SPINE Volume 31, Number 10, pp E277–E284

Graft Resorption With the Use of Bone Morphogenetic Protein: Lessons From Anterior Lumbar Interbody Fusion Using Femoral Ring Allografts and Recombinant Human Bone Morphogenetic Protein-2

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Study Design. This is a prospective cohort study examining the results and radiographic characteristics of anterior lumbar interbody fusion (ALIF) using femoral ring allografts (FRAs) and recombinant human bone morphogenetic protein-2 (rhBMP-2). This was compared to a historical control ALIF using FRAs with autologous iliac crest bone graft (ICBG).

Objective. To determine whether the use of rhBMP-2 can enhance fusion ALIF with stand-alone FRAs.

Summary of Background Data. ALIF is a well-accepted procedure in reconstructive spine surgery. Advances in spinal surgery have produced a multitude of anterior interbody implants. The rhBMP-2 has promoted fusion in patients undergoing ALIF with cages and threaded allograft dowels. The FRA still remains a traditional alternative for anterior support. However, as a stand-alone device, the FRA has fallen into disfavor because of high rates of pseudarthrosis. With the advent of rhBMP-2, the FRA may be more attractive because of its simplicity and remodeling potential. It is important to understand the implications when rhBMP-2 is used with such structural allografts.

Methods. A total of 36 consecutive patients who underwent ALIF with stand-alone FRAs by a single surgeon (E.G.D.) at 1 institute were included. A cohort of 9 consecutive patients who received FRAs filled with rhBMP-2 was followed prospectively. After noticing suboptimal results, the senior author terminated this method of lumbar fusion. A total of 27 prior consecutive patients who received FRAs filled with autogenous ICBG were used for comparison. Analyzing sequential radiographs, flexion-extension radiographs, and computerized tomography with multiplanar reconstructions determined nonunions. Minimum follow-up was 24 months.

Results. Pseudarthrosis was identified in 10 of 27 (36%) patients who underwent stand-alone ALIF with FRAs and ICBG. Nonunion rate was higher among patients who received FRAs with rhBMP-2 (*i.e.,* 5 of 9 [56%]). Statistical significance was not established because of the early termination of the treatment group ($P > 0.3$). Of interest, radiographs and computerized tomography revealed early and aggressive resorption of the FRAs when used with rhBMP-2. This preceded graft fracture and even disintegration, resulting in instability and eventual nonunion.

Conclusion. The use of rhBMP-2 did not enhance the fusion rate in stand-alone ALIF with FRAs. In fact, the trend was toward a higher nonunion rate with rhBMP-2, although this was not significant with the numbers available. This result appears to be caused by the aggressive resorptive phase of allograft incorporation, which occurs before the osteoinduction phase.

Key words: bone morphogenetic protein, structural allograft, anterior lumbar interbody fusion, bone resorption, pseudarthrosis, femoral ring allograft, stand-alone fusion. **Spine 2006;31:E277–E284**

A large variety of lumbar spinal intervertebral body devices have been developed over the past decade or so. These devices are used during anterior lumbar interbody fusion (ALIF) for structural support of the spine at the anterior and middle columns, where the majority of the body's axial load is transmitted. Anterior spinal surgery may be indicated for the repair of clinically significant structural deficits after discectomies, trauma, tumor resections, osteotomies for deformity correction, or for the salvage of posterior fusion pseudarthrosis. The anterior approach to spinal fusion generally has less morbidity than posterior approaches.[1,2] The femoral ring allograft (FRA) still remains a simple and adequate option for interbody structural grafting (Table 1). Mechanically, it is able to support the physiologic loads experienced by the spine, biologically it is capable of incorporating with the host bone, and it is cost effective compared to most of the artificial devices.[3]

However, when used alone for interbody fusion, impacted allografts have had a high rate of pseudarthrosis and subsidence.[4–7] It has been argued that as mere intradiscal spacers, impacted allografts such as the FRA may require additional segmental stabilization. A recent study showed a 52% fusion rate of ALIF with stand-alone FRA packed with autogenous iliac crest bone graft (ICBG).[7] Experience at our own institute has shown a fusion rate of more than 90% when anterior allograft is supplemented by posterior pedicle screw instrumentation.[8] We know from studies of posterior spinal fusion

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Acknowledgment date: March 17, 2005. First revision date: August 11, 2005. Acceptance date: October 7, 2005.
The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.
No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.
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Table 1. Advantages of Structural (FRA) Allografts

Biologic constructs
Remodel with eventual incorporation
Lower risk of later migration
Lower risk of later stress shielding
Mechanically strong (*e.g.,* cortical allograft)
Simple to use
Grafts can be customized in operating room
Easily available
Inexpensive (*vs.* synthetic spinal devices)
Easy radiographic fusion assessment (*vs.* radiopaque devices)

that the addition of instrumentation can increase fusion rates.[9–15]

Recombinant human bone morphogenetic protein-2 (rhBMP-2) (INFUSE®; Medtronic Sofamor Danek, Minneapolis, MN) has promoted osteoinduction and fusion in a series of human patients undergoing ALIF with a tapered cylindrical fusion cage.[16] A more recent study has shown that when used with stand-alone allograft threaded dowels, rhBMP-2 also increases the rate of interbody fusion.[17] This effect begs the question whether it can do the same for FRAs. This is a study of the effect of rhBMP-2 on interbody fusion rate when used with stand-alone FRAs, along with a radiographic analysis of the fusion process followed over time.

■ Materials and Methods

Study Design. This is a retrospective study of 36 consecutive patients who underwent ALIF with stand-alone FRA by a single surgeon (E.G.D.) at a single institution. Patients received FRAs (Synthes, Inc., Paoli, PA) packed with either autogenous ICBG or absorbable collagen sponges soaked with rhBMP-2. The first 27 consecutive patients received FRAS with ICBG. The senior author noted the relatively low fusion rate with this technique and then, in an attempt to increase the fusion rate, the next 9 consecutive patients were given allografts with rhBMP-2. The previous patients of the same surgeon served as historical controls for evaluation of the BMP; these were the most recent 27 consecutive patients who underwent stand-alone ALIF with FRA and ICBG before rhBMP-2. There was no difference in selection criteria because this was the only method used by this single surgeon to treat isolated intractably symptomatic lumbar degenerative disc disease. After preliminary results became available, the practice of stand-alone ALIF with FRAs was then stopped altogether to compare the results and analyze radiographic findings of the process.

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 positive diagnostic imaging findings. Patients with primary symptoms of low back pain were included in the study; they may or may not have also had referred leg pain or sciatica. All patients had these disabling symptoms for at least 6 months, and did not have improvement with nonoperative treatment regimens that included activity modification, medications, physical therapy with methods, spinal injections, braces, *etc*.

Positive diagnostic imaging findings included ≥1 of the following on plain radiographs, magnetic resonance imaging, computerized tomography (CT), or myelographic techniques: (1) collapse of disc space of >2 mm, as determined by anteroposterior and lateral radiographs; (2) osteophyte formation on the vertebral endplates; (3) osteophyte formation or hypertrophy of the facet joint; (4) disc disruption manifested by resorption and narrowing of the disc space; (5) scarring and/or thickening of the anulus fibrosis, ligamentum flavum, and/or facet joint capsule; or (6) herniated nucleus pulposus. In addition, some patients had spinal instability, as defined by >4 mm of translation and/or >5° of angulation on flexion-extension radiographs, but no higher than grade I spondylolisthesis. Excluded from the study were patients who had: (1) undergone any prior anterior lumbar spine surgeries or posterior destabilizing surgeries; (2) osteopenia, osteoporosis, or osteomalacia; or (3) bone growth stimulation.

Surgical Procedure. The surgical technique and surgeon were the same in all cases. The FRA was implanted through an anterior retroperitoneal lumbar spinal approach. An appropriate bump was placed underneath the supine patient's lower back to lordose the lumbar spine. The amount of great vessel mobilization was limited to that required for insertion of the instruments and graft. A standard block discectomy was performed, including the careful removal of posteriorly herniated fragments if present. The endplates were prepared with complete removal of the cartilage, while exposing but preserving the bleeding subchondral bone. A sharp curette and rasp were used to débride the endplates. A trial sizer was then placed in the disc space to determine the graft size to maintain appropriate distraction based on the normal adjacent disc spaces (as seen in intraoperative lateral radiographs) and tightness of fit.

The intramedullary canal of the FRA was packed with autogenous ICBG or rhBMP-2 soaked absorbable collagen sponges (INFUSE®). ICBG was harvested through separate fascial incisions over the anterior iliac crests. Corticocancellous pieces of bone were obtained in sizes small enough to place inside the FRA. Alternatively, the rhBMP-2 powder (INFUSE®) was reconstituted at a concentration of 1.5 mg/mL using sterile water. The solution was applied to an absorbable collagen sponge with a syringe, left to soak for at least half an hour, then placed inside the FRA.

A mallet was then carefully used to place the FRA into the intervertebral space. In the ICBG group, additional bone graft was packed into the disc space around the FRA as possible. In the BMP group, remaining strips of absorbable collagen sponges were laid in the disc space around the FRA. No patient received both iliac crest graft and BMP. A final intraoperative lateral radiograph was checked to confirm appropriate placement and size of the FRA.

Follow-Up. Patients were evaluated perioperatively, after surgery at 6 weeks, 3, 6, 12, and 24 months, and as needed in between scheduled appointments. Patients were given lumbar corsets, which they wore when out of bed for the first 6 weeks and weaned out of by 3 months. Activity was advanced at the discretion of the senior surgeon.

Radiographic Outcome Measurement. Radiographs were routinely obtained at follow-up visits beginning at 6 weeks. Flexion-extension radiographs were only obtained at 6 months and later. Unscheduled radiographs or CT with fine slices (1 mm) through the fusion construct were obtained on an as needed basis. An independent, blinded radiologist interpreted

all radiographs and CT. Fusion was defined in a manner similar to other published studies.[7,17] It was defined as bridging bone connecting the adjacent vertebral bodies, either through the FRAs or around the FRAs, less than 5° of angular motion, ≤3 mm of translation, and an absence of radiolucent lines around more than 50% of the graft. A fusion was considered successful only if all 4 conditions were met. Some of the nonunions diagnosed by these criteria were confirmed by surgical exploration (*i.e.,* patients in whom symptoms indicated the need for a salvage posterior fusion).

Statistical Method. Statistical analysis was performed using Microsoft Excel software (Microsoft, Corp., Redmond, WA) and statistical tables. For continuous variables, analysis of variance was used, and for categorical variables, the χ^2 test was used to arrive at *P* values.

■ Results

Demographics

A total of 36 patients underwent ALIF with stand-alone FRAs (Table 2). There were 5 males and 22 females in the ICBG group, whereas the BMP group was comprised of 3 males and 6 females. Thus, the groups were not matched for gender, but the power was too low for the difference to be of significance. Mean age in the ICBG group was 53.4 years and 51.2 years in the BMP group. Mean follow-up was 36 months in the ICBG group and 26 months in the BMP group. The fusion levels in the ICBG group consisted of 19 at L5–S1, and 8 at L4–L5. In the BMP group, 6 fusions were at L5–S1, 2 were at L4–L5, and 1 was at L3–L4.

Radiographic Outcome

All patients were observed for a minimum of 24 months (Table 3). In the ICBG group, 17 of 27 (63%) patients fulfilled the radiographic criteria for fusion at last follow-up. Of those 17 patients, 4 did not have full fusion by our criteria at 12 months but were not significantly symptomatic and went on to have fusion by final follow-up. These 4 patients were categorized as having "delayed fusion." Nonunions were diagnosed in 10 of 27 (37%) patients. Of these 10 patients, 7 (70%) underwent posterior spinal fusion as a salvage surgery, during which pseudarthrosis was confirmed by interspinous motion. At final follow-up, the other 3 patients still had radiographic evidence of nonunion but were satisfied with nonsurgical treatment.

In the BMP group, 4 of 9 (44%) patients fulfilled the criteria for radiographic fusion (or lacked radiographic evidence for nonunion) at final follow-up. Of these 4 patients, 2 did not have full fusion at 12 months but went on to have fusion by final follow-up and, thus, were placed in the "delayed fusion" category. Nonunions were diagnosed in 5 of 9 (56%) patients. Of the 5 nonunion patients, 3 (60%) underwent salvage posterior fusion, all between 9 and 12 months after surgery. The remaining 2 nonunion patients remained sufficiently asymptomatic at final follow-up.

Table 2. Patient Demographics, Radiographic Outcomes, and Secondary Surgeries

	FRA+ICBG	FRA+BMP	*P*
No. patients	27	9	$P > 0.1$
No. males	5	3	
No. females	22	6	
Levels of fusion			$P > 0.1$
No. L5–S1	19	6	
No. L4–L5	8	2	
No. L3–L4	0	1	
Mean age (ys)	53.4	51.2	
Mean follow-up (mos)	36	26	
No. radiographic nonunions (%)	10 (37)	5 (56)	$P > 0.1$
No. delayed fusion (>12 mos)	4 (14%)	2 (22%)	
Fusion rate	63%	44%	
Levels of nonunion			$P > 0.1$
No. L5–S1 (%)	6 (31)	3 (50)	
No. L4–L5 (%)	4 (50)	2 (100)	
No. L3–L4	0	0	
No. secondary surgical procedures	7	3	
No. revisions	0	0	
No. removals	0	0	
No. posterior instrumented fusions	7	3	

Additional Surgery

Patients who went on to have pseudarthroses and intractable symptoms attributable to the surgical levels develop were treated with salvage posterior fusion with instrumentation. In the ICBG group, 7 of 10 (70%) patients with nonunions underwent posterior fusion, and 3 of 5 (60%) with nonunions in the BMP group did so. In the ICBG group, 3 patients underwent posterior fusion between 9 and 12 months after surgery, and 4 did so between 12 and 15 months. In the BMP group, all 3 salvage surgeries were performed between 9 and 12 months. In all salvage surgeries, nonunion was confirmed by noting instability or motion between spinous processes of the fused levels on distraction loading with a lamina spreader.

Radiographic Characterization of Fusion Process With rhBMP-2

In general, the BMP appeared to accelerate the radiographic changes of the fusion process. Most apparent was the initial osteolytic phase. Resorption of the graft and, to some extent, the endplates was seen to occur earlier and more aggressively with the use of BMP (Figure 1) compared to the use of autogenous ICBG (Figure 2). Graft remodeling and incorporation were more complete with rhBMP-2 (Figure 3). In the cases of nonunion with BMP, extensive osteolysis of and around the FRA was seen, causing fracture, fragmentation, and collapse of the graft. Because the nonunions were followed over some time, instability was seen to increase on flexion-extension radiography, and the graft appeared to disintegrate and resorb even further (Figure 4). This result was especially visible on thin-slice CT with sagittal and 3-dimensional reconstructions (Figure 5). The bone formation stage was never evident in the pseudarthrosis cases but was eventually seen in the cases of fusion, although in several cases in delayed fashion (Tables 2, 3).

Table 3. Patient List

Patient No.	Fusion Construct	Gender	Age (ys)	Level	Outcome	Diagnostic Method	Further Treatment	Follow-Up (mos)
1	FRA+BMP	M	49	L5–S1	Fusion, delayed	Radiographs, CT	None	29
2	FRA+BMP	F	51	L5–S1	Nonunion	Radiographs	None (symptoms controlled)	28
3	FRA+BMP	F	55	L4–L5	Nonunion	Radiographs	None (symptoms controlled)	28
4	FRA+BMP	F	54	L5–S1	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	27
5	FRA+BMP	M	43	L5–S1	Fusion	Radiographs	None	26
6	FRA+BMP	F	55	L5–S1	Nonunion	Radiographs	Salvage posterior fusion	26
7	FRA+BMP	F	52	L3–L4	Fusion, delayed	Radiographs, CT	None	25
8	FRA+BMP	F	51	L5–S1	Fusion	Radiographs, CT	None	25
9	FRA+BMP	M	51	L4–L5	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	23
10	FRA+ICBG	F	61	L4–L5	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	55
11	FRA+ICBG	F	47	L5–S1	Fusion	Radiographs	None	46
12	FRA+ICBG	F	48	L4–L5	Fusion	Radiographs	None	46
13	FRA+ICBG	F	58	L4–L5	Fusion	Radiographs	None	42
14	FRA+ICBG	F	48	L5–S1	Fusion	Radiographs	None	41
15	FRA+ICBG	F	59	L4–L5	Nonunion	Radiographs	None (symptoms controlled)	41
16	FRA+ICBG	M	47	L5–S1	Fusion	Radiographs	None	40
17	FRA+ICBG	M	51	L5–S1	Fusion	Radiographs	None	40
18	FRA+ICBG	F	64	L5–S1	Fusion	Radiographs	None	39
19	FRA+ICBG	M	49	L4–L5	Fusion, delayed	Radiographs, CT	None	38
20	FRA+ICBG	F	48	L5–S1	Nonunion	Radiographs, Surgical exploration	Salvage posterior fusion	38
21	FRA+ICBG	F	56	L4–L5	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	37
22	FRA+ICBG	F	46	L5–S1	Fusion	Radiographs	None	35
23	FRA+ICBG	F	52	L5–S1	Fusion	Radiographs	None	35
24	FRA+ICBG	M	51	L5–S1	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	33
25	FRA+ICBG	F	57	L5–S1	Nonunion	Radiographs	None (symptoms controlled)	33
26	FRA+ICBG	F	63	L5–S1	Fusion	Radiographs	None	33
27	FRA+ICBG	F	47	L4–L5	Fusion	Radiographs	None	32
28	FRA+ICBG	F	59	L5–S1	Nonunion	Radiographs	None (symptoms controlled)	32
29	FRA+ICBG	F	53	L5–S1	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	32
30	FRA+ICBG	M	48	L5–S1	Fusion, delayed	Radiographs, CT	None	31
31	FRA+ICBG	F	57	L4–L5	Nonunion	Radiographs, CT	Salvage posterior fusion	31
32	FRA+ICBG	F	49	L5–S1	Fusion, delayed	Radiographs, CT	None	30
33	FRA+ICBG	F	57	L5–S1	Fusion	Radiographs	None	30
34	FRA+ICBG	F	66	L5–S1	Fusion	Radiographs	None	30
35	FRA+ICBG	F	53	L5–S1	Fusion, delayed	Radiographs, CT	None	29
36	FRA+ICBG	F	49	L5–S1	Nonunion	Radiographs, surgical exploration	Salvage posterior fusion	29

F indicates female; M, male.

In the ICBG group, the FRA never seemed to be completely resorbed. In the cases that went on to fusion, the structural outline of the FRA was still visible, even at last follow-up (longest was 36 months). In the cases of nonunion with FRA and ICBG, the structural integrity of the graft, for the most part, remained intact, even if radiolucency surrounded the graft with evidence of instability on flexion-extension (Figure 6).

■ Discussion

The biologic events of successful bone graft incorporation can be divided into 2 distinct but overlapping stages: an initial inflammatory response with bone resorption followed by a bone growth phase. Rasmussen[18] and Goldberg[19] *et al* have described the process. When cancellous autograft is used, hemorrhage and inflammation characterize the local response shortly after the surgical procedure. The osteoconductive trabeculae provide a trellis for new bony ingrowth. Full integration of the graft into the native bony structure is well underway by 6 months and usually complete by 1 year. When cancellous allograft is used, the same sequence of events occur, although more slowly. There is a period of intense inflammatory activity that can last up to 2 weeks. Osteoconduction and osteoinduction are preserved but are not as robust as with autograft. Because of the already available cancellous channels, "creeping substitution" occurs *via* directed capillary and osteoblast ingrowth.

Cortical autografts undergo the same incorporation process as cancellous autograft but at a slower rate because of its compact nature. High bone density limits angioneogenesis, and incorporation can only occur after it is invaded by osteoclasts. Initially, this process leads to a mechanically weaker construct because resorption pro-

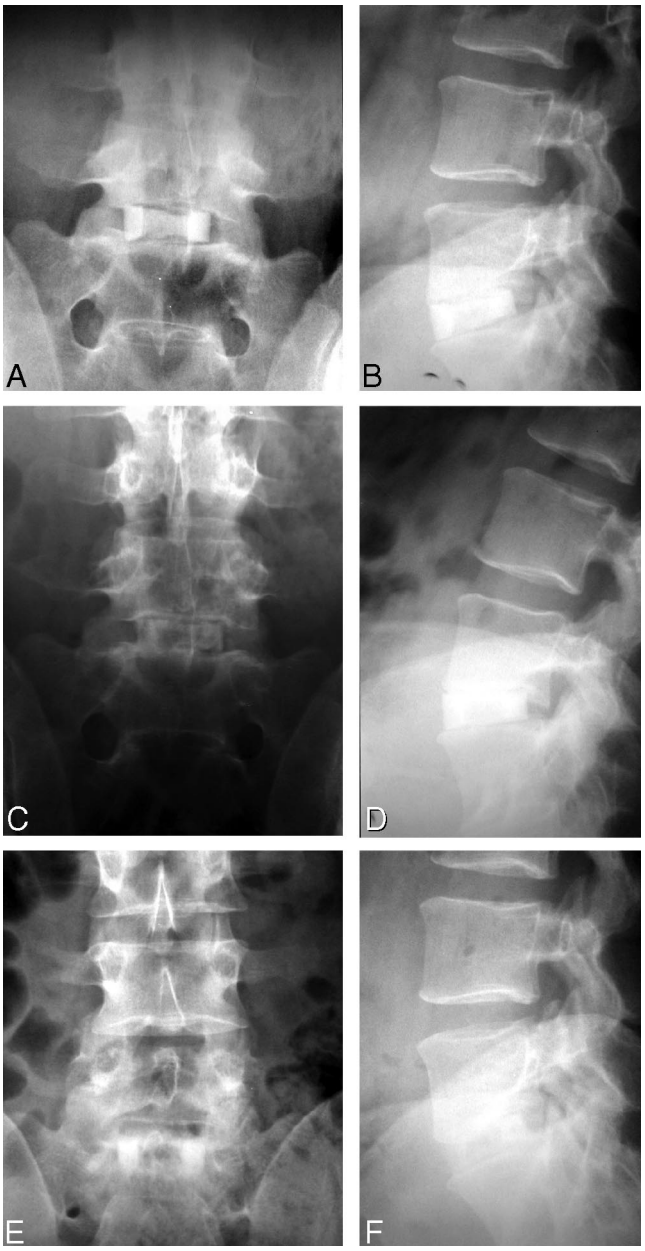

Figure 1. Sequential radiographs of ALIF with FRA and rhBMP-2 at various stages after surgery: immediate postoperative (**A**, **B**), 3 months (**C**, **D**), and 6 months (**E**, **F**). Note earlier initiation of trabecular continuity compared to autogenous ICBG use (Figure 2).

ceeds more rapidly than bone formation. This process is known as "reverse creeping substitution" in contrast to what is experienced by cancellous grafts. At 1 year, the graft persists as a chimera of new and grafted bone. In the case of cortical allograft, incorporation proceeds as outlined for cortical autograft. It also induces an intense inflammatory response with osteolysis, while the incorporation rate is limited by restricted neovascular ingrowth.[3,18,20] If the graft is subjected to excessive strain, micro cracks may develop, and, if revascularization is not adequate, clinically significant fractures may develop before reverse creeping substitution produces a successful fusion. The structural support can decrease by as much as 40% to 50% of the initial strength at 6 months after implantation.[21]

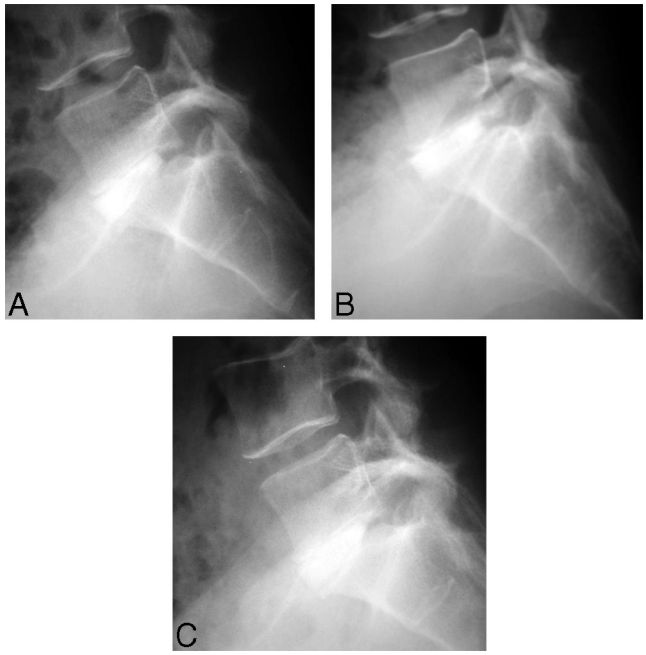

Figure 2. Sequential radiographs of ALIF with FRA and autogenous ICBG at various stages after surgery: 3 months (**A**), 6 months (**B**), and 18 months (**C**). Even when fusion criteria are met, the structural outline of FRA is still visible at later follow-up.

Based on this information, the stand-alone FRA, especially in the high-load region of the lumbar spine, seems vulnerable to mechanical failure as an interbody fusion construct. After experiencing lower than expected fusion rates with this technique, the senior author began using rhBMP-2 inside the FRAs to attempt to increase

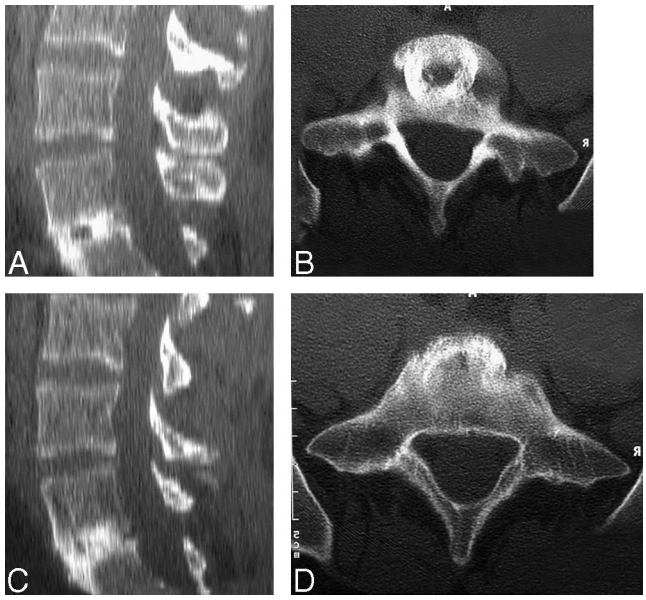

Figure 3. CT reveals prolonged preservation of allograft with the use of autogenous ICBG *versus* rhBMP-2. Scans of FRA and ICBG at 12 months are shown in **A** and **B**, and scans of FRA and rhBMP-2 at 12 months are shown in **C** and **D**.

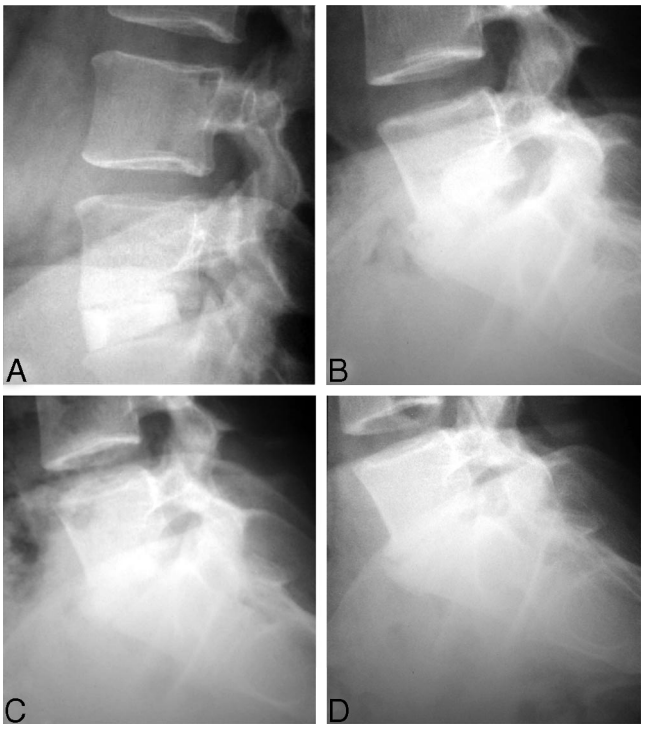

Figure 4. Sequential radiographs of pseudarthrosis development after ALIF with FRA and rhBMP-2 at various stages after surgery: immediate postoperative (**A**), 3 months (**B**), 6 months (**C**), and 9 months (**D**).

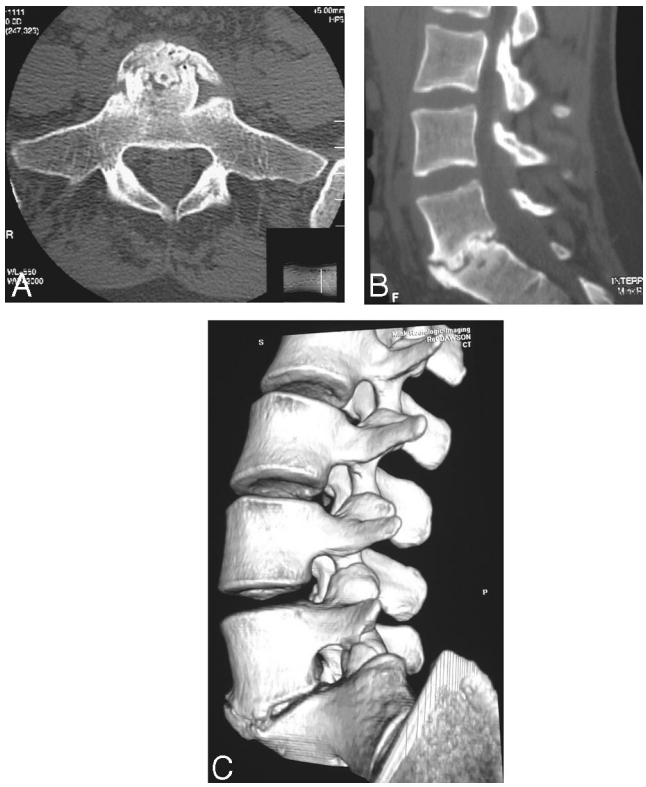

Figure 5. CT of FRA use with rhBMP-2 (in this case at 6 months) reveals extensive bone graft resorption and disintegration. Axial (**A**) and sagittal (**B**) cuts, and a 3-dimensional reconstruction (**C**) are shown.

fusion rates. However, this increase did not happen, and, instead, frequent catastrophic failure of the graft was seen. Poynton and Lane[22] provide some insight into the possible reasons. BMP has a role in the regulation of bone turnover *via* coupled osteoblastic and osteoclastic activity. Itoh *et al*[23] recently showed that BMP-mediated signals are involved in osteoclastic bone resorption. As with fracture healing, the osteoclastic resorption occurs before bone formation by osteoblasts. The exact effect of this in spine fusion is not completely understood. However, Poynton and Lane[22] warn that large doses of BMP may lead to local areas of resorption, which is not desirable in spinal fusion, and strategies to prevent this include careful control of BMP dose and controlled release from the carrier. To our knowledge, our study is the first to show the clinical effect of this property of BMP in human patients *in vivo*.

FRAs are attractive devices for ALIF because they have some osteoinductive and osteoconductive traits, can bear load and provide some immediate stability, and eventually are resorbed and replaced with host bone *via* reverse creeping substitution.[18] In contrast to bone used for posterior or posterolateral fusions, the bone used in interbody constructs has a distinct advantage because it is placed under compressive forces. The Wolff law dictates that mechanical loading elicits an osteogenic response in a loaded bone structure,[24] and it most likely explains the successful use of allograft in interbody fusions compared with its poor success when used in posterior on-lay fusions.[25] However, judging by the high pseudarthrosis rates with stand-alone FRAs and the high fusion rates when anterior impacted allografts are supplemented with posterior instrumentation,[8] this result appears to be true only if the graft is locked in compression by posterior instrumentation, eliminating motion (Figure 7).

A tight intraoperative fit with appropriate distraction of the disc space during insertion of the FRA is not enough to eliminate subsequent motion in the healing period, perhaps in large part because of the resorptive phase of fusion. Experience at our institute has shown us

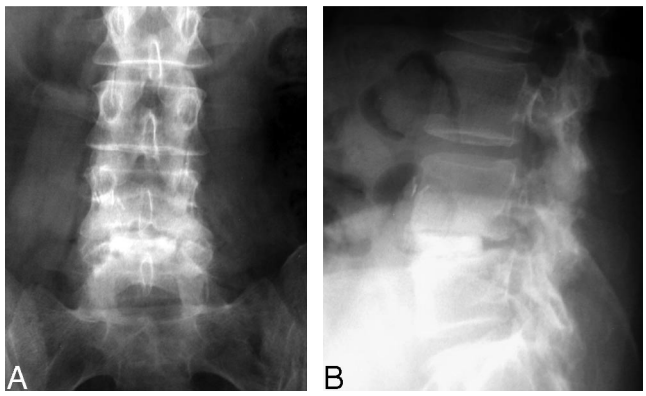

Figure 6. In contrast, aggressive bone resorption and bone graft disintegration were unusual in radiographs of pseudarthrosis after ALIF with FRA and autogenous ICBG (**A**, **B**). Note how the FRA is still structurally intact at 12 months.

that when FRAs with rhBMP-2 are supplementally fixed posteriorly, even with percutaneous instrumentation only (without posterior fusion), the interbody fusion appears to take place early and tends to be robust with an abundant bone formation phase. The additional stabilization seems to allow a smooth transition from the osteolytic to osteoinductive phase, without the risk of instability, which inhibits bony union.

Although additional stabilization seems to be required to ensure high fusion rates with stand-alone interbody fusion with FRAs (and likely other similar impacted spacers), it is not necessary for all interbody devices. Boden *et al*[16] showed that metallic threaded cages with the use of BMP need no supplemental fixation, reporting a fusion rate of 93%. Although this result may be expected for a nonresorbable, tapered, threaded metallic cage that is screwed into the disc space, interestingly the same was found to be true for threaded allograft dowels. Burkus *et al*[17] reported a fusion rate of 100% when threaded bone dowels were used stand-alone for interbody fusion with rhBMP-2. They conclude that cylindrical threaded allograft dowels can be used as stand-alone intervertebral implants that function as an instrumented ALIF; they are not intradiscal spacers that require additional stabilization. Although most of the bone dowels completely resorbed with time, there were no nonunions. The investigators state that the threaded bone dowels resist motion, expulsion, and stabilize the bone-implant interface, in addition to possessing the strength to withstand lumbar compressive loads.

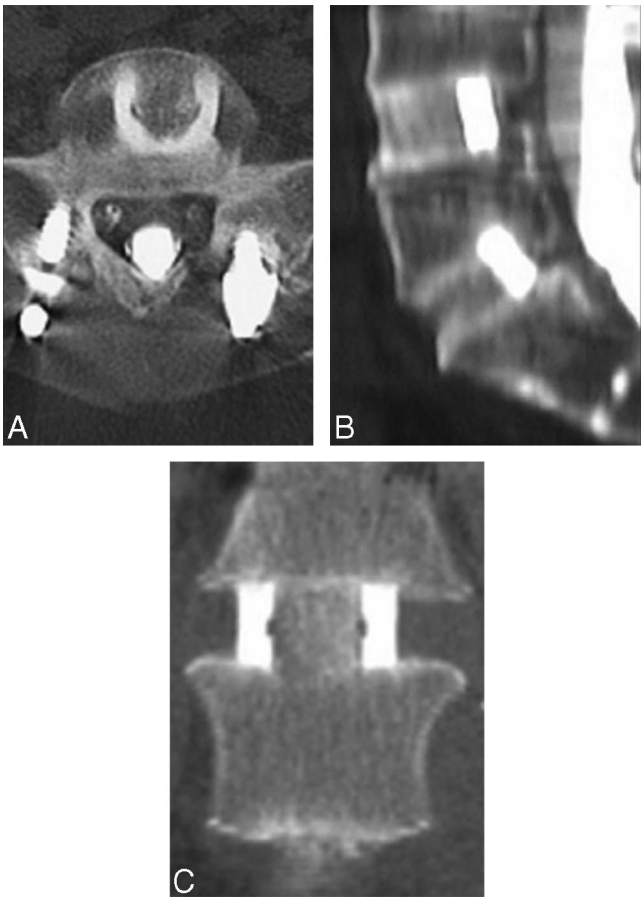

Figure 7. Supplemented with posterior instrumentation, FRAs without any ICBG or BMP have a radiographic fusion rate of more than 90% in more than 100 patients who served as controls for a total disc arthroplasty clinical trial at our institute (**A**–**C**). Twelve-month follow-up CTs are shown.

Optimal bone induction by BMP seems to depend on implant location. There is evidence that the presence of muscle tissue provides favorable conditions for bone induction (*e.g.*, in comparison to subcutaneous implantation of BMP).[26,27] This distinction may be caused by a difference in blood supply, or muscle cells may just be more responsive to BMP because myoblasts in culture treated with BMP show consistent osteogenic differentiation.[28] Unfortunately, the interbody space lacks a good supply of either. Unlike the posterolateral gutters of the spine, there is no muscle in immediate contact with the interbody construct, and preservation of a good load-bearing vertebral endplate compromises the availability of good blood supply. The loads across an interbody graft should be less than its failure load, and the force should be transmitted through the graft without significant motion for immediate load transfer.

A crucial concern with any interbody graft is the graft-bone interface and, in particular, the preservation of the vertebral endplate.[29] The endplate is the strongest supporting structure of the vertebral body, and, therefore, should be preserved to avoid subsidence, loss of correction, and pseudarthrosis.[3] However, if endplate integrity is fully preserved, the interface is less vascularized.

Our experiences and those of others have shown that ALIF with stand-alone FRAs and autogenous bone graft results in lower rates of radiographic fusion, even though the clinical success rates may be satisfactory.[7] In this study, when rhBMP-2 was substituted for autogenous ICBG, fusion was not enhanced. Instead, a possible adverse effect of BMP was highlighted (*i.e.*, there was a trend toward increasing nonunion). As discussed, a number of reasons are possible: the FRA is an impacted interbody graft and offers less than ideal stabilization after discectomy, the endplate-graft interface is not mechanically secure, the blood supply is not plentiful if endplates are preserved for load-bearing, and there is no adjacent muscle tissue.

However, high fusion rates with posteriorly stabilized FRAs and stand-alone nonosseous nonresorbable interbody devices lead us to believe that the primary reason for suboptimal fusion rates with allografts and BMP is the aggressive resorption that is induced and the subsequent mechanical instability. In a situation in which mechanical stability depends solely on a structural allograft (as opposed to posterior onlay grafting), even if it is as strong as a cortical FRA, BMP may cause destabilization. With the increasing popularity and prospects of rhBMP-2 in orthopedic surgery this is an important finding. BMP by itself does not preclude the need for additional stabilization of structural bone grafts.

■ Conclusions

ALIF with stand-alone FRAs as a technique yields low fusion rates. The use of rhBMP-2 soaked in absorbable collagen sponges and placed inside the graft does not increase the fusion rate and, in fact, may cause more nonunions, likely related to a more aggressive early resorptive phase induced by the BMP. Although there was a trend toward a higher nonunion rate compared to the ICBG group, significance could not be established because of the cessation of this surgical technique by the senior author, leading to a low number of patients in the treatment group.

■ Key Points

- The recent Food and Drug Administration approved rhBMP-2 is effective in inducing high rates of fusion in anterior lumbar fusion with cages.
- Structural bone allografts are attractive traditional alternatives to cages in the anterior lumbar spine, and BMP-2 has also been effective in anterior lumbar fusion with paired threaded allograft bone dowels.
- FRAs are intervertebral spacers, that when used in stand-alone fashion, have shown satisfactory clinical results but with low fusion rates. BMP-2 appears to be unable to enhance fusion rates with this type of construct, most likely because of the enhanced graft remodeling and resorption causing destabilization. Additional fixation is still recommended with the use of allograft spacers and BMP-2.

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