Interbody fusion with allograft and rhBMP-2 leads to consistent fusion but early subsidence

R. Vaidya,
R. Weir,
A. Sethi,
S. Meisterling,
W. Hakeos,
C. D. Wybo

From Henry Ford Hospital, and Detroit Receiving Hospital, Detroit, Michigan, USA

We carried out a prospective study to determine whether the addition of a recombinant human bone morphogenetic protein (rhBMP-2) to a machined allograft spacer would improve the rate of intervertebral body fusion in the spine. We studied 77 patients who were to undergo an interbody fusion with allograft and instrumentation. The first 36 patients received allograft with adjuvant rhBMP-2 (allograft/rhBMP-2 group), and the next 41, allograft and demineralised bone matrix (allograft/demineralised bone matrix group). Each patient was assessed clinically and radiologically both pre-operatively and at each follow-up visit using standard methods. Follow-up continued for two years.

Every patient in the allograft/rhBMP-2 group had fused by six months. However, early graft lucency and significant (> 10%) subsidence were seen radiologically in 27 of 55 levels in this group. The mean graft height subsidence was 27% (13% to 42%) for anterior lumbar interbody fusion, 24% (13% to 40%) for transforaminal lumbar interbody fusion, and 53% (40% to 58%) for anterior cervical discectomy and fusion. Those who had undergone fusion using allograft and demineralised bone matrix lost only a mean of 4.6% (0% to 15%) of their graft height.

Although a high rate of fusion (100%) was achieved with rhBMP-2, significant subsidence occurred in more than half of the levels (23 of 37) in the lumbar spine and 33% (6 of 18) in the cervical spine. A 98% fusion rate (62 of 63 levels) was achieved without rhBMP-2 and without the associated graft subsidence. Consequently, we no longer use rhBMP-2 with allograft in our practice if the allograft has to provide significant structural support.

■ R Vaidya, MD, FRCS(C), Chief Orthopaedic Surgeon
■ A. Sethi, MD, Orthopaedic Surgeon
Department of Orthopaedic Surgery
Detroit Receiving Hospital and University Health Center, 4201 St. Antoire Boulevard. 6A, Detroit, Michigan 48201, USA.

■ R. Weir, MD, Resident, Orthopaedic Surgeon
■ S. Meisterling, MD, Resident Orthopaedic Surgeon
■ W. Hakeos, MD, Resident Orthopaedic Surgeon
■ C. D. Wybo, MS, Senior Research Engineer
Department of Orthopaedic Surgery
Henry Ford Hospital, 2799 W Grand Boulevard, Detroit, Michigan 48202, USA.

Correspondence should be sent to Dr R. Vaidya; e-mail: ravaidya@hotmail.com

doi:10.1302/0301-620X.89B3.18270 $2.00

J Bone Joint Surg [Br] 2007;89-B:342-5.
Received 14 June 2006; Accepted 20 September 2006

Bone morphogenetic proteins (BMPs) are a group of osteoinductive proteins that form part of the superfamily of transforming growth factor-β (TGF-β).[1] Using recombinant (rh) gene technology it has been possible to produce unlimited quantities of BMPs, designated rhBMP-1 to rhBMP-9.[2] One of these, rhBMP-2, is capable of promoting new bone and cartilage growth.[1] Within the past few years there has been much published research on the safety and effectiveness of rhBMP-2. Both animal studies and clinical results have been very encouraging.[1,3-10] In 2002, the Food and Drug Agency (FDA) in the USA approved the use of InFUSE (rhBMP-2 applied to a collagen sponge) (Medtronic Sofamor Danek, Memphis, Tennessee) in a lumbar tapered fusion device (LT)-cage (Medtronic Sofamor Danek) for anterior lumbar fusion.[11] Studies suggested that InFUSE could replace autogenous bone graft in spinal interbody fusion,[3,4,12] thereby avoiding complications at the donor site.[13]

At the time, our preferred device for interbody fusion was an MTF allograft spacer (Musculoskeletal Transplant Foundation; Synthes, Edison, New Jersey) combined with autograft. These spacers excited a minimal immune response, were safe with regard to disease transmission because of their extensive processing, were easy to size and use, and had given good clinical results. They remained structurally sound without remodelling and there was little or no subsidence at two years.[14] Reports on the use of InFUSE suggested that it could achieve a quick, consistent fusion with less pain in patients undergoing anterior lumbar fusion.[13] We embarked on a prospective study to determine its effectiveness.

Patients and Methods

We studied 77 consecutive patients (118 levels) who required a cervical or lumbar interbody fusion. The first 36 (55 levels) underwent surgery with allograft and adjuvant rhBMP-2 over a period of eight months. There were 16 men and 20 women in this group, with a mean age of 47.9 years (18 to 71). The operations carried out were 13 anterior lumbar interbody fusions (20 levels), 12 transforaminal

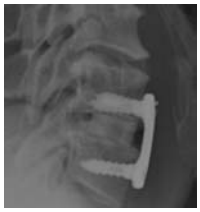

Fig. 1a

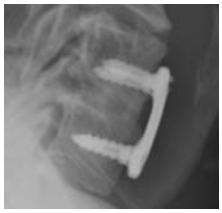

Fig. 1b

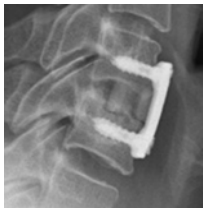

Fig. 1c

a) Immediate post-operative radiograph after allograft placement, b) allograft with rhBMP-2 at four months showing incorporation of the graft and c) allograft without rhBMP-2 at 12 months.

lumbar interbody fusions (17 levels) and 11 anterior cervical decompressions and fusions (18 levels). These were followed up for a mean of 24.1 months (17 to 30).

The next 41 patients (63 levels) underwent surgery using allograft and demineralised bone matrix. There were 18 men and 23 women in this group, with a mean age of 45 years (16 to 77). The operations carried out were 11 anterior lumbar interbody fusions (16 levels), 18 transforaminal lumbar interbody fusions (25 levels) and 12 anterior cervical decompressions and fusion (22 levels). These were followed up for a mean of 24 months (18.5 to 27).

The indications for surgery included adult scoliosis (seven rhBMP-2, five allograft), revision lumbar surgery (nine rhBMP-2, 13 allograft), spondylolisthesis (four rhBMP-2, four allograft), discogenic pain (five rhBMP-2, seven allograft), cervical disc herniation (nine rhBMP-2, nine allograft) and cervical myelopathy (two rhBMP-2, three allograft).

The patients were assessed pre-operatively using the Oswestry Disability Index questionnaire,[15] Visual Analogue Scale (VAS)[16] measurement of spine and limb pain, and a pain drawing.

Patients undergoing anterior cervical decompression and fusion with machined allograft spacers had the fused levels fixed with an anterior locking plate. Those undergoing anterior lumbar interbody fusion or transforaminal lumbar interbody fusion were fixed posteriorly with pedicle screws.

The range of allograft cage sizes used in the rhBMP-2 group was 13 mm to 17 mm for anterior lumbar interbody fusion, 9 mm to 15 mm for transforaminal lumbar interbody fusion, and 7 mm to 10 mm for anterior cervical decompression and fusion. The dose of InFUSE used for lumbar fusion was 2 mg per level, and 1 mg per level for cervical fusion. For a transforaminal lumbar interbody fusion the collagen sponge was packed anteriorly in the disc space, followed by the spacer. No graft or collagen sponge lay behind the spacer. For an anterior lumbar interbody fusion, 2 mg of InFUSE was placed centrally in the allograft spacer. This was supplemented by posterior fusion using iliac crest autograft and any remaining rhBMP-2.

Post-operatively, patients were reviewed at two weeks and six weeks, then at 3, 6, 12 and 24 months. Radiological measurements were made by two independent observers (RW, CDW) on the electronic public access computer system (EPACS; Stentor, Brisbane, California). To reduce error, the initial disc height was measured for each patient and compared with a standard object. This was expressed as a ratio. This ratio was then compared with that derived by the same method from follow-up radiographs. These measurements were compared with those obtained from CT scans and were found to vary by approximately 1 mm. We therefore considered any subsidence of less than 10% to be insignificant. We used the following criteria to determine fusion: radiological loss of the allograft end-plates, the end of progression of subsidence, and the stabilisation of clinical symptoms as measured by the Oswestry Disability Index and VAS. Statistical analysis was carried out on Analyse-It software for Microsoft Excel (Analyse-It Software Ltd., Leeds, United Kingdom), with a p-value < 0.05 considered significant.

Results

Radiological. All patients who had an intervertebral fusion using allograft and rhBMP-2 showed radiological signs of fusion at a mean of six months (3 to 12), but those who had received an allograft with demineralised bone matrix took considerably longer (mean 19 months, 9 to 26) (Fig. 1). One patient in the allograft and demineralised bone matrix group did not fuse. Following anterior cervical decompression and fusion, she had nonunion in one of the two levels operated on. She underwent further surgery at 12 months for ongoing neck pain which confirmed a nonunion at the superior endplate of C7. We removed the plates after which the levels fused posteriorly, which resolved her pain.

Significant subsidence (> 10%) was evident in 24 of 55 levels treated by allograft and rhBMP-2 between six weeks and three months of surgery. There was no significant subsidence after six months. After 12 months, 49% (27 of 55) of levels in the allograft/rhBMP-2 group had subsided, compared with 6.3% (4 of 63) of levels in the allograft/demineralised bone matrix group. This difference statistically significant ($p < 0.0001$, Fisher's exact test). The mean subsidence for the allograft/rhBMP-2 group at 12 months was 16.5% (0% to 58%) compared with that in the allograft/demineralised bone matrix group, which was 4.6% (0% to 15%). This was also statistically significant ($p < 0.0001$, independent *t*-test) (Fig. 2).

At 12 months' follow-up, in the anterior lumbar interbody fusion group, 70% (14 of 20) of levels in the rhBMP-2 group showed signs of early lucency and underwent significant (> 10%) graft subsidence of a mean of 27% (13% to 42%), compared with the allograft/demineralised bone matrix group, in which significant subsidence was seen in 6% (1 of 16). In this patient, there was loss of 15% of the graft height.

In the transforaminal interbody fusion group, early lucency and subsidence of the allograft spacer were seen in 53% (9 of 17) of fused levels in the rhBMP-2 group. The

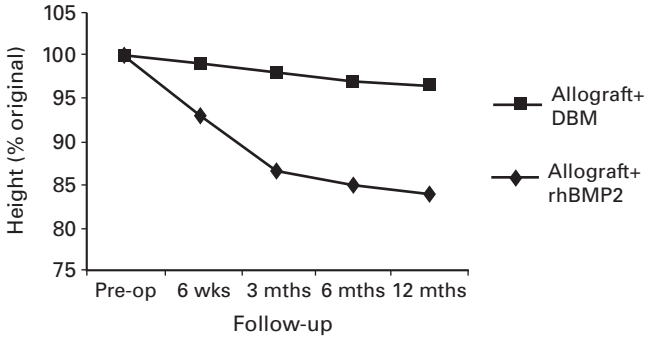

Fig. 2

Graph showing the degree of subsidence with and without rhBMP-2 (DBM, demineralised bone matrix).

mean subsidence was 24% (13% to 40%). In the allograft/demineralised bone matrix group, subsidence was seen in 12% (3 of 25) levels. The mean subsidence was 12% (11.4% to 13.8%) (independent *t*-test, p = 0.018).

In the anterior cervical decompression and fusion group, early lucency and subsidence was seen in 33% (6 of 18) of the levels fused using rhBMP-2. The mean subsidence was 53% (40% to 58%). No subsidence was seen in patients who had undergone fusion with allograft and demineralised bone matrix (independent *t*-test, p = 0.18, not significant).

Despite similar doses of rhBMP-2, the degree of subsidence varied not only between patients but also between levels in those patients who had undergone fusion at more than one level.

CT scans were obtained on 32 patients (42%) during the follow-up period, of which 25 were in the allograft/rhBMP-2 group. These revealed two phenomena that may have contributed to subsidence. First, early lucency and incorporation of the allograft were noted, which may have resulted in a loss of structural support. Secondly, there was significant end-plate erosion in each rhBMP-2 case, an appearance that was not evident in any other scanned patient.

Clinical. We reviewed the serial Oswestry disability index and VAS scores for each patient along with their pain drawings. Between two and six weeks post-operatively, 30% (11 patients) of the allograft/rhBMP-2 group reported an increase in their pain. This improved and settled completely between six weeks and three months. It did not occur in patients in whom rhBMP-2 had not been used, and could not be correlated with the amount of subsidence observed. Indeed, some of the patients with the greatest subsidence reported no increase in pain. The Oswestry scores improved in 32 patients (89%) in the rhBMP-2 group and 36 (88%) in the allograft and demineralised bone matrix group: there was no significant difference between the two groups at final follow-up.

Prolonged dysphagia was noted in 55% of patients (6 of 11) in the allograft/rhBMP-2 group who underwent anterior cervical decompression and fusion, all of whom had prevertebral swelling on their post-operative radiographs. Although this is a well recognised complication of this procedure, its severity and duration was more pronounced than had previously been encountered.

Four patients (11%) in the allograft/rhBMP-2 group underwent further surgery. One patient with an L3/L5 transforaminal lumber interbody fusion had their fusion extended to L5/S1 after 14 months. A second patient was extremely thin and the implants were removed after a year because of discomfort when sitting or lying. Both had a solid fusion. Two patients with long fusions had iliac screws removed after one year because of buttock pain. One was relieved of pain and the other improved.

Five patients (12.2%) in the allograft/demineralised bone matrix group underwent further surgery. One was for post-operative infection in a patient with scoliosis, who required two further debridement procedures and eventually fused. Three other patients had iliac screws removed after surgery for scoliosis because of buttock pain. The pain resolved in each case.

One patient developed a nonunion at one of the two operated levels of an anterior cervical decompression and fusion. The anterior plate was removed after 12 months and a posterior instrumented fusion was carried out successfully.

Discussion

Bone morphogenetic proteins regulate many different processes. The function of BMP-2 is not restricted to bone formation[17] but also affects its absorption.[18,19] It is upregulated by interleukin-1 and TNF-α during the anabolic phase of bone and cartilage turnover. Bone morphogenetic proteins have been shown to enhance osteoclast differentiation from its progenitor cells.[20,21] It would therefore appear that rhBMP-2 enhances both osteoblastic and osteoclastic activity.

Patients in the allograft/rhBMP-2 group who were in pain in the early post-operative period (one to three months) and those in whom significant graft subsidence had occurred underwent a CT scan. These showed that end-plate erosion and allograft resorption with subsidence occurred commonly. There was little subsidence in the other patients, an observation which is consistent with other reports.[14] In our opinion, there are two reasons for this subsidence: first, an early increase in turnover of the rhBMP-2-treated allograft spacer, leading to a loss of its intrinsic strength, followed by subsidence of the graft and loss of intervertebral height; and secondly, erosion of the adjacent vertebral end-plates, perhaps before the graft has fused, would lead to subsidence of the spacer. The relative importance of each of these phenomena is uncertain. The presence of instrumentation, particularly in the lumbar spine, is insufficient to prevent anterior collapse.

Fusion rates of between 94% and 100% have been achieved using rhBMP-2.[13,14,22] In our study the fusion rate was 100%. Our criteria for fusion included radiological loss of the allograft end-plates, the end of progression of subsidence, and the settling of symptoms as measured using the Oswestry disability index and VAS. However, we also achieved a 98% (62 of 63 levels) fusion rate using instrumented allograft without rhBMP-2, and there was minimal subsidence in this group. The clinical outcomes in each group were identical, apart from the high incidence of postoperative dysphagia in the allograft/rhBMP-2 group who underwent cervical surgery.

Allograft treated with rhBMP-2 should be used with caution when the allograft is required to provide structural support. We have abandoned its use in our practice, as allograft spacers and demineralised bone matrix have not only proved to give a better outcome but are also cheaper.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. **Hidehiro I, Sohei E, Mikio K, et al.** Experimental spinal fusion with use of recombinant human bone morphogenetic protein 2. *Spine* 1999;24:1402-5.
2. **Schimandle J, Boden SD, Hutton WC.** Experimental spinal fusion with recombinant human bone morphogenetic protein-2. *Spine* 1995;20:1326-37.
3. **Mummaneni PV, Pan J, Haid RW, Rodts GE.** Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. *J Neurosurg Spine* 2004;1:19-23.
4. **Boden SD, Kang J, Sandhu H, Heller JG.** Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial. *Spine* 2002;27:2662-73.
5. **Burkus JK, Heim SE, Gornet MF, Zdeblick TA.** The effectiveness of rhBMP-2 in replacing autograft: an integrated analysis of three human spine studies. *Orthopedics* 2004;27:723-8.
6. **Burkus JK.** Bone morphogenetic proteins in anterior lumbar interbody fusion: old techniques and new technologies. *J Neurosurg Spine* 2004;3:254-60.
7. **Poynton AR, Lane JM.** Safety profile for the clinical use of bone morphogenetic proteins in the spine. *Spine* 2002;27(Suppl 4):40-8.
8. **Boakye M, Mummaneni PV, Garrett M, Rodts G, Haid R.** Anterior cervical discectomy and fusion involving a polyetheretherketone spacer and bone morphogenetic protein. *J Neurosurg Spine* 2005;2:521-5.
9. **Murnaghan M, McIlmurray L, Mushipe MT, Li G.** Time for treating bone fracture using rhBMP-2: a randomized placebo controlled mouse fracture trial. *J Orthop Res* 2005;23:625-31.
10. **Zhang H, Sucato DJ, Welch RD.** Recombinant human bone morphogenetic protein-2-enhanced anterior spine fusion without bone encroachment into the spinal canal: a histomorphometric study in a thorascopically instrumented porcine model. *Spine* 2005;30:512-18.
11. **No authors listed.** Food and Drug Agency. http://www.fda.gov/cdrh/pdf/P000058.html. (date last accessed 2 July 2002).
12. **Sandu HS, Khan SN.** Recombinant human bone morphogenetic protein-2: use in spinal fusion applications. *J Bone Joint Surg [Am]* 2003;85-A(Suppl 3):89-95.
13. **Burkus JK, Transfeldt EE, Kitchel SH, Watskins RG, Balderston RA.** Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* 2002;27:2396-408.
14. **Janssen ME, Lam C, Beckham R.** Outcomes of allogenic cages in anterior and posterior lumbar interbody fusion. *Eur Spine J* 2001;10(Suppl 2):158-68.
15. **Fairbank JC, Crouper J, Davies JB, O'Brien JP.** The Oswestry low back disability questionnaire. *Physiotherapy* 1980;66:271-3.
16. **Chapman CR, Case KL, Dubner R, et al.** Pain measurement: an overview. *Pain* 1985;22:1-31.
17. **Kaneko H, Arakawa T, Mano H, et al.** Direct stimulation of osteoclastic bone resorption by bone morphogenetic protein (BMP)-2 and expression of BMP receptors in mature osteoclasts. *Bone* 2000;27:479-86.
18. **Fukui N, Zhu Y, Maloney JW, Clohisy J, Sandell LJ.** Stimulation of BMP-2 expression by pro-inflammatory cytokines IL-1 and TNF-α in normal and osteoarthritic chondrocytes. *J Bone Joint Surg [Am]* 2003;85-A(Suppl 3):59-66.
19. **Merrihew C, Soeder S, Rueger DC, Kuettner KE, Chubinskaya S.** Modulation of endogenous osteogenic protein-1 (OP-1) by interleukin-1 in adult human articular cartilage. *J Bone Joint Surg [Am]* 2003;85-A(Suppl 3):67-74.
20. **Udagawa N.** Mechanisms involved in bone resorption. *Biogerontology* 2002;3:79-83.
21. **Otsuka E, Notoya M, Hagiwara H.** Treatment of myoblastic C2C12 cells with BMP-2 stimulates vitamin D-induced formation of osteoclasts. *Calcif Tissue Int* 2003;73:72-7.
22. **Burkus JK, Sandhu HS, Gornett MF, Longley MC.** Use of rhBMP-2 in combination with structural cortical allografts: clinical and radiographic outcomes in anterior lumbar spinal surgery. *J Bone Joint Surg [Am]* 2005;87-A:1205-12.