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RANDOMIZED TRIAL

Prospective, Randomized, Controlled Trial of Silicate-Substituted Calcium Phosphate *Versus* rhBMP-2 in a Minimally Invasive Transforaminal Lumbar Interbody Fusion

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Study Design. Prospective, randomized, controlled trial.

Objective. To compare arthrodesis rates between patients undergoing a primary single-level minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) with either Actifuse or recombinant human bone morphogenetic protein-2 (rhBMP-2).

Summary of Background Data. Preclinical animal studies suggest that silicate-substituted calcium phosphate (Actifuse) bone graft substitute offers equivalent or an increased fusion rate compared with other graft enhancers/extenders and rhBMP-2.

Methods. Fifty-two patients undergoing a single-level unilateral MIS TLIF were evenly randomized into 2 cohorts as follows: the Actifuse cohort received Actifuse combined with 5 mL of bone marrow aspirate (n = 26; 50%), whereas the rhBMP cohort received 4.2 mg of rhBMP-2 (n = 26; 50%). A *pre hoc* G*Power analysis yielded a sample size of n = 26 that was determined through a 2-tailed distribution calculation. Computed tomographic analysis was performed at 6 months and 1 year postoperatively. Pre- and postoperative visual analogue scale scores were obtained to assess the clinical outcomes. Arthrodesis was determined by 2 separate, blinded orthopedic surgeons and a board certified radiologist.

Results. At 1-year follow-up, 65% (17/26) of the Actifuse cohort and 92% (24/26) of the rhBMP-2 cohort demonstrated a radiographical arthrodesis ($P = 0.01$). In both study cohorts, the 1-year postoperative visual analogue scale scores significantly improved ($P < 0.001$). Pseudarthrosis rates at 1 year were 35.0% (9/26) and 7.7% (2/26) for the Actifuse and rhBMP-2 groups, respectively ($P = 0.01$, OR = 6.35, 95% CI = 1.22–33.1). A greater reoperation rate was noted in the Actifuse cohort (35.0%, 9/26) compared with the BMP-2 cohort (7.7%, 2/26; $P = 0.01$). One patient with BMP-2 also experienced symptomatic neuroforaminal bone growth (3.8%, n = 1/26).

Conclusion. Silicate-substituted calcium phosphate was associated with a significantly lower rate of arthrodesis than rhBMP-2 in a MIS TLIF. The patients with pseudarthrosis in both cohorts were all clinically symptomatic with an unimproved visual analogue scale score. Additional analysis of Actifuse and other graft enhancers/extenders are needed prior to the utilization for an MIS TLIF.

Key words: MIS TLIF, arthrodesis, pseudarthrosis, rhBMP-2, ceramics, Actifuse.

Level of Evidence: 2

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An optimal alternative to the iliac crest bone graft for lumbar interbody arthrodesis remains elusive. Recombinant human bone morphogenetic proteins (rhBMPs) are currently the most effective osteobiologic agents to increase the rate of arthrodesis but are often used as an off-label application.[1] Recent studies have investigated the role of ceramic-based grafts that enable large-scale production, biocompatibility, an appropriate safety profile, and the ability to closely mimic physiological bone.[2–5] The 3-dimensional scaffolds that are created by the intrinsic characteristics of ceramics promote osteoconduction that is dependent on the pore diameter and the pore interconnectivity.[1,6]

Recently, the development of the silicate-substituted calcium phosphate (Si-CaP) ceramic has been proposed to be a viable option to enhance and accelerate osteostimulation compared with the traditional ceramics.[7,8] Although animal studies have demonstrated that low levels of silicon result in faster angiogenesis and bone apposition than the traditional ceramic-based grafts,[9–13] the clinical effectiveness of Si-CaP in posterior lumbar interbody arthrodesis has been poorly defined.[9–13]

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The purpose of this study was to evaluate the clinical and radiological effectiveness of a silicate hydroxyapatite ceramic (Actifuse; ApaTech Ltd., Foxborough, MA) as a graft extender in patients undergoing a single-level minimally invasive (MIS) transforaminal lumbar interbody fusion (TLIF).

MATERIALS AND METHODS

Study Design

This study is a prospective, randomized, controlled trial of 52 patients undergoing a single-level minimally invasive transforaminal lumbar interbody fusion from January 2009 through July 2010. Randomization was performed at the time of surgery *via* a random number generator (0, 1; "0" representing no BMP and "1" representing BMP). The patient population was divided into 2 groups as follows: the Actifuse cohort received Actifuse combined with 5 mL of bone marrow aspirate obtained from the lumbar pedicle (n = 26; 50%) whereas the rhBMP cohort received 4.2 mg of rhBMP-2 (InFUSE; Medtronic Sofamor Danek, Memphis, TN) (n = 26; 50%). There were 26 males (50%) and 26 females (50%) included in the study. The ages in the range from 29 to 80 years, with a mean age of 51.1 years for the Actifuse group and 56.3 years for the rhBMP-2 group. All patients had at least 1 year of follow-up. Each patient presented with at least a 6-month history of low back and/or leg pain refractory to conservative treatment. All patients had a diagnosis of lumbar spinal stenosis accompanied by grade I or II degenerative spondylolisthesis (n = 52).

The patient demographics, including the comorbidities determined by the Charlson Comorbidity Index, were similar between the study cohorts (Table 1). All surgical patients entering the practice were provided with an informed consent for data collection that was associated with their treatment. Institutional review board approval was obtained.

Radiographical Outcomes Measurements

Computed tomographic (CT) scans with contiguous 2.0-mm axial cuts perpendicular to the disc space (along with sagittal and coronal reconstructions) were obtained at the operative level at 6 months and 1 year after the index surgery. All imaging studies were blindly interpreted by 2 orthopedic surgeons and a board certified radiologist to assess for arthrodesis. CT assessment of arthrodesis included 3 criteria: (1) contiguous bridging bone on at least 2 consecutive coronal and sagittal reconstructions within the intervertebral space, (2) blurring of the bone graft-endplate junction, and (3) absence of a radiological cleft within the fusion mass. Noncontiguous bone formation, the presence of cage subsidence with endplate cyst formation, haloing around the cage and screws, or graft migration was defined as pseudarthrosis. CT was also used to determine any adverse advents specific to the osteobiologic agents, including ectopic muscle ossification, laminar bone regrowth, neuroforaminal bone growth, and intra/extradural ossification.

Patient Outcome Measurements

Clinical outcomes were collected by using the visual analogue scale (VAS) scores (0, least to 10, most) for low back pain. The data were collected prior to surgery and at the follow-up visits.

Index Surgical Procedure

A unilateral approach was undertaken through a paramedian (4.5 cm laterally to the midline) skin incision using the Wiltse technique under fluoroscopy. After incising the skin and fascia, a plane was developed between the multifidus and longissimus muscles, whereby the pathway to the spine was enlarged with sequential dilators. A high-speed burr was used to remove the facet and pars. A bilateral decompression was accomplished *via* unilateral approach. Local bone graft that had been obtained from the laminectomy and facetectomy was collected in a bone trap. The interbody space was identified under fluoroscopic imaging. Sequential endplate cutters were used to prepare the endplates. An appropriately sized DePuy Concorde PEEK cage with carbon fiber reinforcement (DePuy Spine, Raynham, MA) was filled with either Actifuse or 4.2 mg of rhBMP-2, along with 5 mL of bone marrow aspirate from the cannulated pedicle and local bone graft. Local bone and local bone + Actifuse were placed anterior to the cage in the intervertebral space. Then, the cage was gently impacted obliquely into the intervertebral space. Unilateral pedicle screws were placed percutaneously over a guide wire. Compression was placed across the graft *via* the pedicle screw-rod construct. The laminectomy, bilateral decompression, and transforaminal lumbar interbody fusion were performed with a 21-mm nonexpandable tube. No posterolateral fusion was performed.

Statistical Analysis

SPSS Inc. version 17.0 Graduate Package (Chicago, IL) was used for statistical analysis. Student *t* test was used to assess significant differences between the Actifuse and rhBMP cohorts. Fisher exact probability test was used to evaluate differences between nonparametric data. Cohen kappa inter-rater reliability was calculated between the radiologist and orthopedic surgeon interpretations of the CT scan. A $P < 0.05$ denoted statistical significance between the study cohorts.

A sample size calculation for the primary analysis was conducted with G*Power 3.1 (University of Kiel, Germany) with an anticipated effect size of Cohen d = 0.8, significance $\alpha = 0.05$, and an expected power of $(1 - \beta) = 0.8$. This yielded a sample size of n = 26 that was determined through a 2-tailed distribution calculation.

Two *post hoc* power analyses were conducted for the change in VAS scores in the Actifuse and rhBMP-2 cohorts. Specifically, these comparisons consisted of (1) preoperative VAS scores (Actifuse *vs*. rhBMP-2 total cohorts) and (2) postoperative VAS scores (Actifuse *vs*. rhBMP-2 total cohorts). These 2 calculations generated powers of 0.89 and 0.99, respectively.

RESULTS

Fifty-two patients with a mean age of 53.7 years were enrolled in this study (Table 1). A total of 26 (50%) patients received Actifuse granules (ApaTech Ltd.) and 26 patients

TABLE 1. Demographic Characteristics

Variable	Actifuse (n = 26)	rhBMP-2 (n = 26)	*P*
Sex			1.000
Male	13	13	
Female	13	13	
Age	51.1 (26–79)	56.3 (26–80)	0.202
Race			0.529
Caucasian	18	15	
African American	5	5	
Latino	3	6	
Smoker			0.760
Yes	8	7	
No	18	19	
Payer			0.641
Commercial	11	14	
Worker's compensation	10	7	
Medicare	5	5	
Charlson Comorbidity			0.412
Index score	0.78 ± 0.93	0.59 ± 0.69	
Surgical time (min)	140 ± 44.6	141 ± 32.2	0.932
Estimated blood loss (mL)	101 ± 68.0	91 ± 58.1	0.571
Arthrodesis (1 yr)			0.017
Yes	17	24	
No	9	2	
Pseudarthrosis (1 yr)			0.017
Yes	9	2	
No	17	24	
Other graft complications Neuroforaminal bone growth, adjacent segment disease	0	1	1.000
Average time to reoperation	9.1 mo (277 d)	13.0 mo (395 d)	0.215
Preoperative VAS scores	6.8 ± 1.8	7.7 ± 1.7	0.070

VAS indicates visual analogue scale.

(50%) received a small kit of rhBMP-2. Arthrodesis was assessed *via* CT scan analysis at 6 months and 1 year after the index procedure (Figure 1). The correlation between the ratings of the independent interpreters for all levels was 0.80 ($P < 0.001$) for the diagnosis of pseudarthrosis *versus* solid fusion. Because of this high level of inter-rater reliability, all subsequent results are presented *via* the interpretations of the 2-blinded orthopedic surgeons.

At 6 months from the index procedure, 46% of the Actifuse cohort (n = 12/26) demonstrated a successful radiographical arthrodesis compared with 77% of the rhBMP cohort (n = 20/26, $P = 0.02$). At 1 year from the index procedure, 5 additional patients in the Actifuse cohort (17/26; 65%) developed a successful radiographical arthrodesis. Also, in the rhBMP cohort, 4 additional patients (24/26; 92%) demonstrated a successful radiographical fusion at the 1-year follow-up ($P = 0.01$). These additional patients demonstrated an incomplete, but asymptomatic, fusion at the 6-month follow-up but developed a solid fusion at 1 year after the index procedure.

Clinically symptomatic pseudarthrosis (intractable radiculopathy and/or axial pain) was identified in all patients with

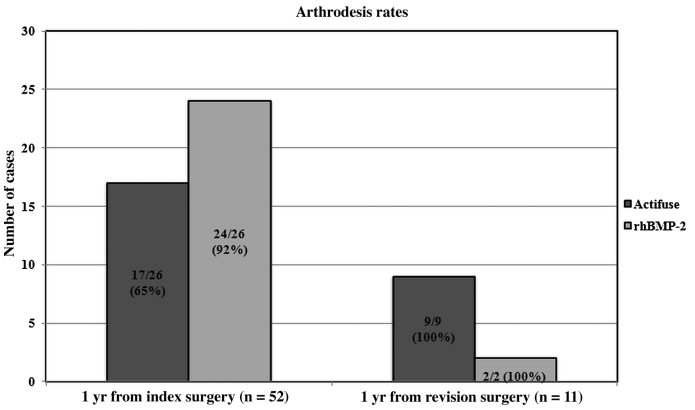

Figure 1. Arthrodesis rates at 1 year from the index and revision procedures. RhBMP indicates recombinant human bone morphogenetic protein-2.

a radiographical nonunion: 35% of the Actifuse cohort (n = 9/26) and 7.7% of the rhBMP-2 cohort (n = 2/26) (P = 0.017, odds ratio = 6.35, 95% CI = 1.22–33.19) (Figure 2). All patients with a symptomatic nonunion had undergone a revision procedure, yielding a 35% (9/26) and 7.7% (n = 2/26) revision rate in the Actifuse and rhBMP cohorts, respectively.

Among the Actifuse-treated patients requiring a reoperation for pseudarthrosis, the ninth patient had a revision surgery at 22 months after the index procedure. This patient's CT scan demonstrated minimal bone consolidation and chronic endplate sclerosis secondary to abnormal loading (Figure 3). In addition, 1 of the 2 reoperations among the rhBMP-treated patients (n = 1/26, 3.8%) was because of a clinically symptomatic complication of the BMP-2 graft (neuroforaminal bone growth), in addition to a CT-confirmed pseudarthrosis (Figure 4). The second patient (n = 1, 3.8%), in the rhBMP cohort, required a revision procedure for a confirmed pseudarthrosis.

Clinical Outcomes

For the Actifuse-treated patients with a CT confirmed arthrodesis at 1 year (n = 17), the average VAS scores improved from a preoperative score of 6.8 ± 1.8 to 2.7 ± 2.2 at the 1-year follow-up (P < 0.001) (Table 2). In the Actifuse-treated patients with a CT confirmed pseudarthrosis (n = 9), the average VAS scores changed from a preoperative score of 6.9 ± 2.0 to 6.4 ± 2.3 at the 1-year follow-up (P = 0.79).

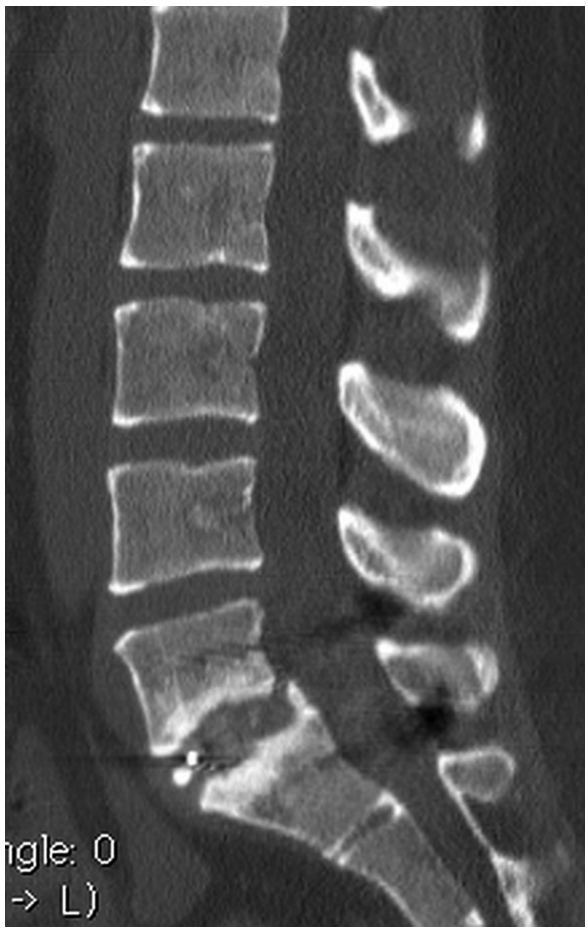

Figure 3. Sagittal CT scan of an Actifuse-treated patient requiring a revision surgery at 22 months due a symptomatic nonunion demonstrating minimal bone consolidation and chronic endplate sclerosis. CT indicates computed tomography.

For the rhBMP-treated patients with a CT confirmed arthrodesis at 1 year (n = 24), the average VAS scores improved from a preoperative score of 7.7 ± 1.7 to 4.0 ± 2.2 at the 1-year follow-up (P < 0.001). In the rhBMP-treated patients with a CT confirmed pseudarthrosis at 1 year (n = 2), the VAS scores changed from a preoperative score of 8.0 ± 0.1 to 5.0 ± 2.8 at the 1-year follow-up (P = 0.19).

Among the Actifuse revision patients (n = 9), the average VAS scores improved from 6.9 ± 2.0 to 3.9 ± 2.6 at 1-year after the revision procedures (P = 0.02). Similarly, for the rhBMP-2 revision patients (n = 2), the average VAS scores

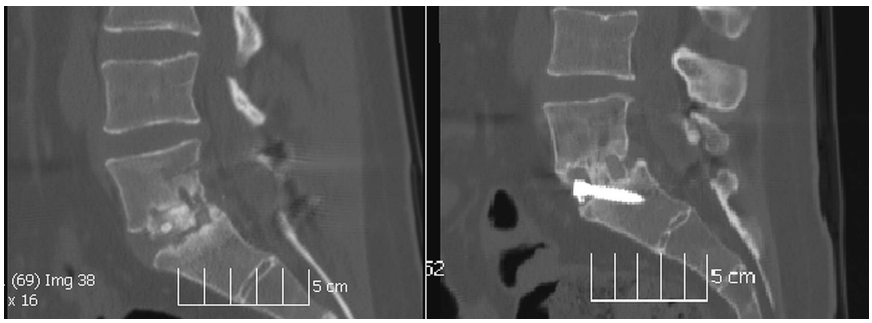

Figure 2. Sagittal CT scans comparing an Actifuse-treated patient with a pseudarthrosis at L5–S1 (left) and the ALIF revision using rhBMP-2 (right). CT indicates computed tomography; ALIF, anterior lumbar interbody fusion.

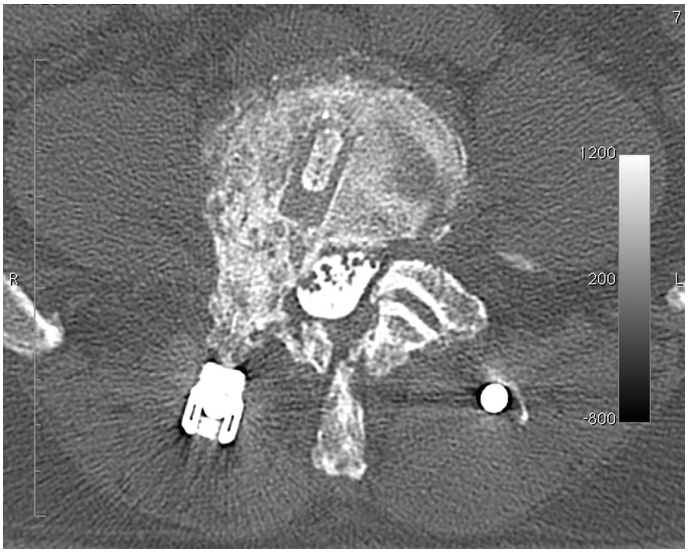

Figure 4. A patient treated with rhBMP-2 developed a clinically symptomatic neuroforaminal bone growth in addition to a CT confirmed pseudarthrosis. CT indicates computed tomography.

improved from 8.0 ± 0.1 to 4.0 ± 2.8 at 1 year after the revision procedures ($P = 0.18$).

Revision Procedures

The approach for the revision procedure was determined by the presence of patient comorbid risk factors (diabetes, smoking). In patients with a high risk for a recurrent pseudarthrosis, an anterior approach was used (n = 3, 11.5%). In all others, a contralateral MIS TLIF was performed. In the rhBMP-treated patient with the pseudarthrosis and concomitant neuroforaminal bone growth, a contralateral MIS TLIF was performed with an ipsilateral foraminotomy and neurolysis of the nerve root. All the rhBMP-2 revision procedures (n = 2) were performed by using local bone marrow from the cannulated pedicle that was compounded with MasterGraft (Medtronic Sofamor Danek). In the Actifuse revision procedures, rhBMP-2 with the local bone graft was used for fusion. Radiographical (CT) arthrodesis at 1 year after the revision procedures was confirmed in both the Actifuse (n = 9/9, 100%) and the rhBMP (n = 2/2, 100%) cohorts (Figure 1 and 2).

DISCUSSION

The minimally invasive surgical technique *via* a transforaminal lumbar interbody fusion is an effective procedure to restore functional outcomes, improve recovery, and reduce healing time.[14–16] However, the type of bone graft/extender that is best suited in this challenging fusion environment remains to be proven. The utilization of rhBMP-2 in an MIS TLIF is commonly performed as an off-label application to increase the rates of arthrodesis.[1] Several reports have established the complications of rhBMP including heterotopic bone growth, although the exact clinical sequelae have several controversial and contrasting viewpoints.[17,18] A recent meta-analysis by the Yale University Open Data Access Project demonstrated that at 24 months, rhBMP increased the rate of arthrodesis but was also associated with greater early postoperative pain than iliac crest bone graft.[19] The authors concluded that the evidence of an increased cancer incidence associated with rhBMP utilization is still inconclusive.[19]

In our prospective, randomized, controlled trial of 52 cases, 2 patients in the rhBMP-2 cohort had radiographical and clinical evidence of pseudarthrosis at the 1-year follow-up (n = 2/26, 7.7%). The VAS scores in these patients did not demonstrate significant improvements after the index surgery ($P = 0.19$). The intraoperative exploration, in both revision cases, demonstrated gross motion of the interbody fusion masses. In addition, heterotopic bone was noted in 1 of these patients resulting in severe neuroforaminal stenosis. In this patient with the pseudarthrosis and concomitant neuroforaminal bone growth, the time to reoperation was 7.7 months. This was 11.2 months earlier than the second patient who was diagnosed with a pseudarthrosis alone (18.9 mo). Although these results are of a small sample size (n = 2), they may suggest that a neuroforaminal bone growth symptomatically presents earlier than a pseudarthrosis with rhBMP-2 utilization in a MIS TLIF.

Actifuse as a bone graft extender has varying levels of efficacy in the surgical literature. Sekhon *et al*[20] compared Actifuse with rhBMP-2 in the setting of an anterior cervical fusion. The authors reported a 17.5% and 3.7% screw pullout rate for the Actifuse and rhBMP cohorts, respectively ($P = 0.004$). However, no differences in pseudarthrosis were demonstrated at the final follow-up with CT imaging. Aubin *et al*[21]

TABLE 2. VAS Scores Comparison of Radiographical Fusion *Versus* Pseudarthrosis

	Arthrodesis			Pseudarthrosis		
	Preoperative	Postoperative	*P*	Preoperative	Postoperative	*P*
Actifuse	6.8 ± 1.8	2.7 ± 2.2	<0.001	6.9 ± 2.0	6.4 ± 2.3	0.79
rhBMP-2	7.7 ± 1.7	4.0 ± 2.2	<0.001	8.0 ± 0.1	5.0 ± 2.8	0.19
Revision Actifuse (1 yr)	6.9 ± 2.0	3.9 ± 2.6	0.02	…	…	…
Revision rhBMP-2 (1 yr)	8.0 ± 0.1	4.0 ± 2.8	0.18	…	…	…

RhBMP indicates recombinant human bone morphogenetic protein; VAS visual analogue scale.

specifically analyzed 25 consecutive patients who had undergone a TLIF with Actifuse and reported a 100% arthrodesis rate at 1-year follow-up. However, the authors noted 2 cases of loosening around the cage construct.[21] Of note, these authors also performed a concomitant posterolateral fusion in addition to the interbody preparation. Oliveira *et al*[22] assessed the arthrodesis rate of 21 Actifuse-treated patients in the setting of an extreme lateral interbody fusion. Postoperative imaging demonstrated evidence of solid fusion, disc height restoration, and adequate neural decompression in all patients except in 1 patient with cage subsidence.[22]

In our series, 9 patients in the Actifuse cohort demonstrated pseudarthroses after undergoing an MIS TLIF (n = 9/26, 35%). These patients developed axial pain and radiculopathy that warranted a revision procedure. Importantly, all of these patients did not report significant improvements in the VAS scores after the index surgery ($P = 0.79$). Intraoperative exploration (anterior approach only) in these revision procedures noted grossly loose intervertebral implants and little consolidation of the silicated bone graft. In addition, cage subsidence was noted in several cases causing a significant disruption of the vertebral endplates.

Our reported arthrodesis rate of 65%, at 1 year, in the Actifuse cohort, is lower than other reported fusion rates with the silicate-substituted ceramics. Pimenta *et al*[23] demonstrated an arthrodesis rate of 98.8% at 1 year in 24 patients after an anterior lumbar interbody fusion with a mixture of hydroxyapatite and β-tricalcium phosphate.[23] Possibly, this higher rate at 1 year may relate to their mixture of 2 calcium phosphates. In addition, the volume of bone marrow aspirate that was used in this study may have differed from our study leading to the discrepancy in the reported arthrodesis rates.[23] Interestingly, none of the patients assessed by Pimenta *et al* after an anterior lumbar interbody fusion reported symptoms related to a pseudarthrosis.[23] It should be noted that the authors used a more stable, anterior cage construct, which may have contributed to the lack of pseudarthrosis and a greater arthrodesis rate. Anterior fusion environments historically have reported higher fusion rates than other surgical approaches.[24] These results contrast with our study, in which every patient with a radiographical pseudarthrosis was clinically symptomatic in both study cohorts.

The limitations of this study should be noted. First, the MIS technique that was used is technically unforgiving in that unilateral instrumentation is applied. This technique places a significant amount of stress across the intervertebral space. In addition, it may predispose the patients to developing pseudarthroses that may not be evident if bipedicular fixation is used. However, the unilateral fixation allowed us to isolate the biologic agent without the aid of significant adjunct fixation. Second, although we performed the same surgical technique for both patient cohorts, the local bone graft volume was not measured, thereby, potentially introducing a bias into our analysis. Lastly, the dosage of Actifuse that was used in this trial (5 mL) may be too low to significantly enhance fusion. Currently, an optimal dose for interbody fusion has not been identified in the literature.

CONCLUSION

In this prospective, randomized, controlled trial of 52 MIS TLIF cases, a Si-CaP (Actifuse) demonstrated a lower rate of arthrodesis than rhBMP-2. At 1-year follow-up, pseudarthrosis rates were significantly greater for Actifuse than rhBMP-2. Our MIS TLIF model with a unilateral fixation is a challenging fusion environment that may increase the likelihood of pseudarthroses. Nevertheless, it does seem that the rate of pseudarthrosis is greater when Actifuse alone is used as a bone graft extender in this environment. On the basis of our clinical findings we conclude that further research into the safety and efficacy of osteobiologic agents in general, including Actifuse, is needed prior to their usage in the difficult environment of a minimally invasive transforaminal lumbar interbody fusion.

➢ Key Points

- ❑ This prospective, randomized, controlled trial demonstrated that in the setting of an MIS TLIF, Si-CaP demonstrated a lower arthrodesis rate and a higher reoperation rate, at 1-year follow-up, than the matched patients in the rhBMP-2 cohort.
- ❑ One-year VAS scores were unimproved in both the silicate-substituted and rhBMP-2–treated patients with a CT confirmed pseudarthrosis.
- ❑ Further research into the safety and efficacy of bone graft alternatives including the Si-CaP, is needed prior to its usage in the difficult environment of minimally invasive transforaminal lumbar interbody fusions.

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References

1. Cahill KS, Chi JH, Day A, et al. Prevalence, complications, and hospital charges associated with use of bone-morphogenetic proteins in spinal fusion procedures. *JAMA* 2009;302:58–66.
2. Zimmermann G, Moghaddam A. Allograft bone matrix *versus* synthetic bone graft substitutes. *Injury* 2011;42:S16–21.
3. Miyazaki M, Tsumura H, Wang JC, et al. An update on bone substitutes for spinal fusion. *Eur Spine J* 2009;18:783–99.
4. Lee YP, Ghofrani H. Bone graft substitutes and extenders. *Contemp Spine Surg* 2009;10:8.
5. Vaz K, Verma K, Protopsaltis T, et al. Bone grafting options for lumbar spine surgery: a review examining clinical efficacy and complications. *SAS J* 2010;4:75–86.
6. Hofstetter C, Hartle R. *Fundamentals of Operative Techniques in Neurosurgery.* New York: Thieme; 2010:883.
7. Seebach C, Schultheiss J, Wilhelm K, et al. Comparison of six bone-graft substitutes regarding to cell seeding efficiency, metabolism and growth behavior of human mesenchymal stem cells (MSC) *in vitro*. *Injury* 2010;41:731–8.
8. LeGeros RZ. Properties of osteoconductive biomaterials: calcium phosphates. *Clin Orthop Relat Res* 2002:81–98.
9. Campion CR, Chander C, Buckland T, et al. Increasing strut porosity in silicate-substituted calcium-phosphate bone graft substitutes enhances osteogenesis. *J Biomed Mater Res B Appl Biomater* 2011;97:245–54.

10. Wheeler DL, Jenis LG, Kovach ME, et al. Efficacy of silicated calcium phosphate graft in posterolateral lumbar fusion in sheep. *Spine J* 2007;7:308–17.
11. Shepherd JH, Best SM. Calcium phosphate scaffolds for bone repair. *JOM* 2011;63:83–92.
12. Patel N, Brooks RA, Clarke MT, et al. In vivo assessment of hydroxyapatite and silicate-substituted hydroxyapatite granules using an ovine defect model. *J Mater Sci Mater Med* 2005;16: 429–40.
13. Hing KA, Wilson LF, Buckland T. Comparative performance of three ceramic bone graft substitutes. *Spine J* 2007;7:475–90.
14. Peng CW, Yue WM, Poh SY, et al. Clinical and radiological outcomes of minimally invasive *versus* open transforaminal lumbar interbody fusion. *Spine (Phila Pa 1976)* 2009;34:1385–9.
15. Wu RH, Fraser JF, Hartl R. Minimal access *versus* open transforaminal lumbar interbody fusion: meta-analysis of fusion rates. *Spine (Phila Pa 1976)* 2010;35:2273–81.
16. Rouben D, Casnellie M, Ferguson M. Long-term durability of minimal invasive posterior transforaminal lumbar interbody fusion: a clinical and radiographic follow-up. *J Spinal Disord Tech* 2011;24:288–96.
17. Wong DA, Kumar A, Jatana S, et al. Neurologic impairment from ectopic bone in the lumbar canal: a potential complication of off-label PLIF/TLIF use of bone morphogenetic protein-2 (BMP-2). *Spine J* 2008;8:1011–8.
18. Joseph V, Rampersaud YR. Heterotopic bone formation with the use of rhBMP-2 in posterior minimal access interbody fusion: a CT analysis. *Spine (Phila Pa 1976)* 2007;32:2885–90.
19. Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data. *Ann Intern Med* 2013;158:877–89.
20. Sekhon L, Tomlinson A, Allen B, et al. 64. Immediate postoperative complications and radiological features of interbody fusion between INFUSE BMP and Actifuse: a randomized prospective trial. *The Spine J* 2009;9:32S–3S.
21. Aubin M, Drew J, Eskander M, et al. Clinical and radiological fusion rates following transforaminal lumbar interbody fusion (TLIF) with silicate-substituted calcium-phosphate bone graft substitute without ICBG for the surgical treatment of degenerative lumbar spine disease. Gp175. *Spine Journal Meeting Abstracts* 2010:317.
22. Oliveira L, Marchi L, Coutinho E, et al. A radiographic assessment of the ability of the extreme lateral interbody fusion procedure to indirectly decompress the neural elements. *Spine (Phila Pa 1976)* 2010;35:S331–7.
23. Pimenta L, Pesántez CFA, Oliveira L. Silicon matrix calcium phosphate as a bone substitute: early clinical and radiological results in a prospective study with 12-month follow-up. *SAS J* 2008;2:62–8.
24. Kozak JA, Heilman AE, O'Brien JP. Anterior lumbar fusion options. Technique and graft materials. *Clin Orthop Relat Res* 1994:45–51.