg per side, in nine patients) was compared with a mixture of local autograft and calcium phosphate ceramic granules (in ten patients) for a single-level posterolateral lumbar fusion with internal fixation in patients with spinal stenosis and degenerative spondylolisthesis. At one year postoperatively, radiographic evidence of fusion was present in seven of the nine patients who had received OP-1 and nine of the ten patients who had received the autograft-ceramic mixture. In sixteen patients, the hardware was removed and the fusion mass was explored. In that group, only four of the seven patients treated with OP-1 and seven of the nine treated with the autograft-ceramic mixture had a solid fusion. The authors concluded that, although OP-1 does stimulate new bone formation at the site of a posterolateral fusion, the rate of solid fusion is low.

Transforaminal Lumbar Interbody Fusion
This procedure, first described by Harms and Rolinger in 1982, allows an anterior interbody fusion and a posterolateral fusion to be achieved through a single posterior approach. An interbody cage with bone graft is placed into a distracted disc space through a posterolateral transforaminal approach, and a standard posterolateral fusion with pedicle screw stabilization is done. To eliminate the need for iliac crest autograft and the morbidity associated with its harvest, “off-label” use of rhBMP-2 in transforaminal lumbar interbody fusion has become increasingly popular (Figs. 2-A through 2-L).

In a preliminary study of transforaminal lumbar interbody fusions, with an average duration of follow-up of nine months, the fusion rate associated with use of rhBMP-2 and autograft (in twenty-one patients) was compared with the fusion rate associated with use of iliac crest autograft alone (in nineteen patients). Of the twenty-one patients who were treated with rhBMP-2 and autograft, twelve received iliac crest autograft and nine received autograft obtained locally from the laminectomy. In this group, the autograft was packed posterior to the rhBMP-2-filled cage. The mean time to fusion was six months in the autograft group, four months in the rhBMP-2/iliac crest autograft group, and three months in the rhBMP-2/local bone group. One patient in the autograft group and one patient in the rhBMP-2/local bone group had a pseudarthrosis. No patient in the rhBMP-2/iliac crest autograft group had a pseudarthrosis or symptomatic foraminal bone formation. The authors concluded that rhBMP-2 is a safe and effective alternative to iliac crest autograft for use in transforaminal lumbar interbody fusion and that it leads to more rapid
fusion while eliminating harvest-site morbidity.

The use of rhBMP-2 in both minimally invasive and open transforaminal lumbar interbody fusion procedures was reported in seventy-four patients followed for an average of twenty months. The study included single-level and multilevel transforaminal lumbar interbody fusions, many of which were performed in the setting of previous lumbar surgery. The BMP-2 was applied on an absorbable collagen sponge and was combined with autogenous local bone and/or allograft bone. All patients in the study had a solid fusion within ten months after the surgery, with a mean time to fusion of 4.1 months. There were no complications or allergic reactions that the authors attributed specifically to the use of the rhBMP-2. Two patients, however, were noted to have persistent, postoperative radiculitis. No ectopic bone formation was observed.

Safety of BMP in Lumbar Spine Surgery

Few documented adverse events can be attributed to BMP. Nonetheless, certain complications and safety issues related to use of BMP in the lumbar spine are concerns. Adverse reactions with repeat BMP exposure include postoperative radiculitis, vertebral osteolysis and edema, and neurocompressive ectopic bone formation (i.e., bone formation in the central canal or intervertebral foramen).

As a foreign protein, BMP has the potential to stimulate the formation of antibodies. Antibodies to BMP can, on reexposure, lead to a hyperinflammatory response with local (e.g., wound) problems and systemic consequences (e.g., anaphylaxis), but there is no clinical evidence to suggest that reexposure to BMP can have detrimental effects. The use of BMP, particularly in transforaminal lumbar interbody fusion and posterior lumbar interbody fusion, has been associated with severe postoperative radiculitis, which can start days after the surgery without neural compression. The cause is thought to be a BMP-related pro-inflammatory reac-
tion and/or ectopic bone formation in the vicinity of the nerve root sleeve and the intervertebral foramen. Postoperative nerve injury (i.e., a new or increased neurological deficit) was reported in 20.7% and 14.3% of patients who had undergone one and two-level minimally invasive transforaminal lumbar interbody fusion with rhBMP-2, respectively. The authors stated that none of the complications were specifically attributed to rhBMP-2. Two of the patients in their study had persistent postoperative radiculitis that was still present at the time of the latest follow-up. In another study, with a retrospective design, radiculitis that lasted more than six months developed in nine of...
thirty-nine patients who had had a transforaminal lumbar interbody fusion with use of rhBMP-2 and only one of twenty-nine patients who had had the fusion with use of iliac crest autograft. The average duration of the postoperative radiculitis in the rhBMP-2 group was 13.4 months. There is anecdotal evidence that the use of a sealant, such as DuraSeal Xact Sealant System (Confluent Surgical, Waltham, Massachusetts), to minimize the amount of rhBMP-2 in the vicinity of the nerve root may decrease the prevalence of postoperative radiculitis. Clinical studies are needed to further explore this issue.

Ectopic bone formation can potentially occur in the anterior epidural space and near the nerve root, along the track of insertion of BMP, when an interbody fusion is performed from a posterolateral or transforaminal approach (Fig. 3). Although the risks of ectopic bone formation developing with BMP use remain unknown, hematoma seems to be a carrier and excessive bleeding can disperse the BMP. Hemostatic agents, such as Gelfoam (Pfizer, New York, NY), have also been implicated as carriers. An early study of the use of BMP in posterior lumbar interbody fusion demonstrated a high rate of substantial ectopic bone formation in the spinal canal. No clinical symptoms, however, developed secondary to this ectopic bone formation. Clinical studies of the use of BMP in transforaminal lumbar interbody fusion have not revealed problems with ectopic bone formation. Placement of the rhBMP-2 anterior to and within the interbody cage in the anterior column, but not in the middle column near the anulotomy, is thought to minimize the risk of ectopic bone formation in the spinal canal and/or intervertebral foramen following a transforaminal lumbar interbody fusion.

Vertebral osteolysis and vertebral edema have been observed after use of BMP in an interbody fusion. The pathophysiology and relevance of the vertebral osteolysis are unknown. It has been reported to occur in 8% to 18% of cases. It seems to resolve spontaneously, but patients may have pain while it is present (Fig. 4). It may be due, at least in part, to a violation of the vertebral body end plate during preparation of the disc space.

**Economics of BMP Use in Spine Surgery**

There have been several economic evaluations comparing the cost of BMP use with the cost of traditional autogenous iliac crest bone-grafting. Most investigators have concluded that BMPs will prove to be cost-neutral. The costs associated with the use of BMPs are largely offset by the prevention of the pain and complications associated with the harvest of autogenous iliac crest bone graft. Ultimately, the largest long-term cost offset may be associated with a reduced number of fusion failures and the reduced need for revision. An economic model based on clinical trial data, peer-
reviewed literature, and clinical expert opinion suggested that, over a two-year period after the surgery, the upfront cost of BMP is likely to be offset to a substantial extent by more efficient use of other medical resources, including a decreased length of hospital stay and decreased use of pain clinics and rehabilitation services.

In an economic prospective, randomized, controlled trial, fifty patients, over sixty years old, who were treated with lumbar spine surgery with rhBMP-2 were compared with fifty-two patients, over sixty years old, who were treated with lumbar spine surgery with iliac crest bone graft, with or without graft extender. All costs during the first three months after the surgery (the perioperative Medicare global billing period) were recorded. A research nurse followed all patients throughout their hospital stay and post-hospitalization recovery to identify any adverse events or additional outpatient medical care. The total payer expenditure for the three months averaged $33,860 in the rhBMP-2 group and $37,227 in the iliac crest bone-graft group. In the rhBMP-2 group, the mean operative time was twenty-two minutes shorter, the mean length of stay in the hospital was almost a day shorter, and inpatient rehabilitation was utilized less frequently.

Overview

The use of BMPs in lumbar fusion surgery has increased over the last several years. Both rhBMP-2 and rhBMP-7 are members of the TGF-β superfamily and have been used with success in both preclinical and clinical trials. The only FDA-approved indication for BMP in the spine is anterior lumbar interbody fusion with use of rhBMP-2 in a titanium tapered cage. “Off-label” uses of BMPs are becoming increasingly popular as enthusiasm for them grows and indications for their clinical application expand. Several randomized trials are currently being performed to study the use of BMPs in both posterolateral lumbar fusion and transforaminal lumbar interbody fusion. These studies have produced promising early results. Important concerns regarding the clinical application of BMP include safety and cost. Finally, the large upfront cost of BMPs appears to be offset by the prevention of complications associated with iliac crest harvest, including a longer operative time, more blood loss, and longer inpatient and rehabilitation stays. Ultimately, if use of BMPs is able to reduce the number of fusion failures, then they will prove to be cost-sparing in the long run.

Fig. 4
Coronal computed tomography scan (A) and sagittal T1-weighted magnetic resonance image (B) demonstrating vertebral osteolysis six months following a transforaminal lumbar interbody fusion performed with use of rhBMP-2. Although this finding is often associated with increased back pain and radiculitis, it seems as though the vertebral body reaction to BMP is a self-limiting process that does not affect the clinical outcome or the rate of fusion.
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