A prospective consecutive study of instrumented posterolateral lumbar fusion using synthetic hydroxyapatite (Bongros®-HA) as a bone graft extender

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Abstract: A prospective, single institution, clinical case-matched, radiographic study was undertaken. Thirty-two patients underwent posterior lumbar interbody fusion with cages containing laminectomized bone chips and posterolateral lumbar fusion with pedicle screws. Autogenous bone graft (3 mL) plus 3 mL of hydroxyapatite was placed in one side of a posterolateral gutter, and 6 mL of autogenous iliac bone graft was placed on the other side. Bony union, volumes of fusion mass, and bone absorption rates were postoperatively evaluated using simple radiographs and 3D-CT scans. Average postoperative Lenke scores at 3 and 6 months in the hydroxyapatite group were statistically higher than in the autograft group, but at 12 months no difference was found between the hydroxyapatite and autograft groups in terms of fusion rate. Complete fusion rates by 3D-CT were 86.7% in the hydroxyapatite group and 88.9% in the autograft group, which are not significantly different. Volumes of fusion mass and bone absorption rates at 12 months were 2.35 mL in the hydroxyapatite group and 1.31 mL in the autograft group. The mean fusion mass volume was greater in the hydroxyapatite group than in the autograft group. Lumbar posterolateral fusion using a mixture of hydroxyapatite artificial bone and autogenous bone graft showed good bony union similar to that shown with autogenous bone only. This study suggests that hydroxyapatite bone chips could be used usefully as a bone-graft extender in short-segment posterolateral spinal fusion. © 2008 Wiley Periodicals, Inc. J Biomed Mater Res 90A: 804–810, 2009

Key words: hydroxyapatite artificial bone; bone graft; fusion rate; lumbar posterolateral fusion; prospective study

INTRODUCTION

Posterolateral intertransverse process lumbar spine fusion is commonly used to treat degenerative spinal disorders, and an autogenous iliac bone graft is frequently used to enhance fusion. However, although autogenous bone grafts are the gold standard for obtaining spinal fusion,[1,2] harvesting bone causes definite morbidity such as infection, pain, blood loss, arterial injury, nerve injury, and cosmetic deformities.[3] Moreover, autogenous bone harvesting is limited in volume and thus available graft may be insufficient, especially in cases requiring multiple segment fusions. For example, posterolateral fusions demand ~15 mL of compacted bone per fused level per side,[4] and this volume of bone cannot typically be obtained from locally decompressed laminar or facet joints.[5]

Allografts are used to supplement autogenous bone graft material and are readily available in large volumes. However, banked allograft bone presents the risk of viral contamination, although the risk is small. The roles of bone graft substitutes are to occupy the defect initially and to facilitate replacement by naive bone.[6] Therefore, to fulfill these requirements, a good bone graft substitute should be bioactive, osteoconductive, and biodegradable.[7,8]

Numerous synthetic materials have been evaluated as substitutes for the autogenous iliac bone grafts required during spinal fusion. Hydroxyapatite

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(HA) is the most widely investigated material and is currently used as a bone graft substitute. Moreover, synthetic HA has some advantages over coralline HA as its pore size and porosity can be controlled during manufacture.

Bongros®-HA is a synthetic HA that has been shown to be an effective bone graft substitute in studies in rabbits[9] and dogs. In this study, substitution with a synthetic bone graft substitute, HA (Bongros®-HA), was prospectively investigated in 32 patients. This study was undertaken to evaluate whether HA bone chips plus autograft are equivalent to autograft alone when used to perform short-segmental posterolateral spinal fusion.

MATERIALS AND METHODS

Bongros®-HA

Bongros®-HA is made of highly pure synthetic hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and has a trabecular structure that resembles the 3D interconnected pore structure of human cancellous bone (pore size 300 μm) with 80% porosity. Particle sizes range from 3.0 to 6.0 mm (Fig. 1).

This prospective, single institution, randomized study of autogenous iliac crest bone grafts alone (control) and a Bongros®-HA (Bioalpha, Seungnam, Korea) plus autogenous iliac crest bone graft mixture was conducted in the setting of instrumented posterolateral fusion. Between May 2004 and May 2005, 33 consecutive patients with degenerative spine disease including spinal stenosis, or Grade I or Grade II spondylolisthesis were prospectively enrolled and managed by decompression and one- or two-level pedicle screw instrumented fusion. This study was carried out with the approval of the institutional review board of Seoul National University Hospital and the Korea Food and Drug Administration. Informed consent was requested and obtained from all participants. The inclusion criteria were one- and two-level lumbar posterior interbody fusion and posterolateral fusion with pedicle screw fixation, the exclusion criteria were pregnancy, malignancy, infection, abnormal laboratory findings, a liver function abnormality, age over 75 years or under 18 years, or metabolic bone disease contraindicating spinal instrumentation or with the potential of inhibiting osteogenesis. Patients with >50% anterior translation of the cranial vertebral body or >25° of angular motion on flexion/extension films were also excluded. The senior author prospectively and independently assessed the extent of the fusions and decompressions when the patients were admitted.

Surgical techniques

All patients underwent surgery under general anesthesia and were administered prophylactic antibiotics. A posterior midline exposure was carried out. Laminectomies, partial or complete medial facetectomies, discectomies, and transpedicular screw/rod instrumentation (Solco, Seoul) were performed on all patients. Bone harvested locally during decompression was stripped of all soft tissue before being morselized into small bone pieces. These were then placed into the disc space using titanium alloy cages (Solco, Seoul). Autogenous iliac crest bone was also harvested and morselized. Care was taken to ensure adequate decortication of the transverse processes and lateral facet surfaces before the placement of autogenous bone grafts and HA + autograft mixtures (HA : autograft = 50 : 50).[10–12]

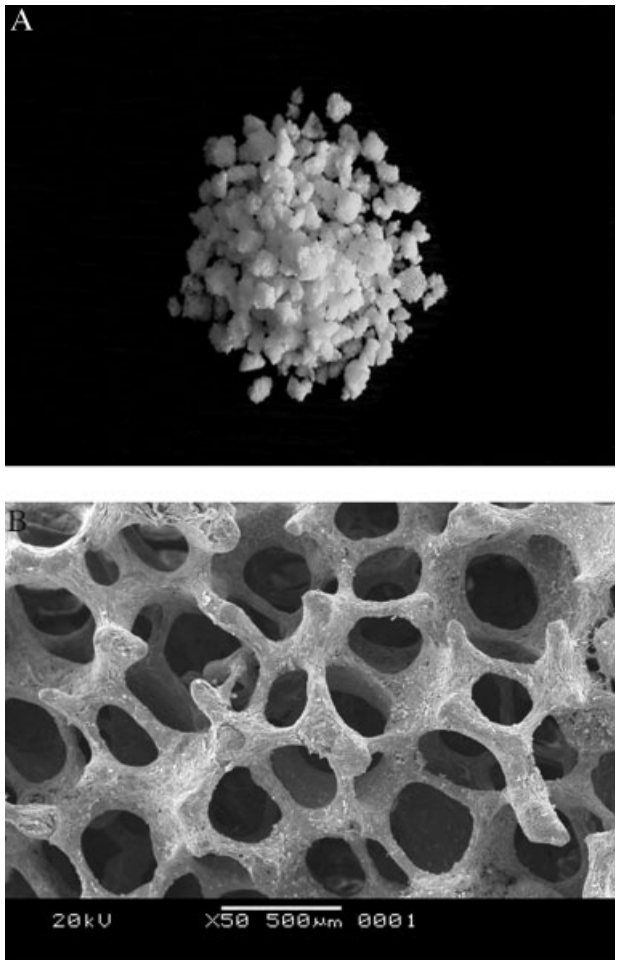

Figure 1. Bongros®-HA. (A) Gross appearance of Bongros®-HA. (B) SEM image of Bongros®-HA.

The test material (HA + autogenous iliac bone) was inserted into one side and the control material (autogenous iliac bone) was inserted into the other side in each patient in a random manner. Thus, individual patients served as controls[13] during the evaluation of the effectiveness of HA as a bone graft extender. Autogenous iliac bone (6 mL; control) was implanted on one side of the intertransverse process area and 3 mL of HA with 3 mL of iliac crest autograft was implanted contralaterally (test; Fig. 2). The postoperative management protocol used was the same for all patients.

Perioperative pain was controlled using parenteral and/or oral narcotic medications as required by the patient and according to the judgment of the treating physician.

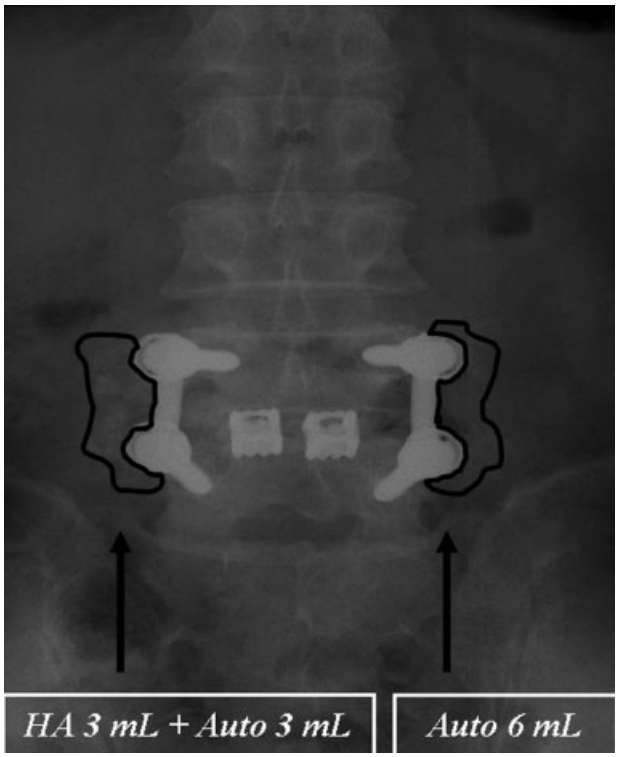

Figure 2. Autogenous iliac bone (6 mL, control) was implanted on one side of the intertransverse process area and 3 mL of Bongros®-HA with 3 mL of iliac crest autograft was implanted contralaterally (test).

Clinical and radiological assessment

Radiographic assessments of fusion and instability in the standing lumbosacral anteroposterior, standing lateral, standing lateral flexion, and standing lateral extension positions were made at 3, 6, and 12 months after surgery. 3D thin cut (1 mm) CT images with axial, sagittal, and coronal reconstructions were obtained 12 months after surgery (Fig. 3). Two independent spine surgeons assessed follow-up radiographs. CT assessments of fusion included assessments of continuous trabecular bone between intertransverse processes, cortication at the peripheral edges of the fusion masses, and the absence of an identifiable radiographic cleft.[14] Surgical sites were considered fused when both observers found no radiographic evidence of nonunion. Fusion on each side was defined as bridging at all levels. Suspected discontinuities at any fusion level or the presence of any apparent gaps in fusion masses on posteroanterior radiographs were classified as nonunion.

Fusion was classified using the Lenke system[15] at 3, 6, and 12 months after surgery (Table I). At 12 months after surgery, the sizes of the fusion masses on both sides of the vertebra were compared using 3D-CT scans and calculated using Rapidia software (version 2.8, Infinitt, Seoul). To measure the volume of the fusion mass, sequential CT scans with a 1-mm collimation and 1-mm scan spacing were obtained at 12 months after surgery. Two independent spine surgeons measured the area of the fusion mass using the manual cursor technique, by tracing from the center of the transverse process of the upper vertebral level to the center of the transverse process of the lower vertebral level. The volume of the fusion mass was summated at each cross-sectional volume which was estimated using the cross-sectional area of 1 mm. If the volume of the fusion mass of autograft was A, the resorption rate of the autograft (%) was ((6-A)/6)100. If the volume of the fusion mass of HA + autograft was B, the resorption rate of the HA (%) was ((3-(B-A/2))/3)100 because the volume HA fusion mass was (B-A/2) and the HA inserted was 3 mL.

Vital signs, subjective symptoms, and laboratory results were evaluated preoperatively and at 3-month intervals postoperatively. Paired-sample and independent samples t tests were performed, and frequencies were calculated to compare treatments. Interobserver and intraobserver measurement variabilities were analyzed. Statistical significance was accepted at the $p < 0.05$ level, and analyses were performed using SPSS Ver. 11.0.

RESULTS

With one exception, all 32 patients were followed for 12 months postoperatively, and 46 segments were checked in the 12-month radiographs and 45 segments in the 12-month CT scans. Patients' age averaged 61.4 years (range, 37–75 years) and included 20 women and 12 men (Table II). Intra-

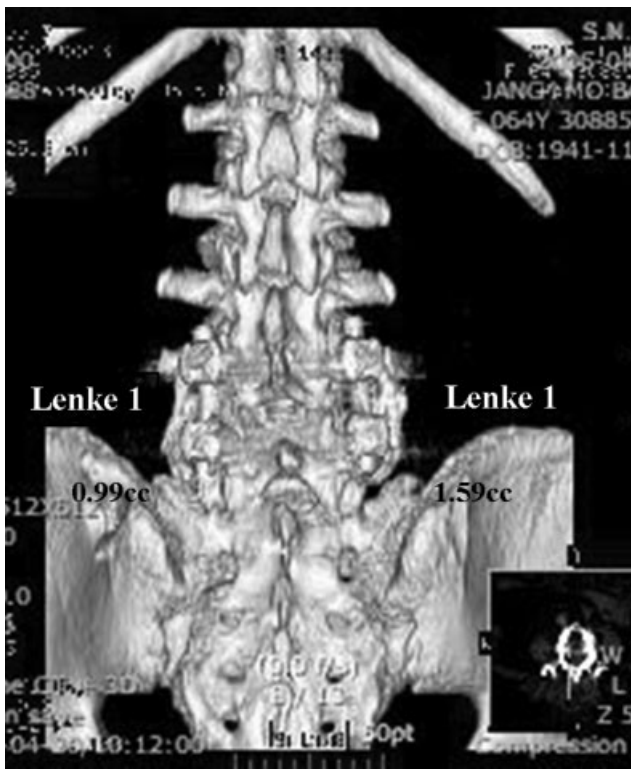

Figure 3. 3D thin cut (1 mm) CT images with axial, sagittal, and coronal reconstructions were obtained 12 months after surgery.

TABLE I
Lenke Score Used for Evaluation of the Radiographs

Lenke score	Description
1	Definitive evidence of contiguous bridging trabecular bone between the transverse processes without evidence of radiolucencies: a solid fusion
2	Thin unilateral fusion mass but probably solid union
3	Evidence of bridging bone extending from the transverse processes but contain radiolucencies, indicating a probable nonunion
4	Sparse fragments of bone between the transverse processes without evidence of fusion: a definite nonunion

and interobserver measurements were found to be highly correlated ($r = 0.97$ and 0.96, respectively).

The average Lenke score by 3-month follow-up radiography in the autograft group (1.23) was significantly lower than that of the HA + autograft mixture group (1.89; $p < 0.01$), as were Lenke scores at 6-month follow-ups (1.04 vs. 1.53; $p < 0.01$), but not at 12 months (1.02 vs. 1.04; $p = 0.323$; Table III). The number of levels that were considered to show complete fusion at 12 months was 40 (88.9%) in the autograft group and 39 (86.7%) in the HA + autograft group, which was not significantly different. For the interbody space containing cages the fusion rate with the local laminectomy bone was 93.3%, which was slightly higher than those of the autograft and HA + autograft groups, but without statistical significance.

TABLE II
Patient Characteristics and Fusion Levels

Variables	Numbers of Cases (Levels)	% of Cases (Levels)
Sex		
Male	12 (19)	37.5 (40.4)
Female	20 (28)	62.5 (59.6)
Total	32 (47)	100 (100)
Age		
30–39	1 (2)	3.1 (4.3)
40–49	4 (4)	12.5 (8.5)
50–59	5 (7)	15.6 (14.9)
60–69	16 (24)	50.0 (51.1)
70+	6 (10)	18.8 (21.3)
Total	32 (47)	100 (100)
Level		
L2-3	(1)	(2.1)
L3-4	(14)	(29.8)
L4-5	(29)	(61.7)
L5-S1	(3)	(6.4)
Total	(47)	(100)
HA insertion site		
Right	(19)	(40.4)
Left	(28)	(59.6)
Total	(47)	(100)

TABLE III
Paired Samples Statistics

Variables		Mean (±Std. Deviation)	*N*	*p*-value
3 Month	Auto	1.23 ± 0.42	47	$p < 0.01$
	HA	1.89 ± 0.31	47	
6 Month	Auto	1.04 ± 0.20	47	$p < 0.01$
	HA	1.53 ± 0.50	47	
12 Month	Auto	1.04 ± 0.20	46	$p = 0.323$
	HA	1.02 ± 0.14	46	

Both the mean fusion mass volume and the mean fusion mass resorption rate as determined by 3D-CT were significantly different in the groups at 12 months postoperatively. The mean volume in the autograft group (1.31 mL) was significantly lower ($p < 0.01$) than in the HA + autograft group (2.35 mL), and the resorption rate in the autograft group (78.2%) was significantly higher ($p < 0.01$) than in the HA + autograft group (60.8%; Table IV). The resorption rate of HA was 43.5% and relative resorption rate of HA over autograft was 55.6%.

The characteristics and differences revealed by comparing images from cases with fixation at one level with those with fixation at two levels are described in Table V. The overall results for one and two level fixation were not different.

No definite postoperative complications, such as, infection, abnormal vital signs or abnormal laboratory findings, including calcium and phosphorous levels were observed in these patients.

DISCUSSION

Calcium phosphate bone graft substitutes like HA and tricalcium phosphate, which are currently widely used, should be used in combination with autogenous bone in posterolateral spinal fusion because the posterolateral region of the spine, especially

TABLE IV
Paired Sample Statistics for CT Lenke Scores, CT Volumes (mm^3), and CT Resorption Rates (%) at 12 Months

Variables		Mean (±Std. Deviation)	N	*p*-value
CT Lenke score	Auto	1.11 ± 0.32	45	0.840
	HA	1.13 ± 0.34	45	
CT Volume (mm^3)	Auto	1308.2 ± 587.6	45	$p < 0.01$
	HA	2351.2 ± 766.8	45	
Resorption rate of fusion mass (%)	Auto	78.2 ± 9.17	45	$p < 0.01$
	HA	60.8 ± 13.28	45	

TABLE V
Comparison of the Results of 12-Month CT Scans Between One Level and Two Level Fusions

		1 Level (16 Cases)	2 Levels (29 Cases)	*p*-value
12 mo CT Lenke	Auto	1.06 ± 0.24	1.14 ± 0.36	0.30
	HA	1.18 ± 0.39	1.11 ± 0.31	0.51
12 mo CT Volume	Auto	1334.3 ± 696.7	1290.4 ± 513.7	0.0034
	HA	2147.9 ± 748.1	2489.2 ± 761.4	<0.0001
12 mo Resorption rate of fusion mass	Auto	77.8 ± 11.6	78.5 ± 8.6	0.0007
	HA	64.2 ± 12.5	58.5 ± 12.7	<0.0001

the intertransverse area, is a difficult region to obtain solid fusion when compared with intraosseous regions and the filling of bone defects.[7,16–18] In a previous study, locally harvested morselized bone from decompression sites was mixed with calcium sulfate pellets and then used for fusion at the posterolateral aspect of the lumbar spine, and satisfactory results were obtained.[5] However, previous studies have demonstrated that purely osteoconductive scaffolds, such as, coral and ceramic composites, although acceptable in less challenging environments and when used as bone graft extenders, are unsatisfactory as stand-alone substitutes in posterolateral spine fusion.[19–22] Calcium phosphate bone graft substitutes do not have osteoinductivity, and a porous structure is essential, because the graft must sustain body loading until bony ingrowth has been achieved. To obtain good bony ingrowth, a 3D interconnected porous structure is more important than pore size per se.[23] Numerous calcium phosphate bone graft substitutes, including coralline HA, synthetic HA, and tricalcium phosphate have been evaluated. Natural sea coral has been investigated as a potential bone substitute because it has a 3D porous structure, whereas coralline HA is composed primarily of HA, formed by the hydrothermal conversion of calcium carbonate.[7] However, the 3D structure of coralline HA cannot be well controlled in terms of porosity and interconnecting pore size, which differentiates Bongros®-HA from coralline HA and other synthetic HAs. Bongros®-HA has a 300 μm pore size, a porosity of 80%, and a 3D interconnecting porous structure.

Evaluation of the status of intertransverse process fusions without surgical exploration can be difficult.[24] The most widely used methods to evaluate fusion in clinical studies involve the determination of the presence of bridging bone between the transverse processes on plain anteroposterior radiographs or the measurement of the presence of motion on flexion-extension lateral radiographs.[12,24–26] However, some motion occurs even when posterolateral fusion is solid, and the amount of motion indicating pseudoarthrosis is unknown.[27,28] Moreover, the instrumentation used in this study could have obscured the bridging bone and inhibited motion on flexion-extension lateral radiographs, which is why more accurate assessments of fusion modalities are needed. Rates of intertransverse process fusion in previous reports vary from 60 to 98%,[29] which may be because of the use of plain radiography with flexion-extension views and CT scans, which are known to be inaccurate, with error rates of 20–40%.[30] However, the use of fine-cut CT scans with sagittal and coronal reconstructions may increase the accuracy of fusion assessment.[30] HA is a radio-opaque material and the radio-opacity may affect the Lenke scores of the radiographs, so that they may not represent acceleration of osseous healing. Thus it is difficult to evaluate the Lenke scores exactly using simple radiographs. The Lenke scores for HA at 3 and 6 months were significantly higher than those for autograft, and these results may be affected by the radio-opacity of HA.

The use of 3D-CT to evaluate the presence of a successful arthrodesis represents a major strength of this study, because this thin-cut CT imaging makes bony discontinuities more readily apparent.[14]

Graft resorption and incorporation are mediated by osteoclasts and osteoblasts, and are essential components of the fusion process. In humans, ~55% of the initial graft volume is lost during the first 18 months after surgery. Initial graft volumes are correlated positively with graft volumes remaining at 18 months after surgery and with graft volume loss.[31] It was interesting to find that the proportion of initial grafts that participate in fusion mass formation tends to decrease as initial graft volume increases.[31] In this study, the mean fusion mass volume of autograft was smaller than that of HA + autograft because of the poor resorption properties of HA. In fact, HA is generally considered to be minimally resorbable. Therefore, autograft resorption was significantly higher than HA + autograft resorption. The reason why autograft resorption was much higher in this study than in previous report[31] is because we compared the harvested graft volumes and fused graft volumes at 12 months after surgery and not graft volumes at 2 weeks after surgery with volumes at 18 months after surgery. Graft volumes decreased

significantly immediately after surgery because surgeons pack graft material compactly into the fusion beds. The results of this study are important because it allows surgeons to estimate future fusion volume at 12 months after surgery based on measurable preoperative graft volumes.

Several limitations of this study should be considered. First, the surgeon was aware of the study details and the color and gross morphology of HA differ from those of autograft, although the sides receiving HA were selected at random. However, this lack of blinding was compensated for by preparing the posterolateral fusion beds prior to selecting graft materials and by measuring equal volumes of HA mixture and autograft. Second, posterolateral fusion rates may be influenced by the additional posterior lumbar interbody fusion. Supplemental instrumentation may increase radiographic fusion rates,[25,26,32,33] but the additional stability achieved might equally influence the fusion rates on both HA + autograft and autograft sides. Third, additional posterior lumbar fusion was not necessary in all the patients in this study. However, HA has not previously been used in humans and the expected posterolateral spinal fusion rates could not be estimated. Therefore, this study was designed to minimize the risk of nonunion by additional posterior lumbar interbody fusion and to evaluate the effectiveness of HA by adding a relatively small amount of autograft. In this study, only 3 mL of autograft was inserted into the intertransverse processes of the test sides. This was not sufficient to achieve successful fusion without adding an effective bone graft extender. Fourth, the side-by-side design used with autograft on one intertransverse process and HA + autograft on the other, prevented comparisons of clinical outcomes based on treatment.[34] However, this study was designed to evaluate fusion rate rather than clinical outcomes and the use of 3D-CT for radiological evaluations provided us with a means of assessing fusion masses.[34] In fact, the presence of fusion on one side may affect the other, although this would only become evident if there were no instrumentation. However, instrumentation with pedicle screws and rods decreases the effect of a fusion on one side on fusion on the other. Moreover, the additional interbody fusion by the cages gave strong stability to both posterolateral fusion masses to the same degree. Although this instrumentation cannot eliminate the flaws in this study design, pedicle screw and rod fixation with additional interbody fusion with cages may minimize the effects of fusion on one side and on fusion on the other.

In this study, the combined successful fusion rate for short segment fusion was 86.7% on the HA + autograft sides. This fusion rate is similar to values previously reported in patients that received an autogenous bone graft[35,36] and calcium sulfate bone chips.[5]

Rates of adverse events and radiographic fusion rates at one year follow-up were similar for the HA + autograft and autograft control groups. These findings indicate that HA granules combined with autograft bone chips are as safe and effective as autografts for instrumented posterolateral spinal fusion surgery. Thus, morbidity and the potential complications associated with the harvesting of iliac bone graft may be reduced by using Bongros®-HA.

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