Osteolysis in Lumbar Interbody Fusions: The Role of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)

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ABSTRACT

Osteolysis may occur following lumbar interbody fusion procedures in which recombinant human bone morphogenetic protein-2, more commonly known as rhBMP-2, is used. The actual incidence of this process is unknown. Osteolysis results from an osteoclastic, rather than an osteoblastic response to rhBMP-2 and its carrier on trabecular vertebral bone, early in the sequence of bone graft healing. This osteoclastic response may represent an idiosyncratic reaction in those affected. The patient usually does well in the immediate postoperative period with resolution of their preoperative complaints of axial and radicular pain. However, at 4 to 12 weeks following the index surgery, the patient experiences a recurrence of severe back and radicular pain corresponding to the dermatomal level(s) operated upon. Laboratory studies including erythrocyte sedimentation rate, C reactive protein, and cultures are negative for infection. Imaging studies show areas of bone destruction and cyst formation containing fluid. In the majority of postoperative patients with osteolysis, there is an osteoblastic healing response with symptom resolution. Supportive, nonoperative care is usually effective in managing the patient.

Keywords: Osteolysis, Bone resorption, rhBMP-2, Interbody fusion, Radiculitis.

INTRODUCTION

Bone morphogenetic protein (BMP) has been used for several years as a substitute for autogenous iliac crest bone graft in fracture repair augmentation and spinal fusion procedures. Cahill et al1 recently reported on the complications and hospital costs associated with the use of BMP in spinal fusions. Several investigators have noted osteolysis following lumbar interbody fusion procedures with rhBMP-2.2-8 Osteolysis has not occurred in patients undergoing a posterior lateral fusion in which rhBMP-2 has been used.8 Swelling and edema following its use in anterior cervical fusions has lead to serious complications.10-12 Perioperative radiculitis, hematoma and seroma formation, as well as wound infection have all occurred in patients undergoing transfemoral lumbar interbody (TLIF) with rhBMP-2.2,3,13 Currently, rhBMP-2 is Food and Drug Administration (FDA)-approved for use only in anterior interbody LT-cages® (Medtronic, Memphis, TN) and in fracture repair augmentation.13 Today, most spinal applications of rhBMP-2 are being used off-label.

BMP and rhBMP-2

BMP was discovered by Marshall Urist in 1965 at UCLA Medical Center.14 It is produced from bone in which the marrow has been removed. BMP is extracted through a tedious, low temperature dialysis process utilizing demineralized bone matrix, containing 90% bone collagen. Urist found that BMP induces osteogenesis when placed in the soft tissues of animals and results in healing of bony defects. Specifically, rhBMP-2 is a recombinant human protein produced in mouse cell lines. It is delivered on a bovine collagen carrier sponge. INFUSE® (Medtronic, Memphis, TN) was FDA-approved for use in anterior LT-cages® in 2002.13 Each INFUSE® kit contains 4.9 mg of rhBMP-2 with bovine collagen carrier sponges. Currently, it is recommended that 4.2 mg of rhBMP-2 be placed on two to four collagen sponges, then placed in titanium interbody cages to promote fusion in the lumbar spine. Overall, rhBMP-2 has been used in posterior lateral spinal fusions, TLIF, posterior lumbar interbody fusions (PLIF), extreme lateral interbody fusions (XLIF), direct lateral interbody fusions (DLIF) and axial lumbar interbody fusions (AxiaLIF).15-23

Preparation of the Interbody Fusion Site

Removal of the remnants of the intervertebral disk with portions of the annulus and anterior and posterior longitudinal ligaments is common to all but the AxiaLIF procedure, which is done via transosseous axial channel through the sacrum. The end plates are denuded of any remaining surface cartilage, to the level of subchondral bleeding bone. An attempt is made to distract and realign the interspace before insertion of the polyether ether ketone (PEEK) or metallic interbody cages. The cages may be filled with autogenous bone, allograft bone, or various bone graft extenders, such as tricalcium phosphate or hydroxylapatite composites, as well as rhBMP-2 applied to bovine collagen sponges. Villavicencio et al2,3 postulated that placing rhBMP-2 near exposed endplate-marrow defects would result in osteolysis. Various barrier sealants have been recommended to prevent migration of rhBMP-2 into the epidural space to prevent an inflammatory response and heterotopic bone formation around the dura.4 In most cases, the cage or anterior implant is reinforced with pedicle screw fixation.
Clinical and Radiographic Findings

There are numerous case reports of patients undergoing interbody fusions with rhBMP-2 who have experienced complications in the early postoperative period. Marked swelling in the soft tissues of the neck leading to dyspnea and dysphagia following the use of rhBMP-2 in anterior cervical fusions has been reported. To this effect, the FDA issued a physician warning in 2009 detailing the potential for rhBMP-2 to cause such problems.

Patients undergoing interbody lumbar fusions with rhBMP-2 can experience the onset of severe axial and radicular pain within 4 to 12 weeks postoperatively. Typically, subsequent infectious work-ups are negative, including white blood cell count, erythrocyte sedimentation rate, C reactive protein and cultures. Vaidya et al reported on the complications experienced by ten ALIF and twenty-six TLIF or PLIF patients in whom rhBMP-2 was used. Several of these patients required revision surgery because of worsening neurologic complaints and subsidence of their interbody cages.

Plain radiographs of the lumbosacral spine are typically not helpful in detecting osteolysis. Cage, rod and screw constructs often fail to maintain correction because the bone in which they are placed has undergone osteolysis. Areas of edema and cysts containing fluid are best seen on magnetic resonance imaging (MRI) studies (Figs 1A to 2B). Computed tomography (CT) scans show areas of bone loss in the vertebral body and around the anterior implants and pedicle screws (Figs 3A and B). Some of these osteolytic areas can be quite extensive and tract through perforations in the endplate to adjacent vertebral levels. Fluid-filled cysts in juxta position to nerve roots and the dura may result in radicular complaints.

Cause of Osteolysis

There is speculation that some patients experience an idiosyncratic reaction to rhBMP-2. Instead of inducing osteogenesis through stimulation of mesenchymal and
osteoprogenitor cells, an inflammatory and osteoclastic reaction occurs in the trabecular bone exposed to rhBMP-2. This untoward reaction results in soft tissue edema, cyst formation and bone resorption. Toth et al. reported transient osteoclastic activity in the distal femora of sheep related to increasing dosages of rhBMP-2. Meisel et al. noted transient periimplant osteolysis in a sheep model in which rhBMP-2 was used. Seeherman and Wozney demonstrated that rhBMP-2-soaked collagen sponges placed in contact with trabecular bone of the distal femur resulted in significant transient osteolysis as early as 2 weeks. Laursen et al. using a direct application of rhBMP-7 in five patients with unstable burst fractures, found severe anterior column resorption after 3 to 6 months. Although the osteolysis subsequently resolved, there was loss of vertebral body height and sagittal imbalance. Vaidya et al. found an 82% rate of vertebral endplate resorption in PEEK cages filled with rhBMP-2 used for interbody fusions. Once the acute inflammatory reaction and osteolysis abates, new bone is formed and the interbody fusion heals. If loss of correction and mechanical failure of the implants occurs, revision surgery may be required.

**DISCUSSION**

McClellan et al. found areas of bone resorption in 69% of the operated levels in 26 patients who underwent a TLIF with rhBMP-2. The osteolytic defects found on the postoperative CT scans at 3 months were moderate (5 mm × 5 mm) to severe (1 cm × 1 cm) in nearly half of the patients studied. Graft and implant subsidence were also noted in those with severe defects. The rate of subsidence in interbody cages is related to bone density and integrity of the vertebral endplates. Support of the intervertebral body implants with posterior instrumentation is critical during the osteoclastic and healing phase of osteolysis. Stand-alone cages and anterior implants are not biomechanically sound and require posterior instrumentation for stabilization.

Rihn et al. reported the following complications in 86 patients undergoing a single-level TLIF with rhBMP-2: 14% with postoperative radiculitis, 5.8% with vertebral osteolysis, 2.3% with ectopic bone formation and 3.5% with a wound infection. Balserio and Nottmeier reported on two cases of vertebral osteolysis originating from subchondral cyst endplate defects in patients undergoing TLIF with rhBMP-2. Lewandrowski et al. reported on five patients who presented with worsening back pain and variable radicular pain at 1 to 3 months following a TLIF in which rhBMP-2 was used. They noted that the osteolytic defects filled in and symptoms resolved within 3 months without formal treatment. They suggested that a dose-dependent cellular cascade activation of osteoclasts over the osteoblasts may have occurred as a result of the rhBMP-2 induced inflammatory effects.

In the original reports by Burkus et al. on the use of rhBMP-2 in anterior interbody fusions with femoral ring allografts, cortical allograft dowels and tapered titanium cages, they noted radiolucent lines around some of the implants. Osteolysis most likely occurred in some of these patients, but was not investigated with either MRI or CT scans. Mummaneni et al. in a preliminary report noted rapid creation of interbody fusions in patients undergoing TLIF with rhBMP-2. Joseph et al. noted heterotopic bone formation with the use of rhBMP-2 in posterior, minimal-access interbody fusions. Wong et al. reported on five patients with ectopic bone formation in the spinal canal following a PLIF or TLIF in which rhBMP-2 was used. Three of the five patients required revision surgery for severe radicular pain. Mindea et al. also reported on the occurrence of radiculitis in patients undergoing minimally invasive TLIF with rhBMP-2.
Owens et al. reviewed 204 consecutive patients for perioperative complications following TLIF with rhBMP-2 at 3 months and found complications in 47 patients (21.6%). Thirteen patients (6.4%) had new or worsening postoperative neurologic complaints and six required additional surgery. In four patients, a seroma in the area of the neural foramen caused nerve root compression. Six patients had persistent radiculopathy of unknown etiology found in their imaging studies. These patients improved with oral steroids and other medications on average at 4.0 ± 2.8 months after their index surgery. In order to minimize the potential for postoperative radiculitis and radiculopathy, Villavicencio et al. recommended placing the rhBMP-2 anterior to the structural allografts in TLIF procedures. Rihn et al. noted a decrease in postoperative radiculitis with the use of a hydrogel sealant posterior to the interbody cage. Reported rates of postoperative radiculitis in TLIF procedures using autograft are 2 to 7%. The reported rate of radiculitis in TLIF procedures in which rhBMP-2 is used ranges from 7 to 14%.

In summary, the use of rhBMP-2 appears to be safe in applications where it does not incite an osteoclastic inflammatory response. However, one must be cautious when using rhBMP-2 in interbody fusion applications in which direct contact is made with the exposed trabecular bone of the vertebral body, as often occurs in ALIF, PLIF, TLIF, XLIF and AxiaLIF procedures. Although the osteoclastic response is usually of short duration, instability and loss of correction can occur and necessitate further reconstructive surgery. Management of radiculitis and radiculopathy may require several months of supportive care.

REFERENCES

13. INFUSE bone graft and LT-cage approved by FDA, 2 July 2002, P050053A.


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