SPINE Volume 27, Number 21, pp 2396–2408

Clinical and Radiographic Outcomes of Anterior Lumbar Interbody Fusion Using Recombinant Human Bone Morphogenetic Protein-2

J. Kenneth Burkus, MD,* Ensor E. Transfeldt, MD ,† Scott H. Kitchel, MD,‡ Robert G. Watkins, MD,§ and Richard A. Balderston, MD‖

Study Design. A prospective, nonblinded, multicenter study of outcomes in patients undergoing single-level anterior lumbar discectomy and interbody fusion with InFUSE™ Bone Graft.

Objective. To determine the safety and effectiveness of InFUSE™ Bone Graft applied to an absorbable collagen sponge in anterior lumbar interbody fusion with threaded cortical allografts.

Summary of Background Data. In primates, InFUSE™ Bone Graft used with allograft dowels was shown to increase rates of interbody fusion by promoting osteoinduction and enhancing incorporation of the allograft. Recently, in a small series of human patients undergoing anterior lumbar interbody fusion with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and fusion.

Methods. Forty-six patients underwent a single-level anterior lumbar discectomy and interbody fusion at five investigational sites. They were randomly assigned to one of two groups, and the results in the investigational patients who received threaded cortical allograft dowels with InFUSE™ Bone Graft were compared with those in the control patients who received threaded allograft dowels with autogenous iliac crest bone graft. Patients' clinical outcomes were assessed using neurologic status, work status, and Oswestry Low Back Pain Disability, Short Form-36, and back and leg pain questionnaires. Anteroposterior, lateral, flexion-extension radiographs, and computed tomography scans were used to evaluate the progression of fusion at 6, 12, and 24 months after surgery.

Results. All patients who received InFUSE™ Bone Graft showed radiographic evidence of bony induction and early incorporation of the cortical allografts. All patients in this group had fusions at 12 months that remained fused at 24 months. At 12 and 24 months, the investigational group showed higher rates of fusion and improved neurologic status and back and leg pain when compared with the control group. There were no unanticipated adverse events related to the use of InFUSE™ Bone Graft.

Conclusion. The use of InFUSE™ Bone Graft is a promising method of facilitating anterior intervertebral spinal fusion, decreasing pain, and improving clinical outcomes in patients who have undergone anterior lumbar fusion surgery with structural threaded cortical allograft bone dowels. [Key words: anterior lumbar interbody fusion, bone morphogenetic protein, degenerative disc disease, lumbar spine] **Spine 2002;27:2396–2408**

Cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented anterior lumbar interbody fusion (ALIF). They are not intradiscal spacers that require additional segmental stabilization. The threaded cortical bone dowels can withstand lumbar compressive loads and can promote load sharing between the allograft and the host bone while maximizing device porosity.[4,17] These interbody constructs are implanted within the central portion of the disc space through a controlled insertion technique. Impacted allografts, when used alone for interbody fusion in the lumbar spine, have been reported to have a high rate of pseudarthrosis and subsidence.[9,12,21] Contemporary reports of large clinical series of ALIFs using impacted grafts have shown various rates of fusion and differing clinical outcomes.[1,7,10,13–15,18] The threaded dowels resist expulsion and stabilize the bone-implant interface.[4] In addition, threaded bone dowels offer increased strength to support cancellous graft material.[19] In one clinical series, 43 patients were observed for more than one year and had a high fusion rate and improved clinical outcomes.[5]

InFUSE™ Bone Graft (Medtronic Sofamor Danek, Memphis, TN) is recombinant human bone morphogenetic protein applied to an absorbable collagen sponge. Its use replaces the need for autogenous bone grafts and eliminates the complications associated with iliac crest graft harvesting. In a clinical series of patients undergoing an ALIF procedure with a tapered cylindrical metal fusion cage, InFUSE™ Bone Graft has been shown to promote osteoinduction and increase rates of fusion.[3] Our report presents the two-year clinical and radiographic results of the use of InFUSE™ Bone Graft (rhBMP-2) with a collagen sponge carrier inside a cylin-

From the *Hughston Spine Service, The Hughston Clinic, Columbus, Georgia, †Twin Cities Spine Service, Minneapolis, Minnesota, ‡Orthopedic Healthcare NW, Eugene, Oregon, §The Center for Spinal Surgery, Los Angeles, California, and ‖Pennsylvania Hospital, Philadelphia, Pennsylvania.

This study was sponsored by Medtronic Sofamor Danek, Memphis, Tennessee.
Acknowledgment date: August 13, 2001.
First revision date: February 5, 2002.
Second revision date: April 22, 2002.
Acceptance date: April 29, 2002.
The device(s)/drug(s) that is/are the subject of this manuscript is/are being evaluated as part of an ongoing FDA-approved investigational protocol (IDE) or corresponding national protocol.
Corporate/Industry funds were received to support this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript: e.g., honoraria, gifts, consultancies.

DOI: 10.1097/01.BRS.0000030193.26290.DD

Table 1. Patient Demographic Data

Demographic Data	Investigational (InFUSE Bone Graft) Group	Control (Autograft) Group
No. of patients	24	22*
Age (yrs)	41.5	45.6
Weight (lbs)	172.7	175.9
Sex (male/female)	8/16	10/12
Worker's compensation (%)	5 (21)	7 (32)
Spinal litigation (%)	4 (17)	4 (18)
Tobacco use (%)	8 (33)	6 (27)
Previous surgeries (%)	11 (46)	7 (32)

* One patient died an accidental death at six mos after surgery, and one patient was lost to follow-up.

drical threaded cortical allograft dowel in patients undergoing ALIF.

■ Materials and Methods

Study Design. This prospective, randomized, nonblinded study was conducted under an approved investigational device exemption (IDE).

Patient Selection Criteria. Patients with single-level lumbar degenerative disc disease were included in the study. This diagnosis was based on the patient's history and symptoms, physical findings, functional deficits, and radiographic findings. Patients with primary symptoms of low back pain were included in the study; they may also have experienced low back pain with or without referred leg pain or sciatica. Patients also had a preoperative Oswestry Low Back Pain Disability Index score of 35 points or more and were included with and without objective neurologic deficits. All patients had had these disabling symptoms for a minimum of six months and had failed to respond to a nonoperative treatment regimen that included aerobic conditioning, medications, spinal injections, and, in some patients, spinal manipulation.

The following correlative radiographic findings were necessary for inclusion in the study: instability as defined by segmental angulation of 5° or translation of 4 mm, or both; osteophyte formation; decreased disc height of at least 50%; thickening of ligamentous tissue, or disc protrusion and herniation, or both. The radiographic inclusion criteria did not require patients to have discography, although some were performed. Radiographic findings could be established on one or more studies: plain radiographs, magnetic resonance imaging, computed tomography (CT) scanning, or discography. Isolated "facet joint syndromes" were not evaluated.

Patients were excluded from the study if they had a medical condition that required postoperative medications such as steroids or nonsteroidal anti-inflammatory drugs (NSAIDS) that interfere with fusion. Low-dose aspirin for prophylactic anticoagulation was allowed. Nonsteroidal anti-inflammatory drugs were used as part of the preoperative treatment regimen; however, these medications were avoided during the clinical trial.

Patient Population. Forty-six patients at five investigational sites had ALIF surgery between April and August 1998. All patients were between the ages of 19 and 68 years and had symptomatic degenerative disc disease at the L4–L5 or L5–S1 levels. The patients were randomly assigned to one of two study groups. The investigational group (24 patients) received InFUSE™ Bone Graft, which is rhBMP-2 applied to an absorbable collagen sponge carrier, used in conjunction with the MD-II™ threaded cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL) (Table 1). The control group (22 patients) received autogenous iliac crest bone graft. In the control group, 1 patient was lost to follow-up and was excluded from the study, and 1 patient died in a house fire at 6 months after surgery, leaving 20 patients in this group who were followed for a minimum of 24 months after surgery.

Data were collected before surgery, intraoperatively, and at 6 weeks and 3, 6, 12, and 24 months after surgery. Operative procedure details and adverse events were also recorded.

Table 2. Intraoperative Data

Surgical Data	Investigational (InFUSE Bone Graft) Group	Control (Autograft) Group
Operative time (mins)	103	114
Blood loss (mL)	124.1	245.0
Levels (%)		
L4–L5	11 (46)	8 (36)
L5–S1	13 (54)	14 (64)
Hospital stay (days)	3.4	3.7

Surgical Technique. The patients underwent an open ALIF using either a transperitoneal or retroperitoneal approach to the lumbosacral spine. In each patient, a complete discectomy was carried out. An incision was made in the anulus fibrosus, and the nucleus pulposus and the cartilaginous end plates were circumferentially removed; however, the bony end plates were preserved before reaming and tapping of the endplate for receipt of the dowel. Two allograft bone dowels were then inserted into each disc space.

Table 3. Neurologic Outcomes

Period	Variable	Investigational (n = 24) (%)	Control (n = 22) (%)
6 wks	Overall		
	Success	21 (87.5)	18 (90.0)
	Failure	3 (12.5)	2 (10.0)
	P value*	1.000	
3 mos	Overall		
	Success	21 (87.5)	20 (95.2)
	Failure	3 (12.5)	1 (4.8)
	P value*	0.611	
6 mos	Overall		
	Success	21 (87.5)	17 (89.5)
	Failure	3 (12.5)	2 (10.5)
	P value*	1.000	
12 mos	Overall		
	Success	23 (95.8)	16 (84.2)
	Failure	1 (4.2)	3 (15.8)
	P value*	0.306	
24 mos	Overall		
	Success	21 (87.5)	11 (73.3)
	Failure	3 (12.5)	4 (26.7)
	P value*	0.396	

* *P* values are from Fisher exact test.

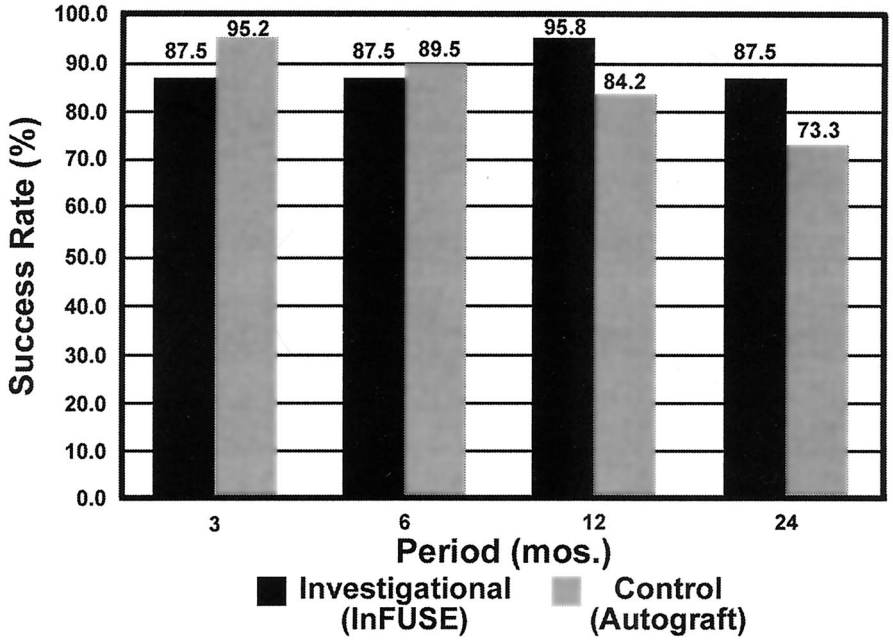

Figure 1. Comparison of neurologic outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft). Success was based on postoperative neurologic condition being improved or no worse than the preoperative condition.

The rhBMP-2 was reconstituted using sterile water, and a single dose at a concentration of 1.5 mg/mL was administered. The concentration was the same in all patients. The solution was applied by syringe to an absorbable collagen sponge. Next, the collagen sponge was placed into the central portion of the bone dowel. The total dose (8 to 12 mL) depended on the capacity of the bone dowel (16, 18, or 20 mm) used. Additional InFUSE™ Bone Graft (or rhBMP-2–prepared sponges) was placed between the bone dowels. No autogenous grafts were used in the investigational group.

The control group received morcellized autogenous iliac crest graft in conjunction with the threaded cortical bone dowels. The iliac grafts were harvested 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 cortex was preserved in all grafts; no bicortical iliac grafts were obtained. The central opening of the dowels were packed with the bone graft before their insertion into the disc space. Additional bone graft was packed between and anterior to the dowels.

Postoperative Care. All patients were instructed to wear an external orthosis for 6 to 12 weeks after surgery. Patients were encouraged to ambulate immediately after surgery. Physical activities were advanced at the discretion of the attending surgeon.

Clinical Outcome Measurements. Assessments were completed before surgery, during the patient's hospitalization, and after surgery at 6 weeks and 3, 6, 12, and 24 months. Clinical outcomes were measured using well-established instruments: Oswestry Low Back Pain Disability Questionnaire,[8] Short Form 36 (SF-36),[16,23] and neurologic status, work status, patient satisfaction, and back, leg, and graft-site pain questionnaires. The Oswestry Low Back Pain Disability Questionnaire was self-administered and was used to measure the level of pain and disability associated with various activities. Neurologic status assessment was based on four objective clinical measurements: motor, sensory, reflexes, and sciatic tension signs. Neurologic outcome success was based on maintenance of or improvement in each variable tested. The SF-36 is a self-administered questionnaire that measures specific health concepts related to physical functioning, social functioning, and

Table 4. Back Pain Outcomes

Period	Variable	Investigational (n = 24)	Control (n = 22)
Preop	N	24	22
	Mean	16.3	16.3
	SD	2.6	2.2
6 wks	N	24	21
	Mean	8.9	10.4
	SD	4.5	4.2
	P value*	0.297	
Improvement from preop	Mean	−7.4	−6.0
	P value†	<0.001	<0.001
3 mos	N	24	21
	Mean	7.9	10.9
	SD	4.3	4.5
	P value*	0.038	
Improvement from preop	Mean	−8.4	−5.4
	P value†	<0.001	<0.001
6 mos	N	24	20
	Mean	6.8	9.9
	SD	4.3	5.1
	P value*	0.034	
Improvement from preop	Mean	−9.5	−6.4
	P value†	<0.001	<0.001
12 mos	N	24	19
	Mean	7.4	9.2
	SD	5.3	6.3
	P value*	0.338	
Improvement from preop	Mean	−8.9	−7.2
	P value†	<0.001	<0.001
24 mos	N	24	17
	Mean	7.4	10.9
	SD	6.0	6.0
	P value*	0.047	
Improvement from preop	Mean	−8.9	−5.2
	P value†	<0.001	<0.001

* *P* values for difference between the treatment groups are from analysis of variance.
† *P* values for change from preop in each group are from paired tests.
SD = standard deviation.

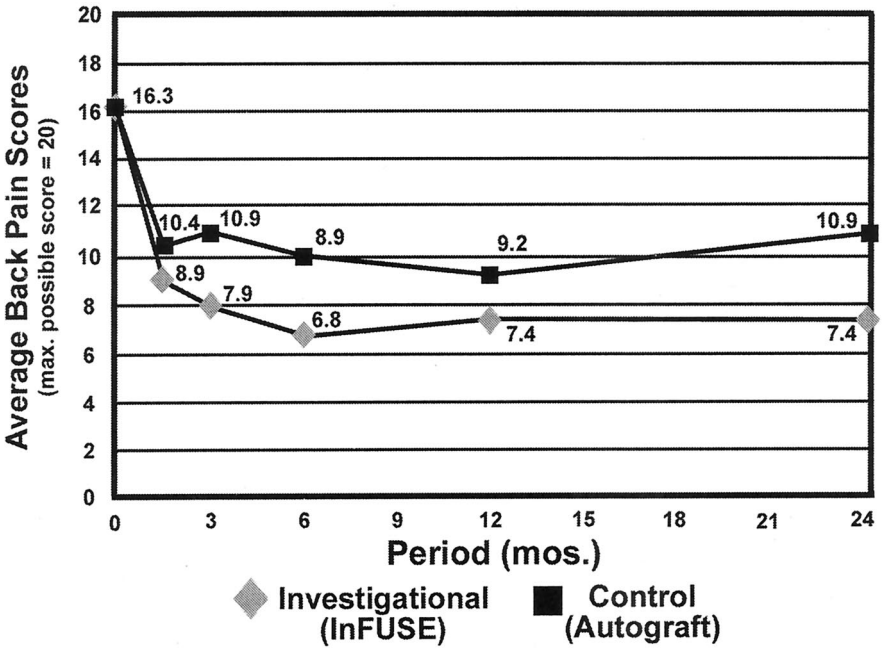

Figure 2. Comparison of back pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

health perceptions. It comprises a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Three patient satisfaction questions were administered at each postoperative time period. A successful answer to each question was defined as either a "definitely true" or "mostly true" response. Low back, leg, and iliac graft-site pain was evaluated using numerical rating scales that identified both pain intensity and duration. Standard visual analog scales were used for pain intensity and duration of the painful symptoms. The two scores were added together to derive a composite score.

Radiographic Outcome Measurements. Radiographs and CT scans were used to evaluate fusion at 6, 12, and 24 months after surgery.[6] Two independent, blinded radiologists interpreted all radiographs and CT scans. A third independent radiologist was used to adjudicate conflicting fusion findings.

Fusion was defined as bridging bone connecting the adjacent vertebral bodies either through the implants or around the implants, less than 5° of angular motion, less than or equal to 3 mm of translation, and an absence of radiolucent lines around more than 50% of either of the implant surfaces. Stability and radiolucent lines were assessed on plain radiographs using anteroposterior, lateral, and flexion-extension views. Thin-slice (1 mm) CT scans with sagittal reconstructions were evaluated at 6, 12, and 24 months. The presence of continuous trabecular bone formation between the vertebral bodies was assessed using radiographs and CT scans. A fusion was considered successful only if all four criteria were achieved: 1) bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels as evaluated by thin-cut CT scans and radiographs; 2) no angular motion of 5° or more on dynamic plain radiographs; 3) no sagittal translation of more than 3 mm on dynamic plain radiographs; and 4) no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral end plates.

Statistical Methods. The data from this clinical trial were analyzed using the statistical software package SAS® version 6.12. For continuous variables, *P* values are from ANOVA, and for categorical variables, they are from the Fisher exact test or χ^2 test.

Table 5. Leg Pain Outcomes

Period	Variable	Investigational (n = 24)	Control (n = 22)
Preop	N	24	22
	Mean	12.8	14.6
	SD	5.7	4.1
6 wks	N	24	21
	Mean	7.0	8.8
	SD	5.9	5.9
	P value*	0.933	
Improvement from preop	Mean	−5.8	−5.6
	P value†	0.001	0.001
3 mos	N	24	21
	Mean	6.2	8.3
	SD	4.4	5.8
	P value*	0.874	
Improvement from preop	Mean	−6.7	−6.4
	P value†	<0.001	<0.001
6 mos	N	24	20
	Mean	5.0	6.1
	SD	4.7	4.4
	P value*	0.654	
Improvement from preop	Mean	−7.9	8.7
	P value†	<0.001	<0.001
12 mos	N	24	19
	Mean	5.5	8.1
	SD	5.5	6.1
	P value*	0.818	
Improvement from preop	Mean	−7.3	−6.8
	P value†	<0.001	0.001
24 mos	N	24	17
	Mean	6.3	11.5
	SD	6.0	6.3
	P value*	0.142	
Improvement from preop	Mean	−6.5	−3.5
	P value†	<0.001	0.023

* *P* values for difference between the treatment groups are from analysis of variance.
† *P* values for change from preoperative in each group are from paired tests.
SD = standard deviation.

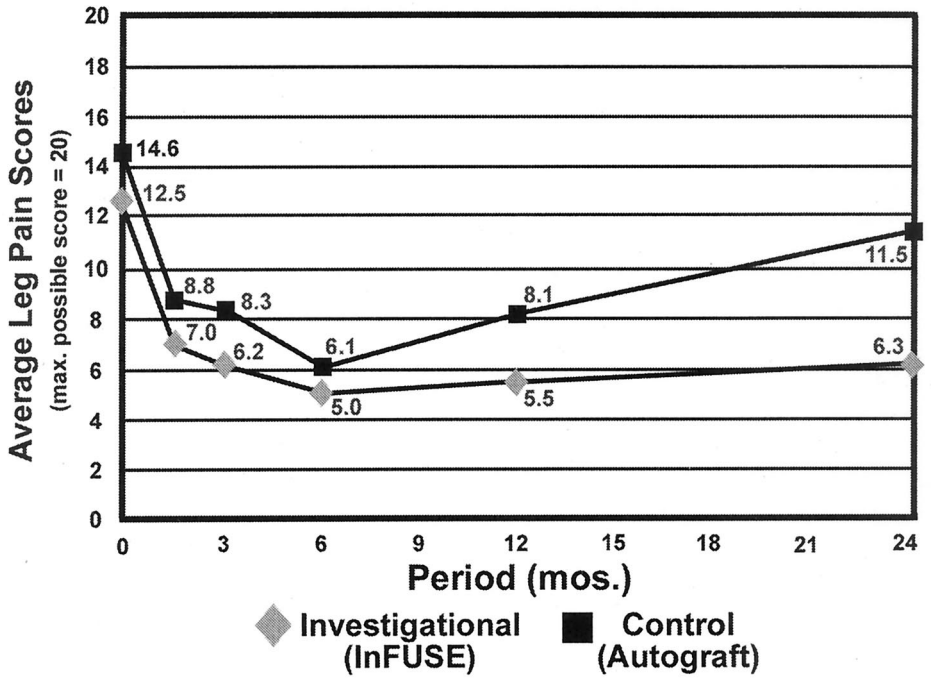

Figure 3. Comparison of leg pain outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Results

Surgery

In the investigational group, 11 patients (45.8%) had surgery at the L4–L5 level, and 13 (54.2%) had surgery at the L5–S1 level (Table 2). In the control group, surgery was performed at the L4–L5 level in 8 patients (36.4%) and at the L5-S1 level in 14 patients (63.6%). The mean operative time was slightly longer in the control group. The investigational group had surgery more commonly at the L4–L5 level. This exposure of the L4–L5 disc space often involves a tedious mobilization of the iliac vessels and requires more time when compared with the exposure at the L5–S1 level. The average blood loss was less in the investigational group than in the control group ($P = 0.026$). The average hospital stay was similar in both groups.

Clinical Outcomes

No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft (rhBMP-2 and the collagen sponge carrier) occurred during the course of the study.

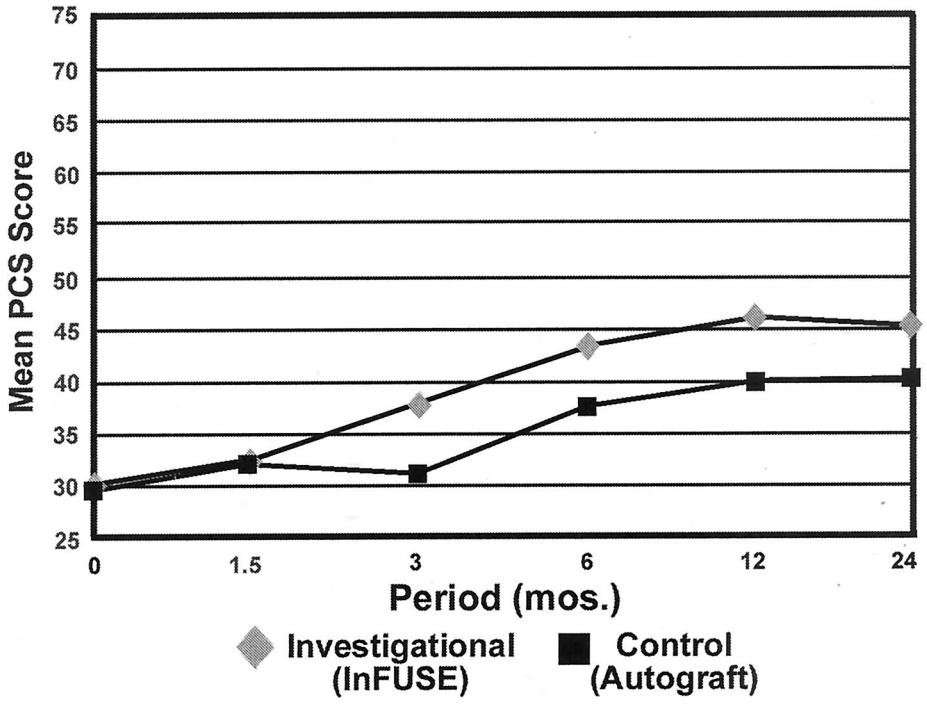

Figure 4. Comparison of Short Form 36 Physical Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

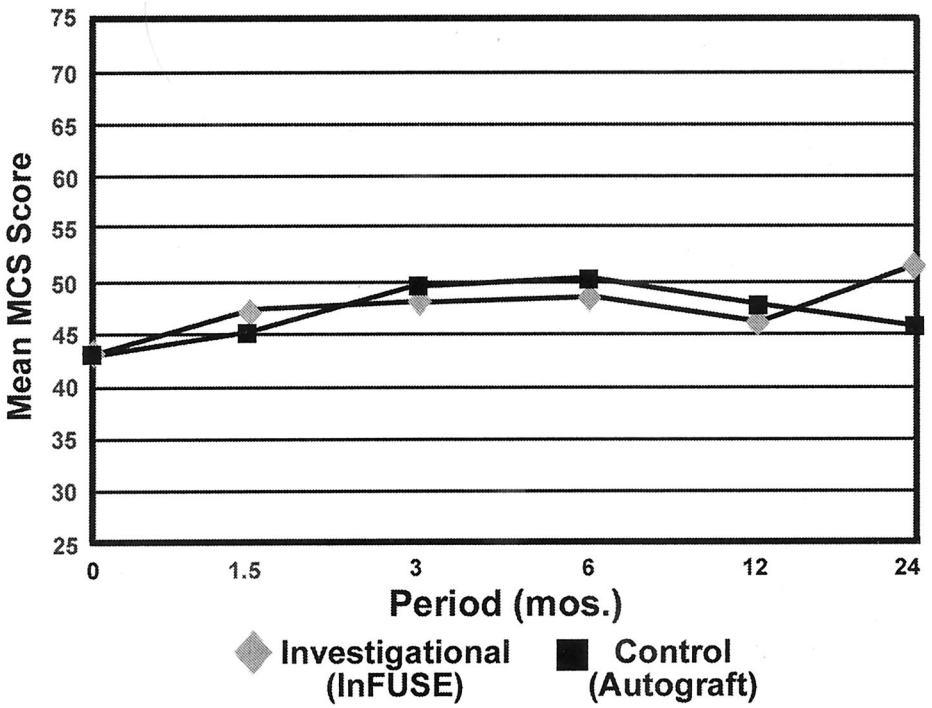

Figure 5. Comparison of Short Form 36 Mental Component Scores in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

Neurologic Outcomes

At 12 and 24 months, the investigational patients showed a higher rate of success than the control patients in their overall neurologic success scores (Table 3 and Figure 1). More than 87% of patients in the investigational group were considered to be a neurologic success (defined as equivalence or improvement from the preoperative condition) at 3 months after surgery. These results were maintained at the final 24-month follow-up. More than 95% of patients in the autograft control group were considered to be a neurologic success at 3 months after surgery. However, these clinical results deteriorated to 73.3% at 24 months.

Back Pain Outcomes

Patients in the investigational group showed an improvement in back pain analog scores (maximum score = 20) of more than 7 points at their initial postoperative visit at 6 weeks (Table 4 and Figure 2). In this group, back pain continued to improve and averaged close to a 9-point improvement in pain scores at 24 months after surgery. The control group's improvement in back pain followed a similar pattern. However, at 24 months, average back pain scores improved only 5 points in this group. The mean improvement scores for low back pain in the investigational group were significantly greater than those reported in the control group at 3, 6, and 24 months ($P = 0.038$, $P = 0.034$, and $P = 0.047$, respectively).

Leg Pain Outcomes

Before surgery, there was no difference between the leg pain scores of the two groups (investigational, 12.8; control, 14.6 [$P = 0.2291$]). After surgery, the investigational group showed greater relief of leg pain compared with the controls (Table 5 and Figure 3). In the investigational group, leg pain improved by more than 5 points within 6 weeks of surgery. These results remained virtually unchanged at the last follow-up at 24 months. However, while the autogenous graft group showed initial improvement of greater than 5 points, the improvement at 24 months decreased to 3.1 points.

General Health Outcomes

In both the PCS and MCS portions of the SF-36, a successful outcome was defined as a maintenance or improvement in results from preoperative. The investigational group showed higher success at 24 months than the control group (Figures 4 and 5). However, these results were not found to be statistically significant.

Patient Satisfaction Outcomes

At 24 months, the success rate was more than 83% in the investigational group for all three questions. For the control group, the success rate for the three questions ranged from 55% to 65% (Table 6).

Oswestry Disability Questionnaire Outcomes

The Oswestry Disability Questionnaire was used to assess pain with activity (Table 7 and Figure 6). At all follow-up intervals, the investigational group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively). At 24 months, the mean improvement in Oswestry scores was 33.5 points.

Seventy-one percent of the patients in the investigational group showed an improvement of at least 15 points in their disability scores at 3 months. This improvement compared favorably with the 43% of patients

Table 6. Patient Satisfaction

Period	Variable	Investigational (n = 24) (%)	Control (n = 22) (%)
6 mos	I am satisfied with the results of my surgery		
	Definitely true	17 (70.8)	12 (60.0)
	Mostly true	3 (12.5)	4 (20.0)
	P value*	0.503	
	I was helped as much as I thought I would be by my surgery		
	Definitely true	14 (58.3)	6 (30.0)
	Mostly true	6 (25.0)	9 (45.0)
	P value*	0.229	
	All things considered, I would have the surgery again for the same condition		
	Definitely true	18 (75.0)	13 (65.0)
	Mostly true	1 (4.2)	3 (15.0)
	P value*	0.312	
12 mos	I am satisfied with the results of my surgery		
	Definitely true	11 (45.8)	7 (35.0)
	Mostly true	8 (33.3)	7 (35.0)
	P value*	0.460	
	I was helped as much as I thought I would be by my surgery		
	Definitely true	12 (50.0)	6 (30.0)
	Mostly true	7 (29.2)	4 (20.0)
	P value*	0.169	
	All things considered, I would have the surgery again for the same condition		
	Definitely true	15 (62.5)	11 (55.0)
	Mostly true	4 (16.7)	1 (5.0)
	P value*	0.130	
24 mos	I am satisfied with the results of my surgery		
	Definitely true	13 (54.2)	6 (30.0)
	Mostly true	7 (29.2)	5 (25.0)
	P value*	0.084	
	I was helped as much as I thought I would be by my surgery		
	Definitely true	13 (54.2)	6 (30.0)
	Mostly true	9 (37.5)	5 (25.0)
	P value*	0.249	
	All things considered, I would have the surgery again for the same condition		
	Definitely true	15 (62.5)	11 (55.0)
	Mostly true	6 (25.0)	2 (10.0)
	P value*	0.137	

* *P* values are from the χ^2 test.

Table 7. Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational	Control
Preop	N	24	22
	Mean	52.4	55.3
	SD	13.1	13.5
6 wks	N	24	21
	Mean	39.9	47.2
	SD	16.8	18.8
	P value*	0.307	
Improvement from preop	Mean	−12.5	−7.9
	P value†	<0.001	0.024
3 mos	N	24	21
	Mean	29.0	42.0
	SD	14.7	19.0
	P value*	0.032	
Improvement from preop	Mean	−23.4	−14.3
	P value†	<0.001	<0.001
6 mos	N	24	20
	Mean	21.4	34.4
	SD	16.1	21.8
	P value*	0.039	
Improvement from preop	Mean	−31.0	−20.9
	P value†	<0.001	<0.001
12 mos	N	24	19
	Mean	20.8	30.0
	SD	14.9	21.2
	P value*	0.171	
Improvement from preop	Mean	−31.6	−24.7
	P value*	<0.001	<0.001
24 mos	N	24	17
	Mean	18.9	32.8
	SD	14.5	22.7
	P value*	0.039	
Improvement from preop	Mean	−33.5	−21.5
	P value†	<0.001	<0.001

* *P* values for difference between the treatment groups are from analysis of variance.
† *P* values for change from preoperative in each group are from paired tests.
SD = standard deviation.

who showed improvement in the control group ($P = 0.075$). At 12 months, 83% of the investigational group patients improved more than 15 points compared with 58% of the controls. This finding was similar at the 24-month follow-up.

Return-to-Work Status

Higher percentages of patients in the investigational group were also able to return to work (Figure 7). In the investigational group, 45.8% of patients were working before their surgery. At 24 months after surgery, 66.7% were working. These patients were also able to return to work earlier than those in the control group. In the control group, 40.9% were working before surgery, and at 24 months, 35.0% were working.

Iliac Crest Graft Site Pain

Autograft bone was not harvested from the iliac crest in the investigational group; therefore, bone graft site pain was not measured and was assumed to be zero in this group. In the control group, the intensity and frequency of pain and morbidity from the graft harvesting was measured on a 20-point rating scale. At discharge from the hospital, the mean graft-site pain was highest (11.3). Graft-site pain persisted at 24 months in these patients with a mean score of 2.2 (Figure 8).

Additional Surgery

No patients treated with InFUSE™ Bone Graft required an additional surgical procedure in the immediate perioperative period; one control patient required an early return to surgery to remove residual disc material (Table 8). Four patients (one investigational, three control) underwent supplemental posterior fixation procedures after their primary surgery. The investigational patient continued to have persistent low back pain at 24 months. The patient's radiographs met the criteria for fusion; however, the attending physician elected to reoperate and supplement the interbody grafts with insertion of posterior pedicle fixation. The attending physician was

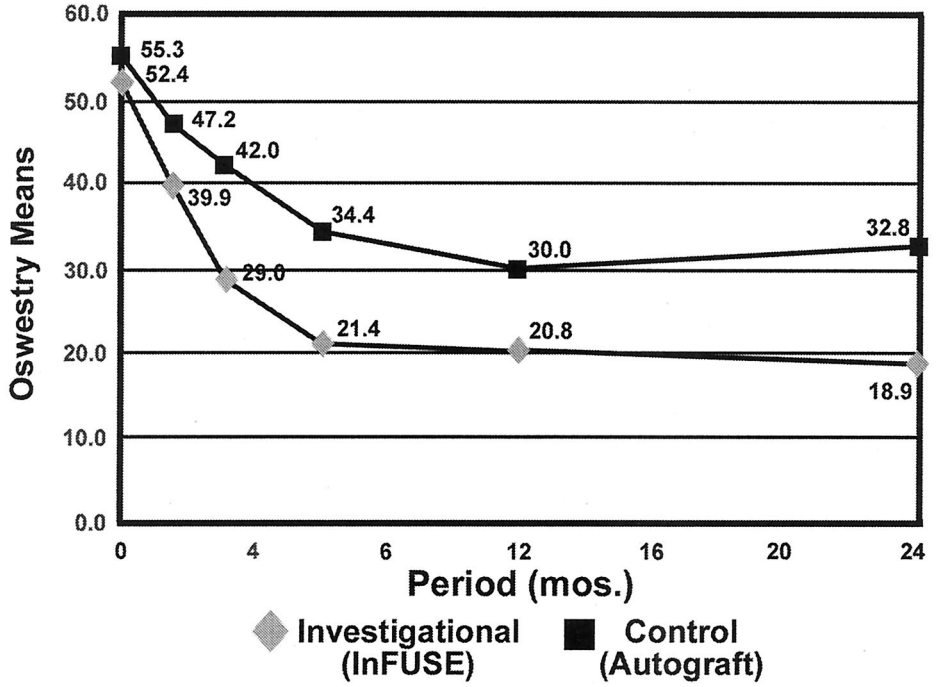

Figure 6. Comparison of Oswestry Disability Questionnaire outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

able to identify "slight motion" in the posterior facet joints despite the presence of an adequate fusion across the anterior disc space. The three patients in the control group had supplemental posterior fixation inserted from 7 months to 20 months following their initial surgeries. In each of these cases, the patient reported persistent low back pain and, in some instances, referred leg pain.

Radiographic Outcomes

At 6 months after surgery, 21 patients in the investigational group were able to return for follow-up evaluation. Of these, 19 patients (90.5%) who were treated with InFUSE™ Bone Graft had evidence of interbody fusion compared with 13 of the 20 patients (65%) in the control group ($P = 0.067$; Figure 9). At 12 months, all patients (24/24, 100%) in the investigational group had evidence of fusion compared with 17 patients (89.5%) in the control group. Based on their radiographs at the final follow up at 24 months after surgery, all patients (100%) in the investigational group showed evidence of remaining fused (Figure 10).

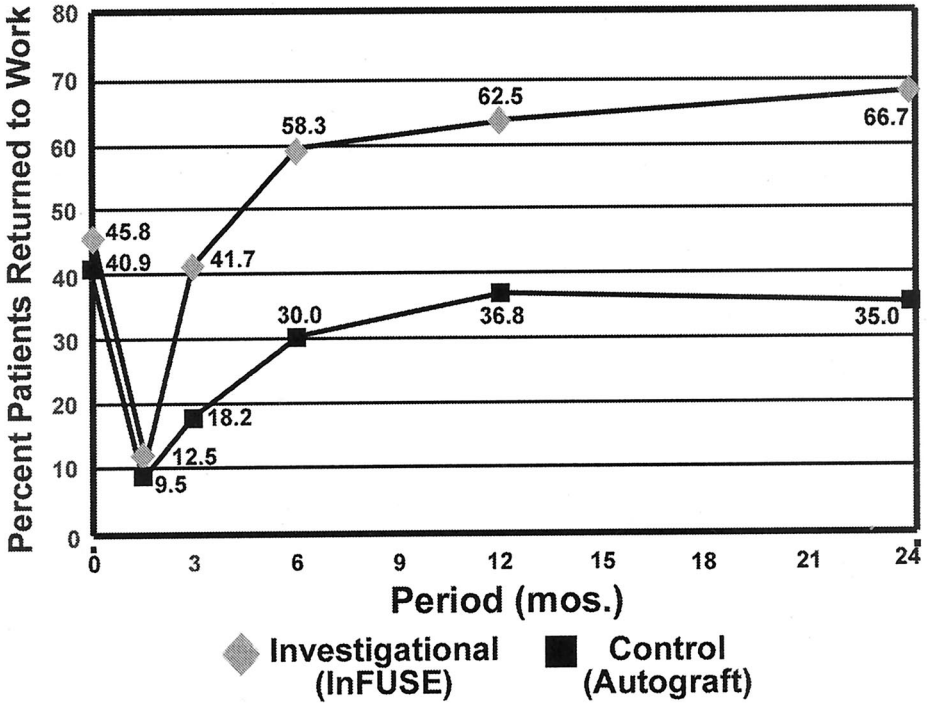

Figure 7. Comparison of return-to-work status in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

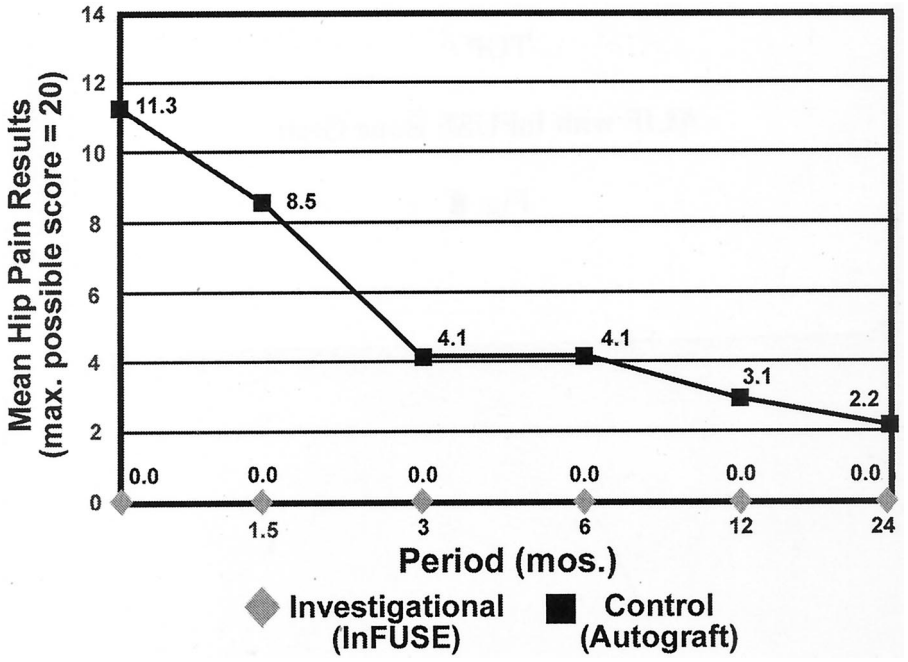

Figure 8. Iliac crest bone graft harvest site pain in the control group.

One patient in the investigational group did meet the criteria for fusion but underwent supplemental posterior fixation after the final 24-month follow-up examination.

Table 8. Additional Surgeries

Procedure	Investigational (InFUSE Bone Graft) Group	Control (Autograft) Group
Removals	0	0
Revisions	0	0
Supplemental fixation (%)	1 (4.2)	3 (13.6)
Reoperation (%)	0	1 (4.5)

In this patient, the attending physician identified motion within the facet joints and elected to add supplemental posterior fixation to the spinal motion segment just after the 24-month visit. By the criteria of this study, this patient was recorded as having a successful interbody fusion at the 12- and 24-month follow-up examination and is not considered a failure until the 36-month follow-up examination. All patients were found to have bony integration of the allografts to the vertebral end plates and trabeculated new bone formation across the fused interspace. By considering this investigational patient as a fusion failure because of the need to use supplemental

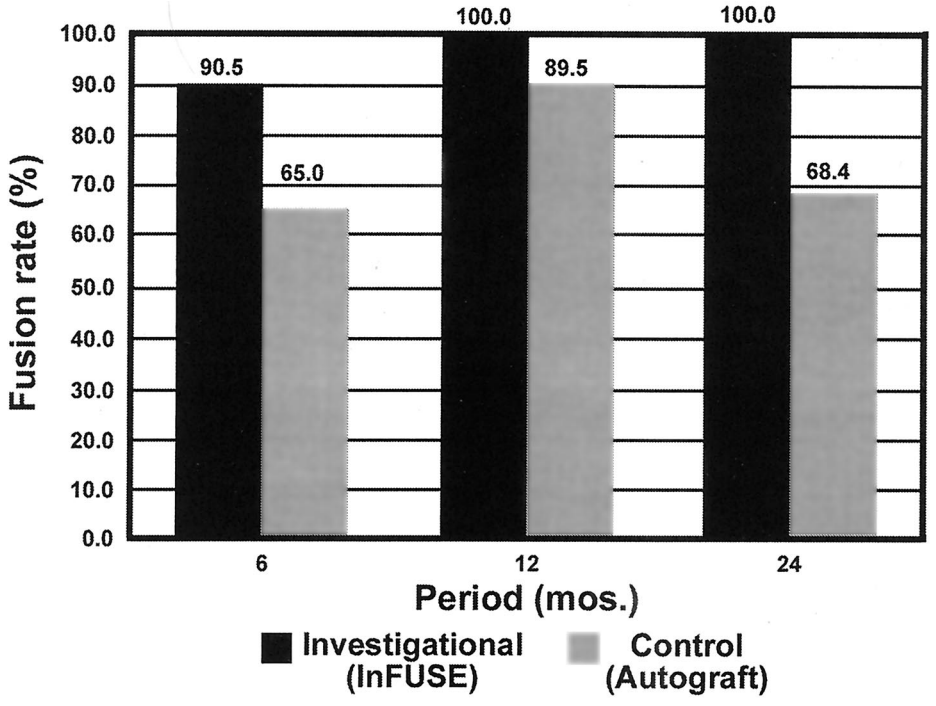

Figure 9. Comparison of postoperative fusion outcomes in the investigational group (InFUSE™ Bone Graft) and the control group (iliac crest autograft).

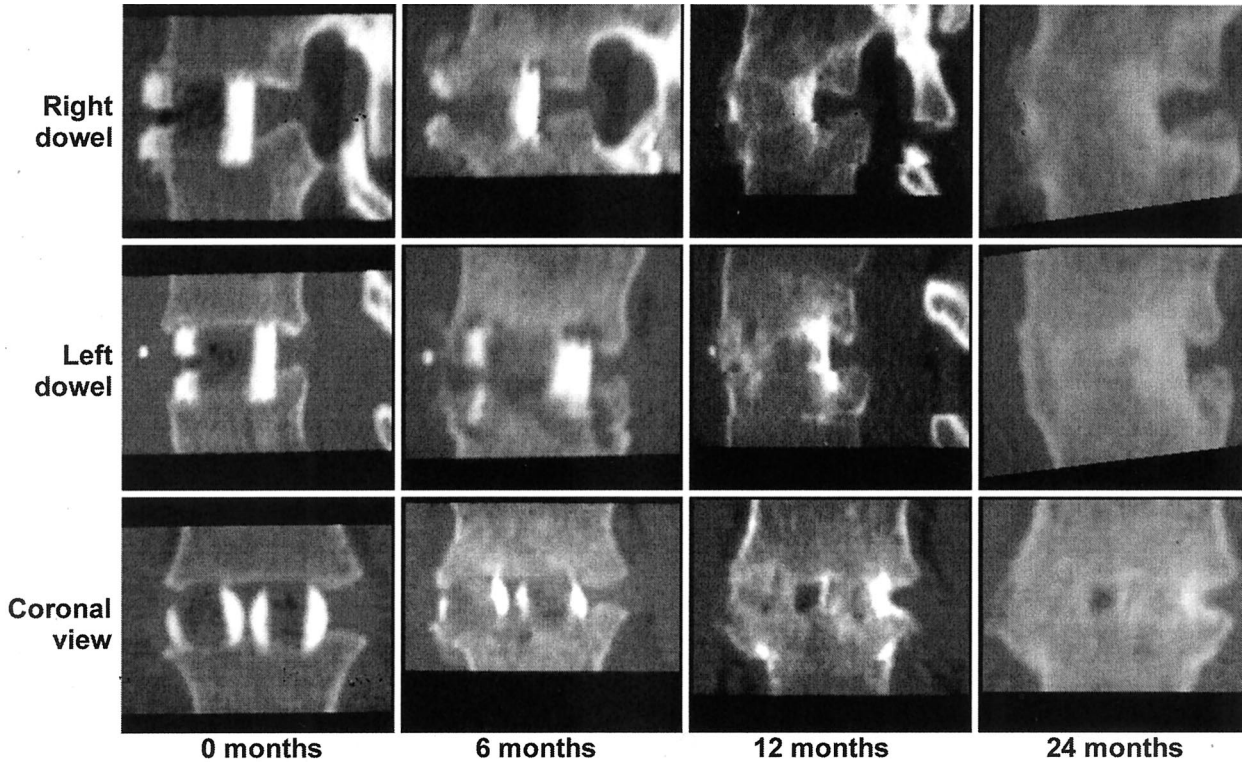

Figure 10. Serial thin-cut CT scans after an L5–S1 fusion using InFUSE™ Bone Graft. Sagittal and frontal CT reconstructions through both the right and left dowels show the progression of the interbody fusion. The immediate postoperative reconstructions show that the dowels have not been incorporated into the vertebral end plates, and there is no bone formation in the central portion of the dowels. At six months, the dowels are incorporated into the vertebral end plates, and there is new bone formation within the dowels. At 12 months, there is new bone formation connecting the adjacent vertebral bodies both inside and outside of the dowels. At 24 months, the dowels have almost been completely reabsorbed and replaced with new trabecular bone formation.

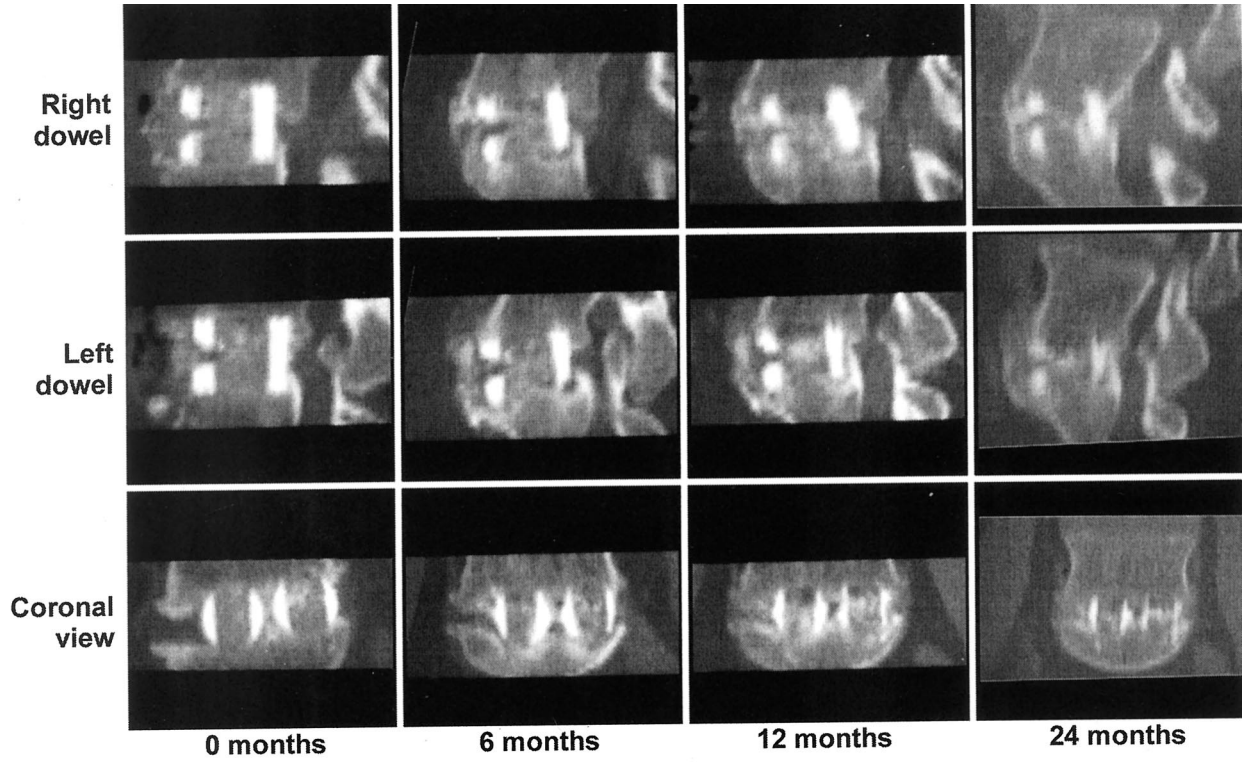

Figure 11. Serial thin-cut CT scans after an L5–S1 fusion using autograft demonstrate the progression of the interbody fusion. Immediate postoperative scans show corticocancellous graft within the dowels. At six months, trabecular bone connects the adjacent vertebral bodies through the dowels and anterior to the dowels. At 12 and 24 months, there is maturation of the interbody fusion with more bone formation and incorporation of the dowels into the vertebral end plates.

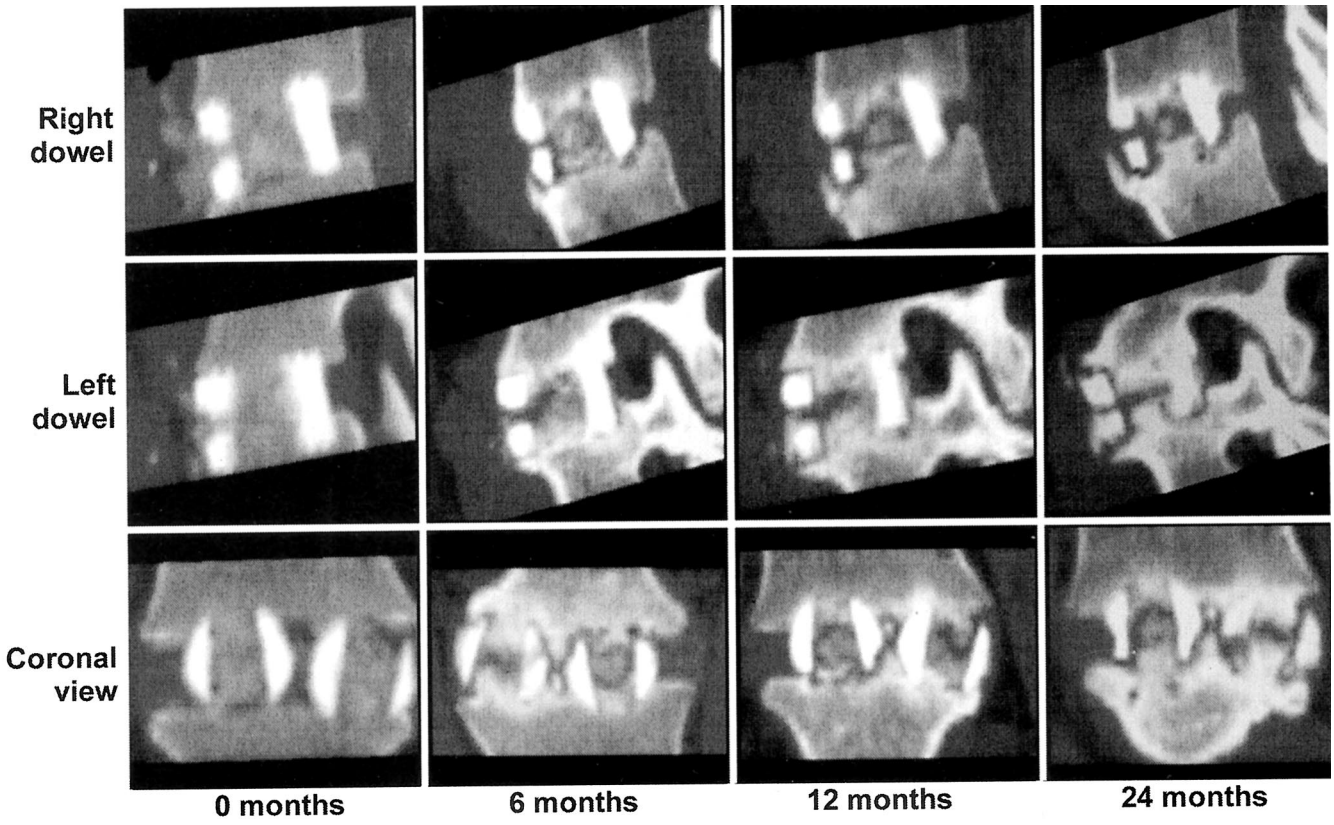

Figure 12. Serial thin-cut CT scans after an L5–S1 fusion using autograft show the development of a pseudarthrosis. At six months, the grafts within the dowels and the dowels themselves appear to have become attached to the adjacent vertebral end plates. At 12 months, lucencies appear separating the dowels from the vertebral end plates. By 24 months, a radiolucent line involving the inferior portion of both dowels highlights noncontiguous bone formation between the vertebrae consistent with a pseudarthrosis.

posterior fixation, the fusion rate for the investigational group was 95.8%.

At 24 months in the control autograft group, 19 patients were available for radiographic evaluation, and 13 of these patients (68.4%) were considered to have fusions (Figure 11). In the control group, there were no failures of the allograft dowels. Three control group patients underwent supplemental posterior fixation for pseudarthrosis. Radiographic lucencies developed at the interface of the allograft to the vertebral endplate between the 12- and 24-month follow-up examinations (Figure 12). This led to the decrease in the fusion rate in the control group. There was no migration of the implants.

■ Discussion

Recombinant human bone morphogenetic protein-2 is an osteoinductive growth factor.[2,20] Urist discovered the capabilities of demineralized bone matrix to induce ectopic bone formation in a rat muscle pouch and introduced the concept that bone growth factors can induce new bone formation independent of the bone tissue environment.[22] Bone morphogenetic protein-2 is one of several proteins identified from bone tissue that acts a osteoinductive cytokine and induces the differentiation of pluripotential precursor cells along an osteogenic line. A pure form of this protein can be produced through standard recombinant technology. The human cDNA sequence is created through the use of oligonucleotide probes, and these clones are then spliced into a viral vector and transfected into a carrier cell in a process called recombination. These production cells (Chinese hamster ovary cells) have the ability to produce large quantities of rhBMP-2. Creating recombinant human proteins in this manner avoids potential complications associated with disease transmission from allograft or xenograft sources.

The availability of rhBMP-2 in pure "unlimited" sources has the ability to greatly enhance spinal fusion results while lowering pain scores associated with a bone graft harvesting procedure. The purpose of this study was to assess the efficacy of this recombinant protein impregnated on a collagen sponge in a threaded cortical allograft dowel for the treatment of degenerative disc disease by an anterior lumbar interbody fusion.

To date, in both animal and human studies, rhBMP-2 has been shown to be capable of inducing new bone formation.[2,19] In a study of anterior lumbar interbody fusion in nonhuman primates, rhBMP-2 and an absorbable collagen sponge carrier was shown to promote fu-

sion through osteoinduction.[11] New bone formation appeared to be superior to autogenous iliac crest graft with cortical dowel allograft. Similarly, in a preliminary clinical study involving the use of InFUSE™ Bone Graft and a tapered cylindrical titanium cage in humans, arthrodesis was found to occur more reliably in patients treated with rhBMP-2 than in controls treated with autogenous bone graft.[3]

This study is the first clinical report of the effectiveness of rhBMP-2 used with cortical allograft to promote anterior lumbar intervertebral fusion in humans. No unanticipated adverse events that were related to the use of InFUSE™ Bone Graft occurred during the course of the study. Because the investigational group did not undergo the bone graft harvesting procedure, there was a statistically significant reduction in operative time and decreased blood loss during the surgical procedure.

Overall, the investigational group, who received rhBMP-2 on a collagen sponge carrier, showed higher rates of success in the reduction of back and leg pain associated with degenerative lumbar disc disease than the control group. At their initial postoperative visit, patients in the investigational group showed an improvement in back pain of more than seven points. Back pain scores continued to improve throughout the study period and averaged approximately a 9-point improvement at 24 months. In the investigational group, leg pain improved by more than 5 points within 6 weeks of surgery and remained unchanged at the last clinical follow-up at 24 months. When compared with the control group, the investigational group showed greater relief of leg pain at all clinical follow-up intervals. Similarly, at 12 and 24 months, the investigational patients showed a higher rate of success than the control patients did in their overall neurologic success scores. The use of rhBMP-2 obviates the need for autogenous bone graft and the potential for donor site morbidity. The control group had complaints of hip pain throughout the 24-month study period.

Coinciding with the reduction in painful symptoms was the investigational group's greater and faster functional recovery. At all time periods, the investigational group had greater improvements in Oswestry Disability Questionnaire scores than the control group. The mean improvements in Oswestry scores at 12 and 24 months (31.6 and 33.5 points) are among the highest reported in the literature. Return-to-work status was also assessed to evaluate functional recovery of the patients in the study. Similarly, higher percentages of patients in the investigational group were also able to return to work. In this group, 45.8% of patients were working before surgery, and 66.7% were working at 24 months after surgery.

The investigational group also showed improved general health status after surgery. In both the PCS and MCS portions of the SF-36, which was used to measure specific health concepts related to physical and social functioning and limitations, the investigational group showed higher mean scores at 24 months than the control group. As would be expected from these improved outcomes, patient satisfaction was higher in this group. At 24 months, 83% of patients in the group responded positively to all three questions that asked if they were satisfied with their surgical outcome.

Fusion Rate

The investigational group showed higher rates of fusion when compared with the control group at 6, 12, and 24 months. In our study, fusion was defined as radiographically identified bridging bone, no motion ($<5°$ angulation, ≤ 3 mm translation), and absence of radiolucent lines around more than 50% of either implant. In the control group, there were patients who were thought to be fused radiographically at 12 months, and later, at 24 months, they were thought not to be fused radiographically. This confusion regarding fusion was due to the radiolucent line criteria. Although there was bridging bone and no motion at 12 and 24 months in these patients, radiolucent lines were not evident at 12 months. It was not until 24 months after surgery that these lucencies around the cortical implants were seen. This occurrence is very likely due to the nature of the control group's implant. The dowels were packed solid with autograft bone, and lucencies resulting from failure of the allograft to fully incorporate to the vertebral end plates are not evident early on but are seen over time. After all, that is why the radiographic follow-up evaluations were carried out to two years. Because of early incorporation of the allograft to the vertebral end plates in the BMP group, this radiolucent line issue was not seen after surgery in the investigational group.

Criteria other than radiographic were used to determine the rate of fusion, or fusion success. Fusion success was, in part, defined by the need for secondary surgeries. If a patient in the investigational group had a secondary surgery (*i.e.*, supplemental fixation), that patient was called a fusion failure from that time forward. We did not go back and classify this patient as a fusion failure at earlier visits because at these visits, the patient met the protocol requirements of radiographic fusion. The pseudarthrosis diagnosis may have been in response to persistent low back pain, not a deviation from the fusion criteria. At the time of surgery on this investigational patient, the attending surgeon found that the spinal motion segment "was extremely stable and contained only micromotion noted after the facet joints were debrided."

InFUSE™ Bone Graft was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels. These improved outcomes were due, in part, to the successful combination of the anterior surgi-

cal approach, the use of threaded allograft dowels, and a high rate of successful interbody fusion.

■ Key Points

- At 6, 12, and 24 months after surgery, fusion rates in the rhBMP-2 group were higher than in the control group.
- At all follow-up intervals, the investigational rhBMP-2 group had greater improvements in Oswestry scores than the control group. At 3, 6, and 24 months, the differences in improvement scores were statistically significant ($P = 0.032$, $P = 0.039$, and $P = 0.039$, respectively).
- At all postoperative assessment intervals, patients in both treatment groups showed improvement in back and leg pain outcomes.
- The use of rhBMP-2 in anterior lumbar interbody fusion procedures eliminates the complications of iliac crest bone harvesting including postoperative pain and scarring.

References

1. Blumenthal SL, Baker J, Dossett A, et al. The role of anterior lumbar fusion for internal disc disruption. Spine 1988;13:566–69.
2. Boden SD, Schimandle JH, Hutton WC. Volvo Award Winner in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part II: Study of dose, carrier, and species. Spine 1995;20:2633–44.
3. Boden SD, Zdeblick TA Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Spine 2000;25:376–81.
4. Boyd, LM, Estes, BT, Liu M. Biomechanics of lumbar interbody constructs, effect of design and materials. In: Husson JL, LeHuec JC, eds. Chirurgie Endoscopique et Mini-invasive du Rachis. Montpelier, France: Sauramps Médical; 1999:181–92.
5. Burkus JK, Dorchak JD, Sanders DL, et al. Single-level anterior lumbar interbody fusion using threaded cortical bone allografts. Presented at: North American Spine Society Meeting of the Americas; 1999; Miami, Florida.
6. Burkus JK, Foley K, Haid R, et al. Surgical Interbody Research Group. Radiographic assessment of interbody fusion devices: fusion criteria for anterior interbody surgery. Neurosurg Focus 2001;10:1–9.
7. Crock HV. Anterior lumbar interbody fusion: indications for its use and notes on surgical technique. Clin Orthop 1982;165:157–63.
8. Fairbank JC, Couper J, Davies JB, et al. The Oswestry Low Back Pain Disability Questionnaire. Physiotherapy 1980;66:271–3.
9. Flynn JC, Houque MA. Anterior fusion of the lumbar spine. J Bone Joint Surg Am 1979;61A:1143–50.
10. Harmon PH. Anterior excision and vertebral fusion operation for intervertebral disc syndromes of the lower lumbar spine: three to five year results in 244 cases. Clin Orthop 1963;26:107–27.
11. Hecht BP, Fischgrund JS, Herkowitz HN, et al. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) to promote spinal fusion in a nonhuman primate anterior interbody fusion model. Spine 1999;24:629–36.
12. Kumar A, Kozak JA, Doherty BJ, et al. Interspace distraction and graft subsidence after anterior lumbar fusion with femoral strut allograft. Spine 1993;18:2393–400.
13. Lane JD, Moore ES. Transperitoneal approach to the intervertebral disc in the lumbar area. Ann Surg 1948;127:537–51.
14. Loguidice VA, Johnson RG, Guyer RD, et al. Anterior lumbar interbody fusion. Spine 1988;13:366–69.
15. Leong JC, Chun SY, Grange WJ, et al. Long-term results of lumbar intervertebral disc prolapse. Spine 1983;8:793–99.
16. McHorney CA, Ware JE Jr, Lu RJF, et al. The MOS 36-Item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40–66.
17. Morales RW, Pettine KA, Salib RM. A biomechanical study of bone allografts used in lumbar interbody fusions. Presented at: North American Spine Society 6th Annual Meeting; 1991; Keystone, Colorado.
18. Sacks S. Anterior interbody fusion of the lumbar spine. J Bone Joint Surg Br 1965;47:211–23.
19. Sandhu HS, Kanim LEA, Toth JM, et al. Experimental spinal fusion with recombinant human bone morphogenetic protein-2 without decortication of osseous elements. Spine 1997;22:1171–80.
20. Schimandle JH, Boden SD, Hutton WC. Experimental spinal fusion with recombinant human bone morphogenetic protein-2. Spine 1995;20:1326–37.
21. Stauffer RN, Coventry MB. Anterior interbody lumbar spine fusion. J Bone Joint Surg Am 1972;54:756–68.
22. Urist MR. Bone. Formation by autoinduction. Science 1965;150:893–99.
23. Ware JE Jr, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.

Address correspondence to

J.K. Burkus, MD
The Hughston Clinic, PC
6262 Veterans Parkway
Columbus, GA 31908-9517
E-mail: jkb66@knology.net