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Is INFUSE Bone Graft Superior to Autograft Bone? An Integrated Analysis of Clinical Trials Using the LT-CAGE Lumbar Tapered Fusion Device

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Summary: Multicenter human clinical studies of patients undergoing anterior lumbar fusion have been conducted using recombinant bone morphogenetic protein or rhBMP-2 on an absorbable collagen sponge, marketed as INFUSE Bone Graft, or autograft implanted in the LT-CAGE Lumbar Tapered Fusion device. An integrated analysis of multiple clinical studies was performed using an analysis of covariance to adjust for preoperative variables in a total of 679 patients. Of these patients, 277 had their cages implanted with rhBMP-2 on an absorbable collagen sponge and 402 received autograft transferred from the iliac crest. The patients treated with rhBMP-2 had statistically superior outcomes with regard to length of surgery, blood loss, hospital stay, reoperation rate, median time to return to work, and fusion rates at 6, 12, and 24 months. Oswestry Disability Index scores and the Physical Component Scores and Pain Index of the SF-36 scale at 3, 6, 12, and 24 months showed statistically superior outcomes in the rhBMP-2 group. **Key Words:** Anterior lumbar interbody fusion—INFUSE Bone Graft—Bone morphogenetic protein—Fusion cage—Degenerative disc disease—Lumbar spine—rhBMP-2.

INTRODUCTION

The surgical technique and indications for implanting the LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek, Memphis, TN, USA) and reports of outcome measurements in patients in whom it has been implanted have been reported in the literature (1–3). The history, development, and method of use of the protein product, called rhBMP-2 (recombinant human bone morphogenetic protein), used in our study have also been reviewed (4–7). The prospective, randomized trial that led to the product's approval by showing equivalency in outcome between the INFUSE Bone Graft (Medtronic Sofamor Danek) and autograft was published in 2002 (2). INFUSE Bone Graft is composed of rhBMP-2 and an absorbable collagen sponge. The advantages to the patient and to the surgeon of not having to create a second surgical site and the complications and pain of iliac crest harvesting have also been reviewed (8).

The purpose of our analysis was to investigate the potential statistical superiority of INFUSE Bone Graft to autograft used inside the LT-CAGE Lumbar Tapered Fusion Device in surgical parameters, hospital stay, and clinical outcome in single-level spinal fusions. We integrated, or pooled, the results from similar large-scale clinical trials of the same device used for the same indication and measured in the same manner to check for statistical superiority. These data came from both published (2,3) and unpublished studies.

INFUSE Bone Graft with the LT-CAGE device was approved by the U.S. Food and Drug Administration on

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July 2, 2002, for treating patients with degenerative disc disease and up to grade 1 spondylolisthesis using a single-level anterior spinal fusion procedure. The approval was based primarily on the clinical data from a prospective, randomized, controlled clinical trial that is discussed in detail elsewhere (2). That study used the INFUSE Bone Graft with the LT-CAGE Tapered Lumbar Fusion Device in the investigational group patients and compared their results with those of the control group patients who received autograft inside the LT-CAGE device in open surgical procedures. Wyeth BioPharma (Cambridge, MA, USA) genetically engineered the rhBMP-2 component. The absorbable collagen sponge component is manufactured by Integra LifeSciences (Plainsboro, NJ, USA). Together, the components are distributed commercially under the trade name INFUSE Bone Graft (Medtronic Sofamor Danek).

The clinical trial was designed to establish statistical equivalence (noninferiority) between the INFUSE group and autograft group. The fusion success rate in the INFUSE group was 94.5% at 24 months after surgery compared with 88.7% in the autograft group. The probability of noninferiority of INFUSE Bone Graft to autograft was shown to be essentially 100%. The probability of superiority was 90.2%, which, albeit high, did not meet the minimum superiority criterion of 95% predefined in the prospective, randomized protocol. Fusion superiority was not shown probably because of insufficient sample size and, therefore, insufficient statistical power because that clinical trial was designed and sized only to show equivalence. Because the number of patients enrolled in that single study was not adequate to demonstrate statistical superiority, we combined the patient data from that randomized study with two additional studies to assess the statistical superiority of the results in the INFUSE patients over those in the autograft controls.

METHODS

Our analysis combines data sets from a published randomized trial (2) that had two arms with those from two additional clinical trials to increase the sample size and statistical power. Patients who were included in the open trials were randomly assigned in a 1:1 manner to one of two groups: the investigational group, which received INFUSE, or the control group, which received autogenous iliac crest bone graft. These two additional patient data sets were from studies in which the fusion cage was implanted laparoscopically. One of these two patient data sets is from the clinical trial in which INFUSE Bone Graft was used with the LT-CAGE Tapered Lumbar Fusion Device and implanted laparoscopically. This study used the identical inclusion–exclusion criteria and procedures as the prospective randomized open study. A portion of the results of this study from one site has been published (3). The second set of additional patient data comes from another clinical trial in which autograft and the LT-CAGE device were inserted using a laparoscopic surgical approach to treat single-level degenerative disc disease. The main inclusion–exclusion criteria for these patients were identical to those for the patients in the randomized trial and the other laparoscopic arm of the study with the minor exception of not having a minimum Oswestry low back pain disability score for entry, as was required for the other three sets of patients. These four prospective, multicenter clinical studies are summarized in Table 1. All patients were entered into these studies between 1996 and 1999.

Surgical Techniques

All of the 679 patients had degenerative disc disease with up to grade 1 spondylolisthesis, and all patients had two LT-CAGE devices implanted anteriorly at one lumbar level (Fig. 1). All open surgical procedures were performed using a mini-anterior lumbar interbody fusion (ALIF) approach. A retroperitoneal or a transperitoneal approach to the lumbosacral spine was carried out through a left paramedian abdominal incision. The anterior portion of the L4–L5 or L5–S1 disc space was exposed after mobilization of the great vessels. A box incision of the anulus fibrosus was completed, and a complete lumbar discectomy was carried out under direct visualization. Great care was taken to remove the cartilaginous endplates while preserving the bone endplates. Dilators were used for sequential distraction of the interspace. The vertebral endplates were reamed symmetrically to a depth of 1.5 mm. The tapered fusion devices were placed symmetrically in the disc space, and the cages were packed with either INFUSE or autogenous bone graft (Fig. 2).

In the laparoscopic groups, the lumbosacral spine was approached through a transperitoneal portal. Channel discectomies were followed by disc space distraction. Using a method similar to that in the open mini-ALIF approach, the vertebral endplates were reamed symmetrically to a depth of 1.5 mm. The tapered fusion devices were packed with INFUSE or autogenous bone graft and were inserted sequentially into the disc space.

TABLE 1. *Summary of study groups analyzed*

Study group	Graft type	Surgical approach	Randomized	Prospective	No. of patients
INFUSE open	INFUSE	Open	Yes	Yes	143
INFUSE lap	INFUSE	Laparoscopic	No	Yes	134
Autograft open	Autograft	Open	Yes	Yes	136
Autograft lap	Autograft	Laparoscopic	No	Yes	266

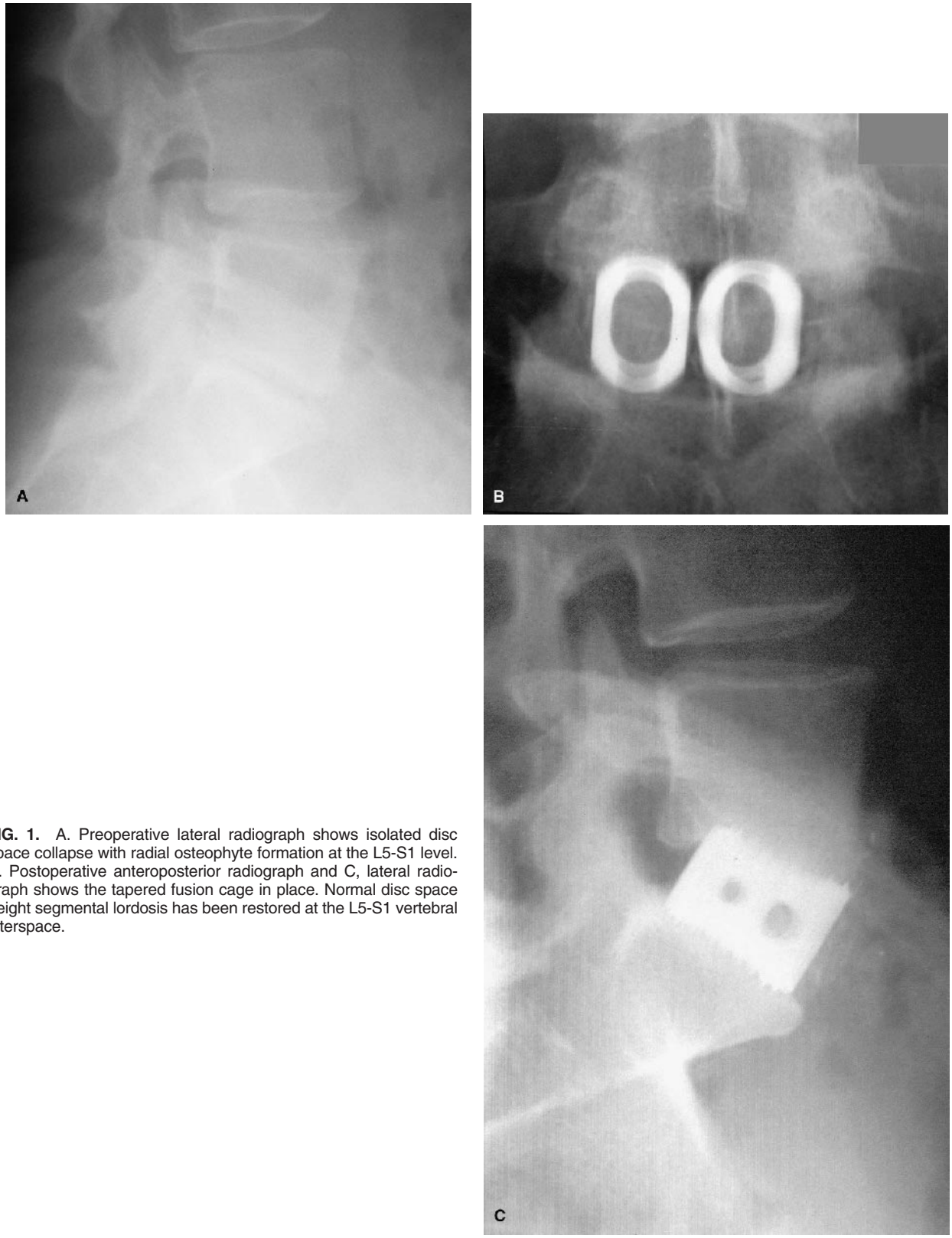

FIG. 1. A. Preoperative lateral radiograph shows isolated disc space collapse with radial osteophyte formation at the L5-S1 level. B. Postoperative anteroposterior radiograph and C, lateral radiograph shows the tapered fusion cage in place. Normal disc space height segmental lordosis has been restored at the L5-S1 vertebral interspace.

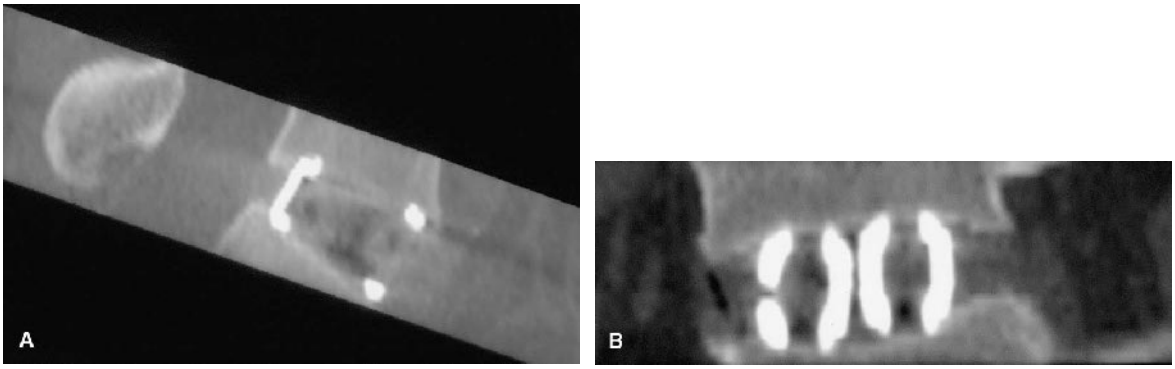

FIG. 2. A. An immediate postoperative (48 hours) sagittal plane, thin-cut (1mm) CT scan reconstruction through the central portion of the LT-CAGE shows the rhBMP-2 soaked collage sponge present in the cage. B. Coronal plain CT scan reconstructions show the cages well placed centrally in the disc space. No autogenous grafts were placed in the interspace.

Clinical Studies

The two treatment factors in these four patient data sets are bone graft type (INFUSE Bone Graft or autograft) and the surgical approach (open or laparoscopic). Our goal was to compare and analyze the results in the patients who received INFUSE Bone Graft with those in the patients who received autograft. The results from the two surgical approaches were pooled and the effects of surgical approach, if any, such as at early time points, were statistically adjusted so as not to affect the comparison between the graft types. Thus, our analysis compared the results of 277 INFUSE Bone Graft patients with 402 autograft patients. All of the 679 patients were included in prospective, multicenter studies using the same outcome measurement tools and methodology of analysis. More than 60 surgeons at 36 different sites enrolled the 679 patients. No single surgeon performed more than 10% of the cases. Hence, the outcomes represent typical results from a wide variety of surgeons with different degrees of experience.

Because not all of the four prospectively studied groups had a randomized control, the patients' demographic characteristics and prognostic factors could be different among the groups. Tables 2, 3, and 4 summarize demographic information, preoperative medical condition and medication usage, and preoperative measurements of several clinical endpoints, respectively. Among approximately 20 summarized variables, seven were found to be significantly different between the combined INFUSE group and the combined autograft group.

Statistical Analysis

The seven variables that were found to have statistically significant differences were age, previous back surgery, preoperative non-narcotic medication use, weak-narcotic medication use, muscle relaxant medication use, preoperative low back pain score on the Oswestry Disability Index, and preoperative SF-36 Physical Component Score. Because these seven prognostic factors could potentially affect the clinical outcomes and therefore confound the analysis of a study between the INFUSE and autograft groups, a statistical technique called analysis of covariance was performed. With the use of this statistical methodology, the influences of these prognostic factors were adjusted for, and comparisons could then be made between the INFUSE and autograft results. In essence, this statistical method makes it possible to have both groups start at the same level statistically for these seven factors before any differences in outcome are compared.

RESULTS

The statistical analyses of operative time, blood loss, and hospital stay for the INFUSE and autograft groups are shown in Table 5. These analyses reveal superior ($p < 0.05$) benefits of the combined INFUSE group compared with the autograft group for all three variables. The INFUSE group had an average of 0.9 hours (54 minutes) shorter surgery time, lost an average of 66 mL less blood (probably because of the shorter surgery time and not having a second surgery site), and, on average, left the hospital nearly a day (0.9) earlier than the autograft group. No differences were found between the L4–5 and L5–S1 level treated patients.

The fusion success rate in the combined INFUSE group was 94.4% (201 of 213) at 24 months after surgery compared with 89.4% (252 of 282) in the autograft group (Table 6). No differences were found between the patients treated at the L4–5 and L5–S1 levels. This 5-percentage point difference was shown to be statistically significant by an analysis of covariance, with an adjusted p value of 0.022. In short, fusion, the primary goal of performing the original surgery, was found to be statistically superior for the INFUSE patients (Fig. 3).

TABLE 2. *Demographic information*

Variable [n (%)]	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
Age (yr)							
n	143	134	277	136	266	402	0.007
Mean	43.3	42.4	42.9	42.3	40.0	40.8	
SD	9.8	10.5	10.2	9.7	9.6	9.7	
Height (in.)							
n	143	134	277	135	262	397	0.216
Mean	68.1	67.5	67.8	68.0	68.3	68.2	
SD	4.2	4.0	4.1	4.2	3.9	4.0	
Weight (lb)							
n	143	134	277	134	264	398	0.146
Mean	179.1	169.8	174.6	181.1	177.6	178.8	
SD	33.1	38.3	36.0	37.0	37.9	37.6	
Sex [n (%)]							
Male	78 (54.5)	57 (42.5)	135 (4.7)	68 (50.0)	142 (53.4)	210 (52.2)	0.391
Female	65 (45.5)	77 (57.5)	142 (51.3)	68 (50.0)	124 (46.6)	192 (47.8)	
Martial status [n (%)]							
Single	24 (16.8)	24 (17.9)	48 (17.3)	18 (13.2)	52 (19.5)	70 (17.4)	0.983
Married	95 (66.4)	91 (67.9)	186 (67.1)	91 (66.9)	177 (66.5)	268 (66.7)	
Divorced	18 (2.6)	14 (10.4)	32 (11.6)	20 (14.7)	30 (11.3)	50 (12.4)	
Separated	5 (3.5)	2 (1.5)	7 (2.5)	5 (3.7)	5 (1.9)	10 (2.5)	
Widowed	1 (0.7)	3 (2.2)	4 (1.4)	2 (1.5)	2 (0.8)	4 (1.0)	
Education level [n (%)]							
<High school	13 (9.1)	7 (5.2)	20 (7.2)	17 (12.6)	25 (9.5)	42 (10.6)	0.277
High school	45 (31.5)	39 (29.1)	84 (30.3)	39 (28.9)	86 (32.7)	125 (31.4)	
>High school	85 (59.4)	88 (65.7)	173 (62.5)	79 (58.5)	152 (57.8)	231 (58.0)	
Workers' Compensation [n (%)]							
Yes	47 (32.9)	42 (31.3)	89 (32.1)	47 (34.6)	89 (33.7)	136 (34.0)	0.620
No	96 (67.1)	92 (68.7)	188 (67.9)	89 (65.4)	175 (66.3)	264 (66.0)	
Spinal litigation [n (%)]							
Yes	18 (12.6)	11 (8.2)	29 (10.5)	22 (16.2)	29 (11.1)	51 (12.8)	0.398
No	125 (87.4)	123 (91.8)	248 (89.5)	114 (83.8)	233 (88.9)	347 (87.2)	
Tobacco used [n (%)]							
Yes	47 (32.9)	40 (29.9)	87 (31.4)	49 (36.0)	83 (31.2)	132 (32.8)	0.738
No	96 (67.1)	94 (70.1)	190 (68.6)	87 (64.0)	183 (68.8)	270 (67.2)	
Alcohol use [n (%)]							
Yes	39 (27.3)	66 (49.3)	105 (37.9)	43 (31.6)	94 (35.3)	137 (34.1)	0.328
No	104 (72.7)	68 (50.7)	172 (62.1)	93 (68.4)	172 (64.7)	265 (65.9)	
Preoperative work status [n (%)]							
Working	68 (47.6)	70 (52.2)	138 (49.8)	50 (36.8)	118 (44.5)	168 (41.9)	0.050
Not working	75 (52.4)	64 (47.8)	139 (50.2)	86 (63.2)	147 (55.5)	233 (58.1)	

[a]For continuous variables, p values are from ANOVA, and for categorical variables, they are from Fisher's exact test or the chi-square test.

In the combined INFUSE group, preoperative low back pain scores on the validated Oswestry Disability Index improved significantly over those in the autograft group for all time points (3, 6, 12, and 24 months) in the study (Table 7). No differences were found between the L4–L5 and L5–S1 treated patients. The adjusted p values were all highly significant.

The Physical Component and Pain Index scores of the SF-36 Health Survey, which measures a patient's physical well-being after surgery, are shown in Table 8. As with the Oswestry Disability Index low back pain scores, the results showed the statistical superiority of the combined INFUSE group to the autograft group for all time points after surgery.

Additional surgical events in the study patients are summarized in Table 9. Simple Fisher exact tests show that the combined INFUSE groups had statistically fewer reoperations than patients who were implanted with autograft ($p = 0.0036$). At the 2-year time point used in the study, the revision rate in INFUSE patients approached statistical superiority ($p = 0.0631$). No differences were found between the L4–5 and L5–S1 treated patients.

Although the difference was not statistically significant, 103 (74.6%) of the INFUSE patients who were working before surgery returned to work after surgery compared with 109 (64.9%) patients in the autograft group. Again, although not statistically significant, 49 (35.3%) of the INFUSE patients who were not working before surgery returned to work after surgery compared with 73 (31.3%) of the autograft patients. The difference that was found to

TABLE 3. *Preoperative medical condition and medication usage [number (%) of patients]*

Variable	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
Previous back surgery							
Yes	54 (37.8)	33 (24.6)	87 (31.4)	55 (40.4)	110 (41.4)	165 (41.0)	0.012
No	89 (62.2)	101 (75.4)	190 (68.6)	81 (59.6)	156 (58.6)	237 (59.0)	
Previous back surgery							
1	39 (72.2)	16 (50.0)	55 (64.0)	34 (61.8)	78 (70.9)	112 (67.9)	0.574
>1	15 (27.8)	16 (50.0)	31 (36.0)	21 (38.2)	32 (29.1)	53 (32.1)	
Non-narcotic medications							
Yes	80 (55.9)	97 (72.4)	177 (63.9)	75 (55.1)	109 (41.0)	184 (45.8)	<0.001
No	63 (44.1)	37 (27.6)	100 (36.1)	61 (44.9)	157 (59.0)	218 (54.2)	
Weak narcotic medications							
Yes	77 (53.8)	61 (45.5)	138 (49.8)	67 (49.3)	90 (33.8)	157 (39.1)	0.006
	66 (46.2)	73 (54.5)	139 (50.2)	69 (50.7)	176 (66.2)	245 (60.9)	
Strong narcotic medications							
Yes	31 (21.7)	17 (12.7)	48 (17.3)	33 (24.3)	42 (15.8)	75 (18.7)	0.686
No	112 (78.3)	117 (87.3)	229 (82.7)	103 (75.7)	224 (84.2)	327 (81.3)	
Muscle relaxant medications							
Yes	45 (31.5)	49 (36.6)	94 (33.9)	37 (2.2)	39 (14.7)	76 (18.9)	<0.001
No	98 (68.5)	85 (63.4)	183 (66.1)	99 (72.8)	227 (85.3)	326 (81.1)	

[a]p values are from Fisher's exact test.

be statistically significant was the time it took for the patients to return to work. A summary of time-to-event type analysis of return to work is contained in Table 10. The statistical comparison between the INFUSE and autograft groups was adjusted by the preoperative work status, the seven prognostic covariates, and the surgical approach. The median days to return to work was 54.5 days shorter for the LT-CAGE patients implanted with INFUSE Bone Graft. This finding was statistically significant in favor of the INFUSE patients (adjusted p = 0.0156).

DISCUSSION

Surgeons have long sought to find the best way to fuse two bones. Although allograft bone has been used with some degree of success, transplanting living bone from one part of the body to another has become the "gold standard" by which all other procedures are measured (8). Disadvantages to autogenous bone graft harvesting are well known. Clinical trials have shown that there is increased operative time, increased blood loss, cosmetic disfigurement, and pain associated with iliac crest bone graft harvesting (1–3,8). Finding a substitute for human tissue has also been a noble goal of researchers for decades, and finding a bone graft substitute to replace autogenous bone seemed at times an impossible task. What material could researchers develop that would be better than a naturally occurring material?

Since the discovery of bone morphogenetic proteins (BMP) by Dr. Marshall Urist in 1965 (9), his dream, and

TABLE 4. *Preoperative evaluations of clinical endpoints*

Variable	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
Oswestry Pain Score							
n	143	134	277	136	264	400	0.001
Mean	53.7	52.3	53.0	55.1	46.5	49.4	
SD	12.7	11.7	12.2	11.8	15.6	15.0	
SF-36 PCS							
n	142	134	276	136	263	399	0.004
Mean	27.7	28.3	28.0	29.4	29.5	29.5	
SD	5.7	6.1	5.9	6.2	7.3	6.9	
SF-36 Pain Index							
n	143	134	277	136	263	399	0.077
Mean	21.8	22.6	22.2	22.7	24.7	24.1	
SD	11.1	13.4	12.2	13.6	14.7	14.3	

[a]p values are from analysis of variance.

TABLE 5. *Surgery information*

Variable	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
Operative time (hr)							
n	143	134	277	136	265	401	<0.001
Mean	1.6	1.9	1.8	2.0	3.1	2.7	
SD	0.6	0.9	0.8	0.7	1.4	1.3	
Blood loss (mL)							
n	142	134	276	136	263	399	0.024
Mean	109.8	146.1	127.4	153.1	213.6	192.9	
SD	117.3	406.2	295.3	179.1	493.0	414.4	
Hospital stay (days)							
n	143	134	277	136	266	402	<0.001
Mean	3.1	1.2	2.2	3.3	3.0	3.1	
SD	1.6	1.1	1.7	1.3	3.8	3.2	
Treatment levels [n (%)]							
L2–L3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	
L3–L4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.5)	
L4–L5	37 (25.9)	21 (15.7)	58 (20.9)	32 (23.5)	21 (7.9)	53 (13.2)	
L5–L6	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.8)	3 (0.7)	
L5–S1	106 (74.1)	113 (84.3)	219 (79.1)	103 (75.7)	240 (90.2)	343 (85.3)	
Operative approach [n (%)]							
Retroperitoneal	116 (81.1)	28 (20.9)	144 (52.0)	109 (80.1)	9 (3.4)	118 (29.4)	
Transperitoneal	27 (18.9)	106 (79.1)	133 (48.0)	26 (19.1)	256 (96.2)	282 (70.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.4)	2 (0.5)	

[a]p values are from analysis of variance.

that of many others, was to have BMP available in operating rooms as a safe and effective replacement for autograft. In July 2002, his dream became a reality in the United States with the FDA approval of rhBMP-2, a recombinant version of one of the family of BMPs. His goal, and the goal of other researchers like him, was for the substitute to be equal to autograft so harvesting of autograft bone from other parts of the body would no longer be necessary. Preclinical studies (5,6,10–14) have indicated the possibility that osteoinductive protein-containing materials may be superior to autograft in some applications and for some outcome measurements. Wozney (7) suggests that BMP can result in direct intramembranous ossification because in some animal models direct bone formation is observed after administration of the protein. Because chips of transferred autogenous graft may need to be resorbed or remodeled before fusing and rhBMP-formed bone does not, this feature may explain why some animal studies had superior results with rhBMP-containing grafts when compared with autograft.

INFUSE Bone Graft must be used with a cage or some type of supportive structure within the vertebral interspace. The rhBMP-2 protein is applied to an absorbable collagen sponge. For this reason, it cannot resist compressive or shear forces within a vertebral motion segment. A supportive biomechanical environment is required for

TABLE 6. *Summary of success rates of radiographic fusion [number (%) of patients]*

Variable	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
6 months							
Success	128 (97.0)	88 (92.6)	216 (95.2)	115 (95.8)	192 (95.5)	307 (95.6)	0.633
Failure	4 (3.0)	7 (7.4)	11 (4.8)	5 (4.2)	9 (4.5)	14 (4.4)	
12 months							
Success	127 (96.9)	95 (94.1)	222 (95.7)	112 (92.6)	202 (93.1)	314 (92.9)	0.131
Failure	4 (3.1)	6 (5.9)	10 (4.3)	9 (7.4)	15 (6.9)	24 (7.1)	
24 months							
Success	120 (94.5)	81 (94.2)	201 (94.4)	102 (88.7)	150 (89.8)	252 (89.4)	0.022
Failure	7 (5.5)	5 (5.8)	12 (5.6)	13 (11.3)	17 (10.2)	30 (10.6)	

[a]One-sided p values are from logistic regression analysis with the model including bone graft type and surgical approach, adjusting the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

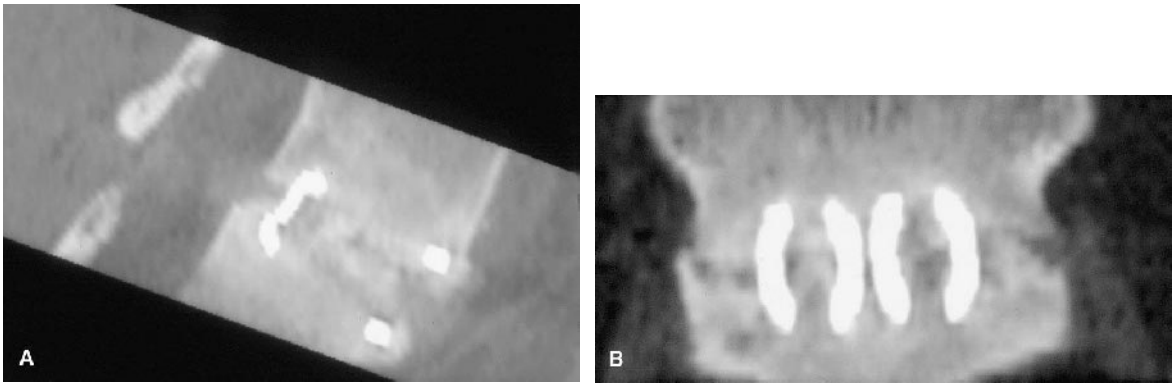

FIG. 3. At 24 months after surgery, thin-cut CT scans were repeated. A. Sagittal reconstruction 24 months after surgery through the midportion of the LT-CAGE shows abundant new bone formation throughout the central portion of the cage. B. Coronal reconstructions shows new bone formation through the cages and lateral to the cages. This new bone formation connects the adjacent vertebral endplates.

bone formation in the disc space. INFUSE cannot be used as a "stand-alone" device within the disc space.

The question remains: Can any recombinant BMP on any carrier ever be superior to autograft (the gold standard) with regard to operative parameters and clinical outcome in humans? Pilot study results of the LT-CAGE Lumbar Tapered Fusion Device in humans (1) and the results from a prospective, randomized study (2) showed a trend toward faster fusion with the INFUSE Bone Graft and other data that were comparable with that in the patients who received autograft. We hypothesized that this trend would become a superior outcome in a larger study.

We used the analysis of covariance method for an integrated analysis of four, large-scale multicenter sets of patient data. This analysis of prospectively gathered data has answered the question of the superiority of INFUSE Bone Graft over autograft for one particular human clinical use. This analysis of 679 patients represents the largest prospective combined study of a single-level anterior procedure using a single device for a single indication in the spinal literature. Because all patients received the same LT-CAGE implants, we had, for the first time, a data set large enough to determine whether INFUSE Bone Graft is equivalent to or superior to autograft bone. Because of the large sample size used in this analysis and its subsequent statistical power, the answer is an unequivocal "yes." The

TABLE 7. *Summary of Oswestry low back pain disability scores*

		INFUSE			Autograft			
Period	Variable	Open (N = 143)	Lap (N = 134)	Total (N = 277)	Open (N = 136)	Lap (N = 266)	Total (N = 402)	p value[a] (INFUSE vs. autograft)
Preoperative	Pain score							
	n	143	134	277	136	264	400	
	Mean	53.7	52.3	53.0	55.1	46.5	49.4	
	SD	12.7	11.7	12.2	11.8	15.6	15.0	
3 months	Pain score							
	n	141	127	268	134	252	386	0.0041
	Mean	33.5	30.2	32.0	34.2	33.7	33.9	
	SD	17.6	19.9	18.8	18.5	19.7	19.3	
6 months	Pain score							
	n	136	120	256	131	239	370	0.0053
	Mean	29.3	25.1	27.3	29.4	29.0	29.1	
	SD	18.8	20.4	19.6	18.2	20.1	19.4	
12 months	Pain score							
	n	130	114	244	125	224	349	0.0013
	Mean	25.5	20.4	23.1	25.6	25.7	25.7	
	SD	18.2	19.8	19.1	19.1	20.5	20.0	
24 months	Pain score							
	n	122	93	215	108	177	285	0.0023
	Mean	23.9	18.7	21.7	23.8	22.7	23.1	
	SD	18.8	19.3	19.2	20.7	20.9	20.8	

[a]One-sided p values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.

TABLE 8. *Summary of SF-36 health survey scores*

Period	Variable	INFUSE Open (N = 143)	INFUSE Lap (N = 134)	INFUSE Total (N = 277)	Autograft Open (N = 136)	Autograft Lap (N = 266)	Autograft Total (N = 402)	p value[a] (INFUSE vs. autograft)
Preoperative	PCS							
	n	142	134	276	136	263	399	
	Mean	27.7	28.3	28.0	29.4	29.5	29.5	
	SD	5.7	6.1	5.9	6.2	7.3	6.9	
	Pain index							
	n	143	134	277	136	263	399	
	Mean	21.8	22.6	22.2	22.7	24.7	24.1	
	SD	11.1	13.4	12.2	13.6	14.7	14.3	
3 months	PCS							
	n	140	127	267	133	249	382	0.0015
	Mean	36.6	37.3	36.9	35.9	35.1	35.4	
	SD	9.7	10.2	10.0	9.4	9.8	9.7	
	Pain index							
	n	141	127	268	134	250	384	0.0002
	Mean	47.4	50.4	48.8	44.1	43.4	43.6	
	SD	23.8	22.5	23.2	23.3	22.3	22.6	
6 months	PCS							
	n	136	119	255	131	234	365	0.0004
	Mean	39.4	41.0	40.1	38.6	37.8	38.1	
	SD	11.3	11.8	11.5	10.9	11.2	11.1	
	Pain index							
	n	136	120	256	131	236	367	0.0002
	Mean	53.0	54.8	53.8	50.5	46.3	47.8	
	SD	27.8	25.4	26.7	24.4	23.8	24.1	
12 months	PCS							
	n	131	113	244	125	223	348	0.0003
	Mean	41.3	43.4	42.3	40.8	40.0	40.3	
	SD	11.0	11.9	11.5	12.1	12.1	12.1	
	Pain index							
	n	131	113	244	125	223	348	0.0002
	Mean	55.0	60.8	57.7	53.5	52.1	52.6	
	SD	26.6	27.8	27.3	26.0	26.0	26.0	
24 months	PCS							
	n	122	94	216	108	177	285	0.0007
	Mean	42.4	45.0	43.6	42.1	42.5	42.4	
	SD	11.9	11.5	11.8	12.8	12.3	12.4	
	Pain index							
	n	122	95	217	108	177	285	0.0008
	Mean	58.5	63.9	60.9	56.4	57.1	56.8	
	SD	27.6	26.2	27.1	28.9	27.4	27.9	

PCS, Physical Component score.

[a]One-sided p values are from analysis of covariance with the model including bone graft type, surgical approach, and their interaction, adjusting the seven prognostic covariates.

INFUSE patients had statistically superior outcomes in the following categories: shortened surgery time, reduced blood loss, shortened hospital stay, higher fusion rate, better Oswestry Low Back Pain Disability Questionnaire scores at all follow-up intervals, better Physical Component Scores and Pain Index scores on the SF-36 Health Survey at all follow-up intervals, fewer reoperations, and an earlier return to work.

TABLE 9. *Summary of second surgeries*

Type of second surgery	INFUSE Open	INFUSE Lap	INFUSE Total (%)	Autograft Open	Autograft Lap	Autograft Total (%)	p-value[a] (INFUSE vs. autograft)
Revisions	0/143	1/134	1/277 (0.36)	0/136	8/266	8/402 (1.99)	0.0631
Removals	2/143	2/134	4/277 (1.44)	0/136	7/266	7/402 (1.74)	0.5106
Supplemental fixations	10/143	7/134	17/277 (6.14)	14/136	14/266	28/402 (6.97)	0.3970
Reoperations	6/143	2/134	8/277 (2.89)	4/136	28/266	32/402 (7.96)	0.0036

[a]One-sided p values are from Fisher's exact test.

TABLE 10. *Summary of time-to-event analysis for days to return to work (median in days)*

INFUSE			Autograft			p value[a]
Open	Lap	Total	Open	Lap	Total	(INFUSE vs. autograft)
165.0	89.0	116.0	386.5	154.0	170.5	0.0156

[a]One-sided p value is from the proportional hazard regression (PHREG) procedure with the model including bone graft type and surgical approach, adjusting preoperative work status and the seven prognostic covariates. The interaction term between bone graft type and surgical approach is not significant and thus is not included.

As can be calculated from Table 7, for all postoperative time points, the change from preoperative scores for INFUSE patients was approximately 5 points better than for the autograft control patients, about a 7–10% greater improvement from the preoperative score in favor of the INFUSE patients. As can be calculated from Table 8, the PCS scores on the SF-36 scale also had approximately a 12–15% greater improvement from the preoperative values in favor of the INFUSE patients than the control patients. Obviously, any statistical decrease in pain at any time point would be considered significant and desirable by the patient. The statistically significant decrease in the INFUSE patients' low back pain must be at least part of the explanation for their returning to work nearly 2 months earlier than the autograft patients.

In one study, iliac crest graft site pain was recorded on a separate 20-point numeric rating scale by the patients who discriminated low back pain from iliac crest harvest site pain (2). In the autograft open group, nearly a third (32%) of the patients continued to have some pain at their harvest site 2 years after the surgery. In addition to pain, the 402 autograft patients treated with open and laparoscopic surgery also had a 3.0% chance of a significant graft site complication: five (1.25%) had infections at their harvest site, two (0.5%) had fractures at the graft site, and five (1.25%) had other adverse events related to their harvest site. The INFUSE patients obviously had none of the pain or problems associated with iliac crest graft harvesting. The elimination of these complications alone could explain, in part, why regardless of fusion status, the INFUSE patients had consistently better results than the autograft control group.

We think that these analyses demonstrate the superiority of using INFUSE Bone Graft. We found no disadvantage to using INFUSE Bone Graft for the surgical, hospital discharge, and major postoperative outcome measurements discussed. In addition, the INFUSE patients did not have the pain, morbidity, or complications associated with the second surgery of iliac crest graft harvest. The results of this integrated analysis coupled with the comprehensive safety profile for the recombinant human bone morphogenetic protein (rhBMP-2) material used in the study (15) indicates that the use of INFUSE Bone Graft is an effective replacement for autograft bone inside the LT-CAGE device for lumbar spinal fusions. With its superiority, INFUSE Bone Graft may now become the new gold standard for replacing autograft bone inside the LT-CAGE device when used for lumbar spinal fusions. INFUSE Bone Graft is now used exclusively for this purpose in our institutions.

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