A Prospective, Randomized, Controlled Trial Comparing Radiographic and Clinical Outcomes between Stand-Alone Lateral Interbody Lumbar Fusion with either Silicate Calcium Phosphate or rh-BMP2

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Abstract

Object Iliac crest autograft has traditionally been considered the gold standard for lumbar spine fusion, though it is not without drawbacks related to harvesting site pain and other complications. Bone graft alternatives, such as recombinant human bone morphogenetic protein 2 (rh-BMP2), are now widely used but also have unique risk profiles and substantially increase costs. The purpose of the current study was to compare the efficacy of rh-BMP2 and synthetic silicate calcium phosphate (SiCaP) as bone graft substitutes on fusion rates and clinical outcomes in patients undergoing single-level lumbar stand-alone extreme lateral interbody fusion (XLIF).

Methods A prospective, randomized, controlled, clinical, and radiographic study was performed at a single institution. Thirty patients with L4–L5 degenerative disc disease (DDD) were enrolled. Patients were randomized into one of two groups, 15 underwent lumbar single-level stand-alone XLIF using SiCaP, and 15 using rh-BMP2. Clinical and radiographic results were compared between the study groups. Pain (visual analogue scale) and disability (Oswestry disability index) were assessed preoperatively and at postoperative weeks 1 and 6 and postoperative months 3, 6, 12, 24, and 36. Radiographic evaluations were performed at 6, 12, 24, and 36 months. Neurological examinations and adverse events were recorded at each visit.

Results No intraoperative complications were observed in either treatment group, and clinical outcomes were similarly improved between bone graft substitutes from baseline to 36 months postoperative. Complications were transient hip flexion weakness (13%), insufficient indirect decompression (7%), subsidence (17%), excessive bone formation (4%), and adjacent segment disease (14%). Complication rates between the groups were similar, though with slightly more instances of subsidence in the SiCaP group and higher rates of excessive bone formation and adjacent segment disease in the rh-BMP2 group. Rates of fusion at different time points were different between the

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groups, with the SiCaP patients progressing more slowly toward solid fusion. However, at 36 months, 100% of patients undergoing XLIF achieved solid fusion.

Conclusions In stand-alone XLIF, SiCaP and rhBMP-2 bone graft substitutes both resulted in complete long-term fusion. rhBMP-2, however, seemed to result in more rapid early postoperative fusion, though with one instance of excessive bone formation in one patient that required subsequent surgical intervention.

Introduction

Spine surgery has been evolving over the past decade through a refinement of approaches and instrumentation to provide equivalent or improved clinical outcomes with decreased risks, lower morbidity, and improved cost-effectiveness.[1,2] Modern surgical approaches utilize mini-open exposures with direct visualization and minimal soft-tissue dissection to preserve healthy tissue and more directly target the diseased area. Extreme lateral interbody fusion (XLIF) has been reported as an alternative approach to conventional anterior lumbar interbody fusion (ALIF) for the treatment of lumbar,[3–6] thoracolumbar,[7–10] and thoracic[11–13] spinal diseases.

Similar to the progression toward less-invasive surgical approaches, alternatives to autologous bone grafts—historically considered to be the gold standard—have been sought to decrease the morbidity associated with iliac crest bone graft (ICBG) harvesting. ICBG, for instance, has been associated with chronic donor site pain, infections, fractures, and hematomas.[14–16] Thus, graft materials and adjuvants other than ICBG were developed, such as synthetics grafts (calcium phosphate injectable cements, hydroxyapatite, and β-tricalcium phosphate),[17–21] allograft cellular bone matrix,[22] gene therapies,[23,24] demineralized bone matrix[25] and recombinant growth factors.[26] However, each of these non-ICBG materials (except for allograft cellular bone matrix) lack the three physiologic mechanisms of bone formation that ICBG possesses: osteoconduction, osteoinduction, and osteogenesis.

The object of this study was to examine outcomes of a 3-year, prospective, randomized study comparing recombinant human bone morphogenetic protein 2 (rh-BMP2) and silicate calcium phosphate (SiCaP) as bone graft substitutes in patients undergoing a single-level, stand-alone lumbar lateral interbody fusion for degenerative disc disease.

Material and Methods

Clinical and radiographic data were collected as part of a prospective, randomized, single-center study. The study was analyzed and approved by the Santa Rita Hospital Ethics Committee.

Patient Selection

Inclusion criteria for enrollment included patients 70 years of age or younger (skeletally mature) having chronic, symptomatic, single-level lumbar degenerative disease at L4–L5 (degenerative disc disease [DDD] with/without grade I degenerative spondylolisthesis) that failed to respond to a conservative treatment regimen. Exclusion criteria included coronal curves >10 degrees, previous surgery at the index level, acute trauma, body mass index (BMI) >35 kg/mm^2, facet hypertrophy ≥ grade 3, 50% or more of canal stenosis, and severe neurogenic claudication. Provocative discography as a diagnostic tool was not mandatory.

Study Cohorts

Simple randomization into two groupps was performed just before surgery in the operating room, in a single-blinded sortition by the senior author (L.P.): 15 patients treated with L4–L5 single-level stand-alone XLIF with 0.8 wt% silicate substituted within a calcium phosphate ceramic (SiCaP, Actifuse®, Baxter International Inc., Deerfield, IL, USA) and 15 patients with recombinant human bone morphogenetic protein 2 in collagen sponge (rh-BMP2, INFUSE®, Medtronic Sofamor Danek, Memphis, TN, USA) as bone graft substitutes. Lateral interbody fusion was performed using extreme lateral interbody fusion (XLIF®, NuVasive, Inc. San Diego, CA, USA), the technique previously described by the senior author (L.P.),[27] without posterior decompression or supplemental instrumentation. Intervertebral cages were 18 mm-wide polyether ether ketone cages (PEEK, CoRoent®, NuVasive Inc, CA, USA) tightly packed with 2.1 mg rhBMP-2 or with SiCaP granules. The height of the cage was selected intraoperatively to best adjust to the index level, with some, but not excessive, disc space distraction.

Clinical Assessment

Preoperatively and at every routine postoperative visit (2 weeks, 6 weeks, 3 months, 6 months, 12 months, 24 months, 36 months), a neurological examination was performed and self-assessment of disability and pain were performed using the Oswestry disability index (ODI) and the visual analog pain scale (VAS) for back/leg symptoms. Complications and reoperations were also recorded at each time point.

Radiological Assessment

Radiological examinations were performed on x-rays and computed tomography (CT) at preoperative and postoperative visits (6, 12, 24, and 36 months) by the authors (L.P.; R.A.) in a blinded fashion. Two patients were lost to follow-up in the SiCaP group but had available treatment and complication data included in the results in the interest of completeness,

Table 1 Demographic, clinical, and surgical data

	Groups		*p* value
	SiCaP	rh-BMP2	
Patients	15	15	0.999
Levels	15	15	0.999
Age (years)	49.1 ± 10.7	45.7 ± 11.4	0.237
Gender (female)	73.3%	53.3%	0.256
VAS	71 ± 22	78 ± 17	0.407
ODI	47 ± 13	49 ± 24	0.201
Blood loss (cc)	< 50	< 50	0.999
Surgery duration (min)	70.7 ± 13.3	67.3 ± 8.8	0.186

ODI, Oswestry disability index; VAS, visual analog pain scale; SiCaP, silicate calcium phosphate; rh-BMP2, recombinant human bone morphogenetic protein 2.
Note: Numbers are referred as mean ± standard deviation.

though long-term radiographic and clinical results for these patients could not be collected.

Subsidence was considered when 50% or more of disc space loss was observed. Fusion status was classified as complete fusion, ongoing fusion, or no fusion. Fusion status was defined as translational motion <3 mm, angular motion <5 degrees on dynamic x-rays, and bone filling >50% of disc space on CT with bridging bone evident throughout at least 50% of the disc space. Absence of bridging bone at the intervertebral space was defined as no fusion.

Statistical Analysis

Student *t*-tests, two-tailed Z-test, Fisher's exact test, analysis of variance (ANOVA), and Pearson's correlation test were used for comparison between variables, with a level of significance defined as $p < 0.05$.

Results

Study Groups and Surgical Procedure

In total, 18 female and 12 male patients were enrolled and treated, with a mean age of 47.4 years (range 26 to 70). Demographic, clinical, and surgical parameters were largely similar between the treatment groups (►**Table 1**). Average operative time was 69 minutes (standard deviation [SD] 11.2), with average blood loss <50 mL and a mean hospital stay of 24 hours (range 12 to 48). No intraoperative complications were observed.

Clinical Outcomes

Statistically significant improvements in VAS were observed at all postoperative visits compared with baseline, with a decrease of 32% seen 1 week after surgery (74 to 50 mm, $p < 0.001$), further decreasing to 46% at last follow-up (40 mm at 36 months, $p < 0.001$). Overall ODI scores improved from 48 at baseline to 33 (31.3%) by 6 weeks after surgery ($p < 0.0001$), with a maintenance of improvement at all follow-up visits. Statistical differences on clinical outcomes between the groups were not observed on VAS (►**Fig. 1A**) or ODI (►**Fig. 1B**) outcomes, though a power analysis was not performed to test statistical power to observe differences between the groups.

Complications

Complications are summarized and stratified by group in ►**Table 2**. Two cases (7%, one in each group) of insufficient indirect decompression following stand-alone XLIF were observed, requiring subsequent mini-open direct decompression. Interbody graft subsidence was observed in five cases (17%), three in the SiCaP and two in the BMP group, one

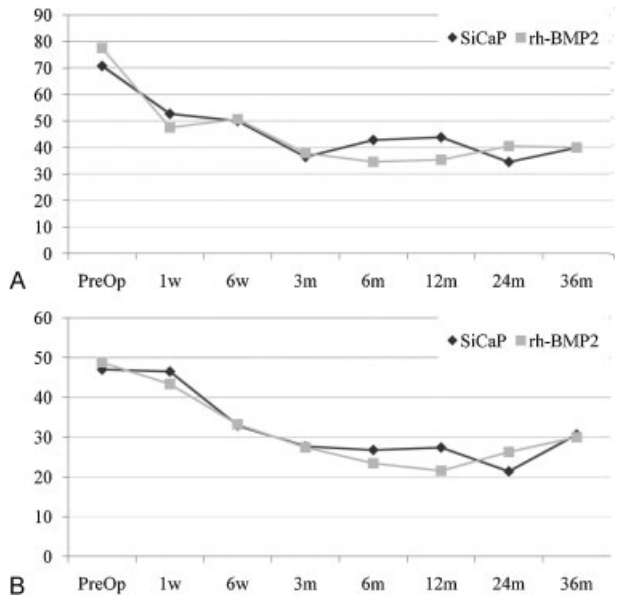

Fig. 1 Clinical outcomes assessments with average (A) visual analog pain scale (VAS) back/leg pain and (B) Oswestry disability index (ODI) scores. (A) Both silicate calcium phosphate (SiCaP) ($p = 0.04$) and rh-BMP2 groups ($p = 0.009$) showed statistically significantly reduced VAS scores at 1 week and at subsequent visits compared with preoperative scores. Groups had no statistical difference among them in VAS scores ($p > 0.09$). (B) Both SiCaP ($p = 0.007$) and rh-BMP2 groups ($p = 0.038$) showed statistically significantly reduced ODI scores at 6 weeks and at subsequent visits compared with preoperative scores. Groups had no statistical difference in ODI scores either ($p > 0.09$).

Table 2 Complications

	Groups		*p* value	Total
	SiCaP	rh-BMP2		
Hip flexion weakness	2/15 (13.3%)	2/15 (13.3%)	1	4/30 (13.3%)
Indirect decompression not achieved	1/15 (6.7%)	1/15 (6.7%)	1	2/30 (6.7%)
Subsidence	3/15 (23%)	2/15 (13.3%)	0.626	5/30 (16.7%)
Excessive bone formation	0/13 (0%)	1/15 (6.7%)	0.541	1/28 (3.6%)
Adjacent surgery	1/13 (6.7%)	3/15 (20%)	0.370	4/28 (14.3%)

Note: Numbers are referred as number of occurrences / cases analyzed (percentage of total cases).
Abbreviations: SiCaP, silicate calcium phosphate; rh-BMP2, recombinant human bone morphogenetic protein 2.

of which in the rh-BMP2 group required a direct posterior decompression. One serious rh-BMP2 complication was observed—excessive bone formation into the foraminal space—which necessitated a direct posterior decompression to correct. In summary, four cases (13%) needed an additional minimally invasive direct decompression and addition of pedicle screws. Surgeries for adjacent segment disease occurred in four (13%) cases, one (7%) in the SiCaP and three (20%) in the rhBMP-2 group. Transient hip flexion weakness (maximum 6 week long) on the side ipsilateral to the approach was observed in four (13%) cases (two in each cohort), due to iliopsoas muscle irritation during the procedure.

Fusion Status

Fusion rates at different time points are shown in ►**Fig. 2**. 6 months after surgery, complete fusion was seen in 5 of 15 (33%) rh-BMP2 cases and only in 1 of 13 (8%) SiCaP cases ($p = 0.107$). 12 months after surgery, complete fusion was observed in 10 of 15 (67%) rh-BMP2 cases and in 7 of 13 (54%) SiCaP cases. At the final evaluation, CT showed that all patients achieved solid fusion at the index level. Progression of fusion for both groups is shown in ►**Fig. 2**, with radiographic examples included in ►**Figs. 3–6**.

Discussion

The current study evaluated clinical and radiological results between between two bone graft substitutes for ICBG in lumbar fusion with the XLIF for single-level degenerative disc disease. Despite some baseline and outcome differences (gender, complications, functional scores) observed between the groups, the study was likely not powered to detect statistical differences. As such, a weakness of the study was the relatively low patient samples (due to high cost of rh-BMP2), and the lost-to-follow-up of some patients. However, a 100% rate of bony fusion was observed at the final 36-month radiological evaluation in both groups, with substantial clinical improvements.

Additionally, a three-reviewer approach for radiographic analysis was not used. However, strict parameters in assessing fusion were used to mitigate potential reviewer bias.

In general, where conservative care fails to adequately manage symptoms related to lumbar degenerative disease with instability, painful degeneration, with or without central or foraminal stenosis, spinal fusion might be indicated. Eliminating painful instability along with decompression of neural structures are primary goals of spine fusion, and only is achieved in the presence of a complete and solid bony fusion.

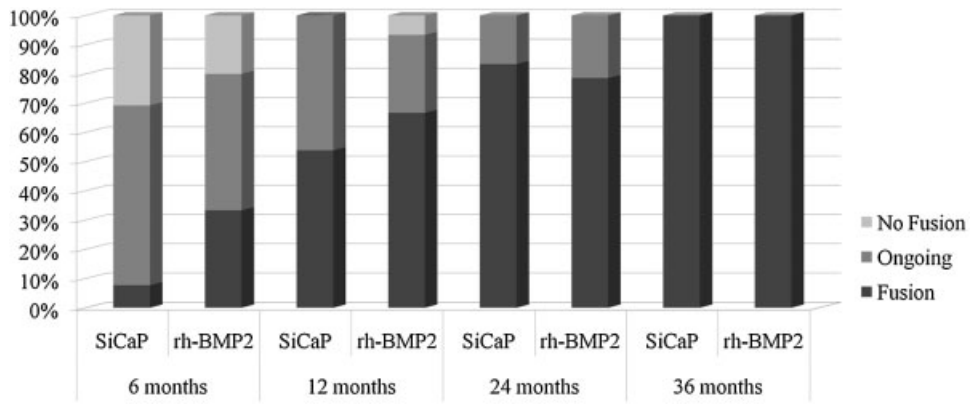

Fig. 2 Fusion status. No statistical difference was found between the two groups. 6-month, $p = 0.170$; 12-month, $p = 0.435$; 24-month, $p = 0.205$; 36-month, $p > 0.999$.

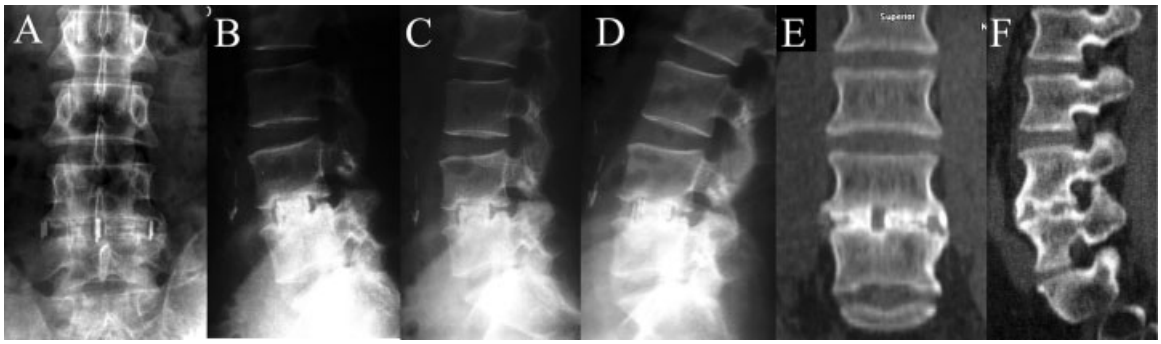

Fig. 3 Case 1. Fusion in a silicate calcium phosphate (SiCaP) case at 12-month follow-up. (A) Anteroposterior x-ray. (B) Flexion lateral x-ray. (C) Orthostatic lateral x-ray. (D) Extension lateral x-ray. (E) Coronal view of a computed tomography (CT) scan. (F) Sagittal view of a CT scan.

Successful bony fusion relies on several factors that the surgeon can manage: (1) quality of fusion site preparation; (2) patient's metabolic status; (3) a stable and loaded construct; and (4) graft (cage, bone graft). Adequate achievement of the first three factors becomes even more important when a synthetic graft is used, as synthetic materials do not inherently induce osteoinduction, osteoconduction, and osteogenesis simultaneously.

Discectomy, removal of cartilage endplate, and creation of bleeding in the cortical bone on a large surface area are pivotal in providing an optimal graft-bone interaction.[28] Next, biologic materials, either endogenous or derived, must be introduced to provide the necessary biologic environment for bone growth, which includes precursor cells (osteogenesis), growth factors (osteoinduction),[29] and graft revascularization. Additionally, a stable construction must exist, eliminating micromotion to prevent the occurrence of pseudoarthrosis.[30]

Since the introduction of rhBMP-2, it has been widely used in spine fusion procedures precisely for its high fusion rate allowing to avoid ICBG.[31–38] However, recent articles[33,34,36–38] have presented several complications and adverse events unique to rhBMP-2, such as uncontrolled bone formation, osteolysis, inflammation, neurological injury, and carcinogenicity. Use of rhBMP-2 other than in ALIF with LT-Cage (Medtronic) is still off-label. In this clinical study, the rates of complication between the groups were mostly similar, though with higher rates of adjacent segment disease and fewer instances of subsidence in the rh-BMP2 group. In one case (1/15; 7%), rhBMP-2 likely contributed to excessive bone formation in the neural foramen after subsidence of the interbody cage. A subsequent posterior decompression was required to remove the excessive bone and decompress the foramen.

A strong capacity to induce bone formation has been shown when using rh-BMP and, as it mimics an endogenous bioactive molecule, may even be considered a drug and should be applied with proper caution. This is particularly evident during the early inflammatory period (resorptive phase).[36] With this in mind, graft material must be safely contained within the cage or area where bone should grow, otherwise the risk for ectopic bone is introduced where the carrier migrates and the environment for bone growth has already been established. This was observed in the current series and required a second surgery to correct.

The synthetic bone graft substitute used in this study has silicate substitution (0.8%) of phosphate ions within a ceramic. A previous analysis of this material has found it to be a stable osteoconductive scaffold, displaying resorption/remodeling of both scaffold and new bone.[39] The silicate

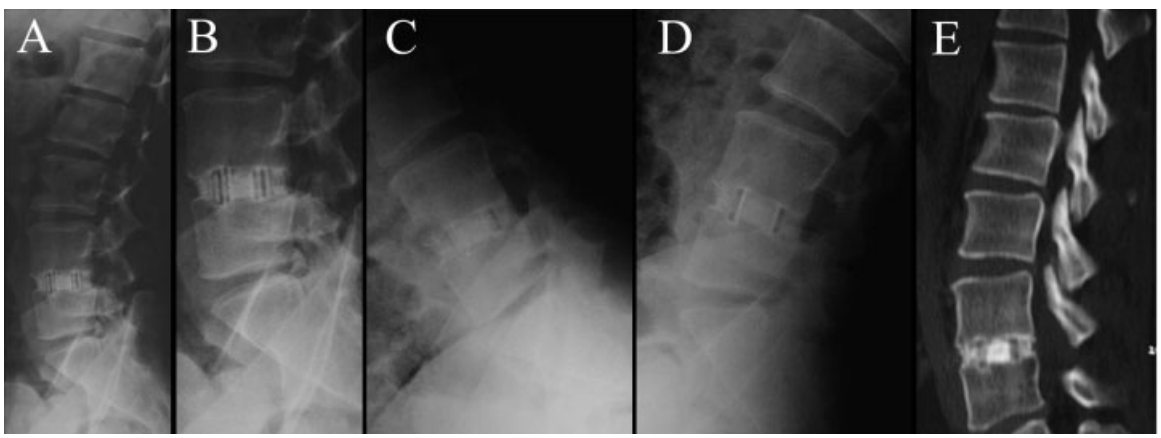

Fig. 4 Case 2. Solid fusion in a silicate calcium phosphate (SiCaP) case at 36-month follow-up. (A) Lumbar spine, lateral x-ray. (B) L4/L5 segment, lateral x-ray. (C) Flexion lateral x-ray. (D) Flexion lateral x-ray. (E) Sagittal view of a computed tomography scan.

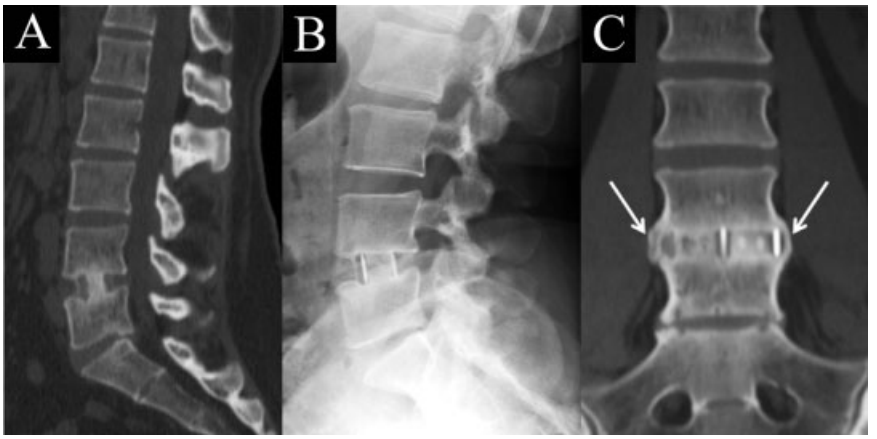

Fig. 5 Case 3. Early fusion in rh-BMP2 case. (A) Sagittal view of a computed tomography (CT) scan at 6 months. (B) Lateral x-ray at 9 months. (C) Coronal view of a CT scan at 12 months. Note bilateral sentinel signs (white arrows).

substitute appears to act as a good osteoinducer, which leads to hastened upregulation of osteoblast proliferation and differentiation, extracellular matrix production, and earlier mineralization of the new tissue.[39,40] The osteogenesis following SiCaP usage was even considered equivalent to that of autograft.[41] Of note, Wheeler et al performed a histologic examination that revealed regenerated bone tissue with SiCaP without an inflammatory response without supplemental fixation with autogenous graft.[41] In a separate clinical trial[21] with posterolateral fusion, SiCaP did not result in the complications seen in either ICBG harvesting or BMP use but the nonunion rate was 24% after 24 months. The differences between those and the results of the current study (0% pseudoarthrosis rate) are likely attributable to the favorable characteristics of XLIF. Through the lateral approach, the surgeon has a direct access to the disc space and the possibility for a wide discectomy with extensive superior and inferior endplate preparation.[27,42] In addition, the interbody cage used in the procedure spans the intervertebral space, resting on the cortical bone of the ring apophysis. This design has been shown to provide the highest amount of reduction in range of motion with a stand-alone device, compared with other interbody constructs.[43] Additionally, the wide apertures of the cage allow for a large surface area for bony growth throughout the cage and disc space. The lack of posterior access–related complications is a benefit of XLIF, but both surgeon and patient have to be aware of possible adverse events, whether major or minor.[3,44,45] The occurrence of subsidence is a concern but does not always lead to restenosis or persistent symptoms. A small degree of subsidence is relatively common in interbody fusion, where mild settling is concurrent with bone remodeling. Higher grades and rates of subsidence, however, are more common in stand-alone constructs and can be largely avoided by using a cage with a wider footprint area.[4,46–50]

Literature reporting bony fusion in XLIF is encouraging, even without the use of either ICBG or rh-BMP2. Rodgers et al[51] reported that 66 XLIF patients treated at 1 to 3 levels with different non-ICBG bone grafts (i.e., a synthetic bone graft, different than those mentioned previously) achieved a 97% rate of fusion at 1 year after surgery. Using synthetic bone graft substitutes, Amaral et al[5] similarly showed a 94% rate of fusion in an 80 XLIF level (46 patients) retrospective series. A lower (87%) yet still high fusion rate if compared with fusion rates in series in which ICBG was used,[52–54] was found by Marchi et al[46] when using synthetic bone graft substitute in stand-alone XLIF for degenerative low-grade spondylolisthesis in 52 spine levels.

Several other articles using rh-BMP2 in XLIF have reported a fusion rate of 100% when treating different thoracolumbar

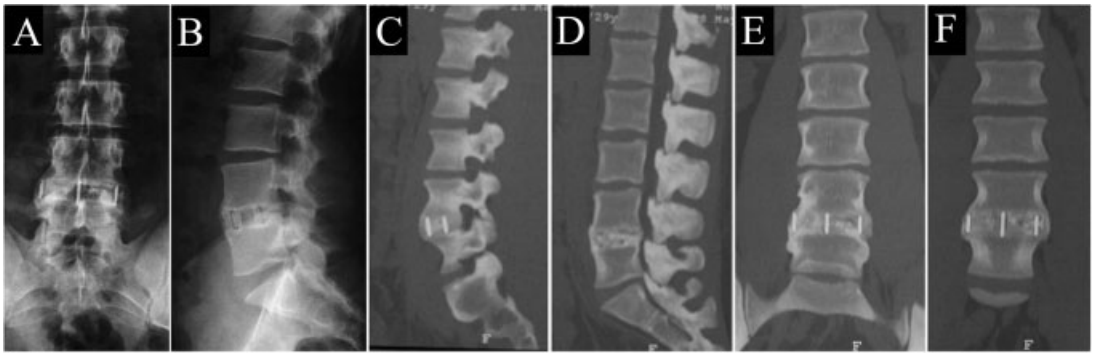

Fig. 6 Case 4. Solid fusion at 36 months in an rh-BMP2 case. (A) Anteroposterior x-ray. (B) Lateral x-ray. (C, D) Sagittal views of a computed tomography (CT) scan. (E, F) Coronal views of a CT scan.

pathologies,[55,56] or single-level degenerative disc disease,[57] and a fusion rate between 91 to 98% when treating degenerative scoliosis.[7,51,58] Other authors[9,59] have reported a combined use of rh-BMP2, demineralized bone matrix, and synthetic bone grafts substitutes in XLIF and have found fusion rates between 91 to 100%.

Conversely, autograft—being considered the gold standard graft material—has been shown to perform less favorably than rh-BMP2 in other high-quality comparative studies in terms of fusion rate in posterolateral fusion,[52] transforaminal lumbar interbody fusion,[53] and ALIF.[54]

Several factors may have been important in contextualizing the findings of this study, and these results do not necessarily predict similar results with other surgical approaches or in other conditions[1]: the surgical procedure allowed for a wide preparation of the endplates and opening of osteogenic pathways[2]; enrollment was based on healthy patients without metabolic conditions[3]; interbody cages were utilized with wide bone-graft contact, tight graft packing, and avoidance of voids[4]; and biomechanically stable constructs were used.

Conclusions

In stand-alone single-level XLIF, a synthetic silicate calcium phosphate bone graft substiture resulted in equal (100%) long-term fusion rates compared with rh-BMP2 without causing any graft–related complications, and thus might be considered an effective and less expensive option for lateral interbody fusion.

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Conflict of Interest

Prof. Dr. Luiz Pimenta is consultant to NuVasive.

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