Use of rhBMP-2 in Combination with Structural Cortical Allografts: Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Surgery

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Use of rhBMP-2 in Combination with Structural Cortical Allografts: Clinical and Radiographic Outcomes in Anterior Lumbar Spinal Surgery

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Background: Recombinant human bone morphogenetic protein-2 soaked into an absorbable collagen sponge (rhBMP-2/ACS) has been shown in a nonhuman primate study and in a pilot study in humans to promote new bone formation and incorporation of an allograft device when implanted in patients undergoing anterior lumbar interbody arthrodesis. However, a larger series with longer follow-up is needed to demonstrate its superiority to autogenous iliac crest bone graft.

Methods: Between 1998 and 2001, a two-part, prospective, randomized, multicenter study of 131 patients was conducted to determine the safety and efficacy of the use of rhBMP-2/ACS as a replacement for autogenous iliac crest bone graft in anterior lumbar spinal arthrodesis with threaded cortical allograft dowels. Patients were randomly assigned to a study group that received rhBMP-2/ACS or to a control group that received autograft. The clinical and radiographic outcomes were determined with use of well-established instruments and radiographic assessments.

Results: The patients in the study group had significantly better outcomes than the control group with regard to the average length of surgery ($p < 0.001$), blood loss ($p < 0.001$), and hospital stay ($p = 0.020$). Fusion rates were significantly better in the study group ($p < 0.001$). The average Oswestry Disability Index scores, Short-Form-36 physical component summary scores, and low-back and leg-pain scores were significantly better in the study group ($p < 0.05$).

Conclusions: In patients undergoing anterior lumbar interbody arthrodesis with threaded allograft cortical bone dowels, rhBMP-2/ACS was an effective replacement for autogenous bone graft and eliminated the morbidity associated with graft harvesting.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

Anterior lumbar interbody arthrodesis is an effective treatment for patients with symptomatic lumbar spondylosis, low-grade spondylolisthesis, and radiculopathy[1,2]. A variety of interbody constructs have been proposed. Some studies have shown an association between fusion and improved clinical outcomes, while others have shown that a successful fusion alone does not guarantee an improved clinical outcome[3-9]. Those studies used various outcome assessment instruments and relied on plain radiographic evidence alone to determine fusion status.

In attempts to improve the rates of fusion, an evolution in interbody construct design from femoral ring allografts to threaded cortical bone dowels has occurred[10]. The use of stand-alone impacted femoral ring allografts has been associated with high rates of pseudarthrosis, graft subsidence, and graft extrusion[11,12]. With threaded allograft bone dowels, the concept of the use of precision-machined allograft constructs was introduced to further enhance the stability of the spinal motion segment[13]. In contrast to intradiscal spacers, threaded interbody fusion devices do not require additional segmental fixation; threaded dowels are designed for use as stand-alone implants. They resist expulsion and stabilize the bone-implant interface. They are designed both to withstand lumbar compressive loads while maximizing device porosity and to promote load-sharing between the allograft and the host bone[14]. There has also been an evolution in bone-grafting techniques, as well as in construct design[3,10,11,15,16].

Recombinant human bone morphogenetic protein-2

TABLE I Patient Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age of ≥18 years	Spinal conditions other than degenerative disc disease
Single-level symptomatic degenerative disc disease	Degenerative disc disease at disc space levels other than L4-L5 or L5-S1
Spondylolisthesis grade of ≤1	Previous anterior arthrodesis at the involved level
Disabling back pain with or without leg pain for >6 months that is unresolved after nonoperative treatment	Obesity (>40% above ideal weight)
	Active bacterial infection
	Medical condition requiring medication that could interfere with fusion (e.g., steroids or nonsteroidal anti-inflammatory medication)

TABLE II Patient Demographic Data

	Study Group (rhBMP-2/ACS)	Control Group (Autograft)
No. of patients	79	52
Average age *(yr)*	40.2	43.6
Average weight *(kg)*	78.2	78.6
Sex (M/F)	32/47	19/33
No. (%) of patients receiving Workers' Compensation	23 (29)	17 (33)
No. (%) of patients with pending litigation	7 (9)	6 (12)
No. (%) of patients who used tobacco	26 (33)	17 (33)
No. (%) of patients who had previous lumbar spine surgeries	29 (37)	17 (33)

(rhBMP-2) is an osteoinductive protein that has the potential to make autogenous bone-grafting unnecessary[17,18]. The use of rhBMP-2 delivered to the surgical site on an absorbable collagen sponge (ACS) carrier has been investigated in preclinical and clinical studies of anterior lumbar interbody arthrodesis with metal interbody cages and allograft bone dowels[19,20]. A pivotal clinical study has indicated that the use of rhBMP-2/ACS provides clinical and radiographic outcomes that are equivalent to those after use of autogenous iliac crest while reducing operating-room time and intraoperative blood loss[21]. Recently, an integrated analysis of three sequential prospective studies has shown that the use of rhBMP-2/ACS is superior to autograft in fusion success (the ability to meet all criteria for fusion) and in clinical outcomes[22].

We assessed the clinical and radiographic outcomes in patients who received rhBMP-2/ACS in combination with threaded cortical allograft dowels and compared them with the outcomes in patients who received autograft in a stand-alone anterior lumbar interbody arthrodesis.

Materials and Methods

A prospective, randomized, multicenter United States Food and Drug Administration-approved investigational device exemption study of patients who were undergoing treatment for degenerative disc disease was conducted in two sequential phases. In the pilot phase, forty-six patients were enrolled at five clinical sites with use of a one-to-one randomization ratio between the study and control groups. In the pivotal phase, eighty-five patients were enrolled at thirteen clinical sites with use of a two-to-one randomization ratio (two rhBMP-2-treated patients to one control patient). Surgeons were blinded to the randomization schedule, which was derived from a statistical program (SAS Institute, Cary, North Carolina) that produced sequentially numbered envelopes specific to each enrollment site. The study protocols for both phases were identical. We analyzed the combined findings for all patients enrolled in the two phases of the study.

A total of 131 patients were enrolled over a three-year period (May 1998 to March 2001). The patients were followed for a minimum of two years after surgery. One control patient died in a house fire before the twelve-month follow-up examination. Patients who underwent a revision, supplemental fixation, or retrieval surgery were classified as having a clinical failure. Once a patient was classified as having a failure, his or her clinical data were no longer included in later follow-up periods. Two patients in the study group and eight patients in the control group were classified as having had a failure over the course of the study. Three patients in the study group and two in the control group were lost to follow-up over the course of the study. Among the patients who were available for follow-up, the return rate was 97% for the study group and 93% for the control group at twenty-four months.

All patients underwent single-level stand-alone anterior lumbar interbody arthrodesis with a pair of threaded cortical

bone dowels (MD-I; Regeneration Technologies, Alachua, Florida). Dowels are retrieved primarily from the femora of human cadavera. The center hole is the former medullary canal. The dowels were 16, 18, or 20-mm in diameter and ranged from 20 to 26 mm in length. The patients in the study group received rhBMP-2/ACS (INFUSE Bone Graft; Medtronic Sofamor Danek, Memphis, Tennessee) as an alternative to iliac crest bone graft. In the control group, autogenous iliac crest bone graft was harvested and used in conjunction with the allograft implants.

Inclusion Criteria

Patients were included in the study if they had radiographic documentation of single-level disc disease and their symptoms were related to the neuroradiographic findings. All patients enrolled were considered good candidates for a single-level standalone anterior lumbar interbody arthrodesis (Table I).

Patient Demographics

Demographic data were compiled for all patients in the study (Table II). With the numbers available, no differences were found between the demographic profiles of the two patient populations.

Surgical Procedure

The patients underwent an open anterior lumbar interbody arthrodesis with use of a transperitoneal or a retroperitoneal approach to the lumbosacral spine[23,24].

The rhBMP-2 was reconstituted with use of sterile water, and a single-dose solution at a concentration of 1.5 mg/mL was achieved. The solution was applied evenly by syringe to appropriately sized absorbable collagen sponges, and the rhBMP-2 was allowed to bind to the sponges for a minimum of fifteen minutes before further handling or preparation took place. A single collagen sponge was placed into the central portion of each bone dowel. One additional rhBMP-2-bound sponge (25 × 102 mm) was placed between the bone dowels. The total dose of rhBMP-2 (8.4 to 12 mg) depended on the capacity of the bone dowel (16, 18, or 20 mm) that was used (Table III).

The control group received morselized autogenous iliac crest bone graft in conjunction with the threaded cortical bone dowels. Although not measured, the bone chips were of various sizes that could be easily packed into the central hole of the allograft dowel. Through a separate incision directly over the iliac wing, the inner or outer table of the ilium was exposed subperiosteally and corticocancellous grafts were harvested. A single iliac cortex was preserved in all graft-harvesting procedures; no bicortical iliac grafts were obtained. The central opening of each dowel was packed with morselized autogenous bone graft before its insertion into the disc space. Additional autogenous grafts were packed between and anterior to the dowels.

Radiographic Outcome Measurements

Stability and radiolucent lines were assessed on plain radiographs with use of anteroposterior, lateral, and flexion-extension views. In addition, thin-slice (1-mm overlapping) computed

TABLE III Allograft Implant Sizes, Volume, and rhBMP-2 Dose*

Dowel Diameter *(mm)*	Size of rhBMP-2/ACS per Dowel *(mm)*	Size of rhBMP-2/ACS Between Dowels *(mm)*	Total Volume of rhBMP-2/ACS *(mL)*	Total Dose of rhBMP-2 *(mg)*
16	25 × 51	25 × 102	5.6	8.4
18	25 × 76	25 × 102	6.6	10.0
20	25 × 102	25 × 102	8.0	12.0

*Three sponges were placed within each disc space. One sponge was placed within each bone dowel. The remaining sponge was placed within the disc space between the bone dowels. The absorbable collagen sponge is hydrophillic. The sponges expand and adhere to the dowels and the adjacent host bone.

TABLE IV Intraoperative Data

Surgical Data	Study Group (rhBMP-2/ACS)	Control Group (Autograft)	P Value
Average duration of operation* *(hr)*	1.4	1.8	<0.001
Average intraoperative blood loss† *(mL)*	87.4	184.7	<0.001
Surgical level *(no. of patients)*			0.785
L4-L5	23 (29%)	14 (27%)	
L5-S1	56 (71%)	38 (73%)	
Average hospital stay *(days)*	2.9	3.3	0.020

*Skin incision to skin closure. †Blood loss was measured from suction device.

TABLE V Oswestry Low Back Pain Disability Index Scores

Period	Study Group (rhBMP-2/ACS)	Control Group (Autograft)	P Value
Preoperative	53.7	56.6	0.144
6 weeks			
Mean score	39.4	47.6	0.008
Mean improvement	–14.2	–9.0	0.060
3 months			
Mean score	28.4	38.5	0.001
Mean improvement	–25.3	–18.5	0.021
6 months			
Mean score	21.5	30.8	0.003
Mean improvement	–32.4	–25.8	0.031
12 months			
Mean score	20.9	29.3	0.018
Mean improvement	–33.0	–27.0	0.074
24 months			
Mean score	20.4	28.9	0.037
Mean improvement	–33.4	–27.0	0.119

tomography scans with coronal and sagittal plane reconstructions were used to assess bridging bone and allograft incorporation. The radiographs and computed tomography scans were reviewed by two independent radiologists in a blinded fashion to critically assess fusion at six, twelve, and twenty-four months. A third independent radiologist was used to adjudicate conflicting findings.

As in previous studies on interbody spinal arthrodesis with rhBMP-2/ACS[19-21,24,25], an arthrodesis was considered successful only if it achieved all four fusion criteria: (1) the presence of bridging trabecular bone connecting vertebral bodies through or around dowels, (2) angular motion of 5°, (3) sagittal translation of 3 mm, and (4) no radiolucent area involving >50% of the interface between dowels and end plates.

Clinical Outcome Measurements

Assessments were completed preoperatively, during hospitalization, and postoperatively at six weeks and at three, six, twelve, and twenty-four months. Clinical outcomes were measured with use of well-established instruments described in previous arthrodesis studies[21,24,26,27].

Monitoring for Antibody to rhBMP-2 and Collagen

Blood samples from the patients were tested separately for an antibody response to exposure of rhBMP-2 and bovine collagen at the preoperative evaluation and at three months postoperatively.

Statistical Analysis

The data from this clinical trial were analyzed with use of the SAS statistical software package (version 6.12; SAS Institute). For continuous variables, p values were determined with use of analysis of variance techniques, and, for categorical variables, they were derived from the Fisher exact test or chi-square test.

Results

Surgery

The study group had better outcomes than the control group with respect to the mean operative time, blood loss, and hospital stay (Table IV).

Clinical Follow-up

Oswestry Low Back Pain Disability Index Questionnaire

Both groups had sustained improvement in the mean Oswestry Disability Index scores[26] after surgery at all time-points throughout the follow-up period (Table V). The study group had significantly better mean Oswestry scores at all time-points than did the control group. Because there was a slight, but insignificant, difference in the preoperative values between the two groups, the average improvement in the Oswestry score was calculated at each time-interval. At all of the intervals studied, the study group had a greater mean improvement in the Oswestry score than did the control group. These differences reached significance at the three and six-month follow-up intervals ($p = 0.021$ and $p = 0.031$, respectively).

Physical Component Summary of the Short Form-36

The physical component summary score was calculated from the Short Form-36 (SF-36) Health Survey, by which a patient evaluated his or her own condition. At six months, the study group had an average improvement of 14.2 points compared with the preoperative status ($p = 0.001$) (Table VI). The scores in the study group were significantly better than those measured in the control group ($p = 0.001$), which had a mean

TABLE VI Physical Component Summary Score Derived from Short-Form-36 Health Survey

Period	Study Group (rhBMP-2)	Control Group (Autograft)	P Value
Preoperative	29.2	27.6	0.184
6 months	43.4	37.0	0.001
12 months	45.3	38.9	0.003
24 months	44.9	39.2	0.015

improvement of 9.5 points ($p = 0.017$). The scores in both groups continued to improve at twelve and twenty-four months.

Back and Leg Pain

Both groups had significant reductions in the mean scores for back and leg pain at all time-points compared with the preoperative condition ($p \leq 0.001$). Although a reduction in back pain was observed as early as six weeks, the mean score for back pain was significantly lower for the study patients than for the control patients, beginning at three months after surgery and continuing throughout the twenty-four-month follow-up (Table VII). The difference in mean back pain scores between the study and the control group was significant at three months ($p = 0.003$). Although both treatment groups maintained this reduction in back pain scores throughout the study, the mean back pain scores in the study group remained significantly lower than those in the control group.

Both groups also had a sustained reduction in mean scores for leg pain; however, the study group had a significantly lower score at most of the follow-up time-points (Table VIII). Although both groups maintained a reduction in leg pain, the control patients reported a slight increase at later follow-up intervals. The mean scores for leg pain were significantly different between the groups at six ($p = 0.043$), twelve ($p = 0.011$), and twenty-four months ($p = 0.011$).

Return to Work

Before surgery, more patients in the study group were working (60%) than were working in the control group (48%). By twenty-four months, more patients from both groups were working than had been working before surgery. However, the working status in the study group improved as early as twelve months. Using survivorship analysis, we determined that the study patients returned to work at an average of eighty-nine days compared with ninety-six days for the control patients. With the numbers available, this difference was not found to be significant.

Pain at the Donor Site of the Bone Graft

Pain at the donor site of the bone graft was not measured in the patients in the study group. Although the mean score for pain at the donor site in our control patients was similar to that described in previous reports[21,22,26,28] on anterior lumbar interbody arthrodesis, the pain was observed to persist at a slightly higher rate of 46.5% for twenty-four months after surgery.

Additional Surgery

Patients who underwent a revision, removal, or supplemental fixation were classified as having had a failure. Two patients (3%) in the study group had an additional surgical procedure for supplemental fixation. Eight patients (15%) in the control group had an additional surgical procedure for supplemental fixation after the primary surgery.

Antibody Formation

Seventy-eight patients in the study group and forty-nine patients in the control group were tested for an elevated antibody response to rhBMP-2 and bovine collagen. Among those tested, no patient from either group had an elevated antibody response to rhBMP-2. However, seven patients (9%) in the study group and four patients (8%) in the control group had an elevated antibody response to bovine collagen. Although the origin of the responsiveness to the bovine collagen is unknown, it could possibly be attributable to a previous exposure through either clinical or environmental means.

TABLE VII Summary of Average Scores for Back Pain

Period	Study Group (rhBMP2/ACS)	Control Group (Autograft)	P Value
Preoperative	15.6	16.8	0.039
6 weeks	8.1	9.6	0.090
3 months	7.5	10.2	0.003
6 months	6.4	9.1	0.006
12 months	6.4	9.5	0.007
24 months	7.0	9.7	0.032

TABLE VIII Average Scores for Leg Pain

Period	Study Group (rhBMP-2/ACS)	Control Group (Autograft)	P Value
Preoperative	12.6	14.2	0.094
6 weeks	6.2	8.6	0.020
3 months	6.4	8.3	0.065
6 months	4.9	6.9	0.043
12 months	5.1	8.0	0.011
24 months	5.8	9.3	0.011

TABLE IX Fusion Success Rates

Period	Study Group (rhBMP-2)	Control Group (Autograft)	P Value
6 months	95.9	85.1	0.047
12 months	98.6	89.4	0.036
24 months	98.5	76.1	<0.001

Fusion Assessment Outcomes

At all follow-up intervals, the study group exhibited a greater rate of fusion success than did the control group (Table IX). At the final two-year radiographic follow-up examination, 99% of the patients in the study group had evidence of fusion compared with 76% of the patients in the control group ($p < 0.001$).

All operations that were classified as fusion failures were in patients who had either a lack of radiographic evidence of fusion or who needed a secondary operation. In the control group, no patient had a fracture or migration or extrusion of the allograft implant. Fourteen (18%) of the seventy-nine patients in the study group had transient localized areas of bone remodeling in the vertebral body adjacent to an allograft dowel. These radiolucent areas were seen extending into the vertebral body at between three and twelve months after surgery. All had resolved by twenty-four months after surgery.

Discussion

Before the pilot[25] and pivotal phases of this clinical study were conducted, a nonhuman primate (rhesus monkey) study was performed with use of allograft bone dowels in the lumbar spine[29]. In three rhesus monkeys, a single smooth allograft bone dowel with rhBMP-2 on an absorbable collagen sponge was implanted anteriorly into the L7-S1 disc space. At three months after surgery, all three study animals showed new bone formation with complete incorporation of the allograft dowels, leaving trabecular bone continuous with the host bone of both adjacent vertebrae. The control animals treated with autogenous grafts demonstrated delays in healing of the allograft implants and in new trabecular bone formation. In contrast to the rhBMP-2-soaked sponge, the transplanted autogenous graft may need to be resorbed or remodeled before fusing[30]. This feature may partially explain why, in these animal studies, investigators found superior healing patterns with rhBMP-2/ACS compared with autogenous iliac crest bone graft.

We combined data from two clinical trials with use of threaded cortical bone dowels and rhBMP-2—first in a pilot study[25] and later in a pivotal study—and the findings are reported in the current study. The use of rhBMP-2/ACS has been shown to induce new bone formation in single-level anterior interbody arthrodeses in humans[19-21]. It was also shown to have clinical outcomes and radiographic fusion rates superior to those with iliac crest bone graft when used with a threaded, tapered titanium cage in three sequential prospective studies with a total enrollment of 679 patients[22].

In our study of 131 patients who had a stand-alone anterior lumbar interbody arthrodesis with threaded cortical bone dowels, the patients who were treated with rhBMP-2/ACS also had superior clinical and radiographic outcomes compared with patients who had received iliac crest bone graft. Many of the differences observed between the two groups in this study reached significance with a patient population much smaller in number than that in the titanium cage studies (131 compared with 679)[19-22].

Both the control and study groups in our investigation had improvement in function and in the pain score compared with the preoperative status. Clinical improvement was documented as early as six weeks postoperatively in this study. However, the improved fusion rates may have contributed to the better clinical outcomes noted among the study group, particularly at the longer follow-up intervals. At six, twelve, and twenty-four months, the rhBMP-2/ACS-treated patients had significantly better improvement than the control patients with respect to the back and leg pain scores, the physical component summary scores of the SF-36, and the Oswestry Disability Index scores.

On the basis of our radiographic assessment, the study group was found to have significantly higher rates of fusion

(all four fusion criteria were met) at all time-points than did the control group. The greatest difference was seen at twenty-four months when the rates were 99% and 76%, respectively ($p < 0.001$). This difference is due, in large part, to a difference in the need for additional surgery to achieve a desired outcome. Only two study patients (3%) had additional spinal surgery compared with eight control patients (15%).

When rhBMP-2/ACS was used as an autograft replacement, the incorporation of the allograft bone dowel with the host bone was increased in some of the serial computed tomography scans compared with that seen in the scans of the control patients. This observation suggests that there is an interaction between the allograft bone and rhBMP-2 that was not previously observed when rhBMP-2 was used with titanium interbody cages. The incorporation varied from patient to patient, ranging from complete to very localized incorporation where there was direct contact with the end plates. Further analysis of the scans is needed to better understand the range in response and the potential factors influencing the amount and rate of allograft incorporation. Similarly, it is not known whether this incorporation will be seen in different fusion sites or when constructs with different configurations (for example, a femoral ring allograft) are used in combination with rhBMP-2/ACS.

Our data demonstrate that rhBMP-2/ACS can successfully replace harvested iliac crest bone without the associated donor site pain that has been reported by others[28,31], and it can be used to help incorporate allograft bone dowels in the lumbar spine of humans. Furthermore, these data support the concept that increased fusion rates are associated with improved functional outcomes and decreases in pain scores. The better improvement in patient outcome with allograft dowels may be attributed, in part, to the acceleration of the incorporation of the allograft dowel, perhaps because the allograft bone dowels have a modulus of elasticity that closely matches that of the host bone. The stability gained at the involved level as a result of fusion was maintained up to twenty-four months and appears to contribute to the long-term clinical success associated with the combination of rhBMP-2 and allograft bone dowels. ■

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