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Use of Nanocrystalline Hydroxyapatite With Autologous BMA and Local Bone in the Lumbar Spine

A Retrospective CT Analysis of Posterolateral Fusion Results

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Study Design: A retrospective, multicenter, medical record review and independent analysis of computed tomographic scans was performed in 46 patients to determine radiographic arthrodesis rates after 1-segment, 2-segment, or 3-segment instrumented posterolateral fusions (PLF) using autograft, bone marrow aspirate (BMA), and a nanocrystalline hydroxyapatite bone void filler (nHA).

Objective: To determine the radiographic arthrodesis rates after instrumented lumbar PLF using local autograft, BMA, and nHA.

Summary of Background Data: The use of iliac crest autograft in posterolateral spine fusion carries real and significant risks. Many forms of nanocrystalline hydroxyapatite have been studied in various preclinical models, but no human studies have reviewed its efficacy as a bone graft supplement in PLF.

Methods: Posterolateral arthrodesis progression was documented approximately 12 months postoperatively using a computed tomographic scan and evaluated by an independent radiologist for the presence of bridging bone. One-year postoperative clinical outcomes were assessed using the PROLO score.

Results: Radiographically, 91% patients treated exhibited bilateral or unilateral posterolateral bridging bone. Ninety-four percent of the segments treated exhibited bilateral or unilateral posterolateral bridging bone, whereas 6% segments exhibited no posterolateral bridging bone on either side. A total of 93% individual sites treated exhibited posterolateral bridging bone. In 1-segment, 2-segment, and 3-segment arthrodesis, 88%, 93%, and 100%, respectively, of individual sites exhibited radiographic bridging bone. One-year postoperative PROLO scores for 77% patients were excellent or good. There were no complications related to the posterolateral graft mass and no symptomatic nonunions.

Conclusions: The arthrodesis rates after instrumented lumbar fusion using local autograft mixed with BMA and the nHA is equivalent to the rates reported for iliac crest autograft in these indications, including stringent indications, such as 3-segment procedures. By approximately 12 months postoperatively, there was no significant difference in the rates of bridging bone between the 1-segment, 2-segment, and 3-segment procedures.

Key Words: nanocrystalline, synthetic, hydroxyapatite, posterolateral spine, lumbar fusion

(*Clin Spine Surg* 2017;30:E192–E197)

Spine fusion is one of the most common procedures performed in spinal surgery. More than 500,000 bone graft procedures are performed in the United States each year and approximately 2.2 million worldwide. The estimated cost of these procedures approaches $2.5 billion per year.[1]

Iliac crest autograft is recognized as the "gold standard" bone graft material against which all other graft materials are compared (ie, corticocancellous allograft chips, synthetic grafts, allograft demineralized bone matrix, and growth factors).[2] Iliac crest autograft provides a calcium phosphate-based scaffold for tissue attachment and remodeling, a source of extracellular matrix bound growth factors to promote bone growth, and a source of living cells that provide the cellular components for osteogenesis.[3,4]

The use of iliac crest autograft can, however, carry real and significant risks including blood loss, increased risk of infection and persistent donor site pain.[3–6] Iliac crest autograft harvest in particular is not risk free, with major and minor complications in 10% and 39% of patients, respectively.[7–10] Consideration of these risks has resulted in an increased use of bone allografts such as corticocancellous chips or demineralized bone matrix. These bone allografts account for approximately one third of the total volume of graft materials used in North America, the largest volumes of which are used in spinal fusion procedures.[6,11,12]

The risks associated with the use of large volumes of autograft and allograft bone (including reduced efficacy, increased infection rates associated with disease transmission from allograft tissue, increased cost, and limited

Received for publication July 17, 2013; accepted February 10, 2014.

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availability) has driven the development of engineered synthetic bone grafts to extend the use of the volume of autograft bone generated during decortication and site preparation.[13,14] A broad range of calcium phosphate ceramics such as hydroxyapatite, silicate substituted hydroxyapatite, tricalcium phosphate, biphasic calcium phosphate (a mixture of hydroxyapatite and tricalcium phosphate), and bio-glass can each provide osteoconductive scaffolds with excellent biocompatibility to facilitate and guide new bone formation.[15]

The subject material for this investigation was a synthetic bone graft extender comprised of nanocrystalline hydroxyapatite and a porcine collagen carrier [nHA (nanOss Bioactive); Pioneer Surgical Technology, Marquette, MI]. This material is indicated for use in non-loading sites in the pelvis and extremities as well as the posterolateral spine.

Historically, many synthetic calcium phosphates used for supporting skeletal reconstruction have been comprised of crystal grains of the mineral ranging from slightly submicrometer up to 10 μm.[16–18] In contrast, native bone tissue contains a mineral phase with hydroxyapatite crystals 50 nm and smaller.[19] This disparity between in-grain size has brought into question the ability of the synthetic materials to support new bone formation and remodelability.[20–22] In addition, numerous studies have found improved cellular response of osteogenic cells to nanosized materials, as compared with micrometer-sized material.[23–26] The nanocrystalline hydroxyapatite evaluated in this study was comprised of crystal grains of approximately 35 nm.

Although different forms of nanocrystalline hydroxyapatite have been studied in various in vitro models, no human studies have reviewed its efficacy as a bone graft supplement in posterolateral fusions (PLF). In this clinical series involving 46 patients, radiographically documented arthrodesis rates from an independent reviewer were studied after 1-segment, 2-segment, or 3-segment posterolateral instrumented arthrodesis using local autograft, nHA, and bone marrow aspirate (BMA).

METHODS

IRB approval was obtained and medical records of patients were retrospectively reviewed at each site. Information from the medical records was retrospectively reviewed and recorded.

Surgical Procedure

Laminectomies, facetectomies, and/or foraminotomies, and/or diskectomies at the treated segment or at an adjacent segment were performed in addition to the posterolateral lumbar arthrodesis. The local bone was saved for use with the nHA bone void filler. BMA was harvested locally from the vertebral body using the pedicles, or at the iliac crest. The amount of local autograft and BMA collected and mixed with nHA were not consistently recorded.

Polyether-ether-ketone interbody fusion (IBF) devices were implanted at 58 segments. IBF devices were inserted using a transforaminal lumbar interbody fusion approach in 80% of the procedures, whereas the remaining IBF devices were inserted using either a posterior lumbar interbody fusion or extreme lateral interbody fusion approach or combined with an anterior approach. Graft material was inserted in and/or around the IBF devices. In 5 of the segments, rhBMP-2 or demineralized bone matrix was also added to the graft material in the interbody space. Pedicle screw systems were used in all cases.

The amount of nHA used in the procedures varied for each patient. The average amounts used for 1-segment, 2-segment, and 3-segment procedures were 10 cm^3 (5 cm^3 per intertransverse process fusion site), 18 cm^3 (4.5 cm^3 per intertransverse process fusion site), and 24 cm^3 (4 cm^3 per intertransverse process fusion site), respectively. Bone grafts were prepared using 2 methods based on the amount of available local bone and the surgeon preferences. BMA was harvested and mixed with nHA to form a cohesive paste. This paste was either (1) compressed and placed on top of local bone autograft or (2) mixed directly with local bone autograft, compressed into a single graft mass. Prepared grafts were placed across the transverse processes of the treated segments.

Radiographic Documentation of Arthrodesis

Qualitative assessments of the computed tomographic (CT) scans for each patient were performed by a single, independent radiographic reviewer without conflicts of interest (Medical Metrics Inc., Houston, TX). An assessment of bridging trabecular bone across the posterolateral gutters, facet joints, and/or transverse processes was performed.

Posterolateral bridging assessment included the entire posterolateral gutter, from the lateral-most aspect of the transverse processes to the medial-most aspects of the facet joints. Bridging between facet joints, between transverse processes, or between facet joint and transverse process were all considered acceptable forms of bridging. Posterolateral bridging was graded separately for the right and left side of each treated segment (individual sites).

The proportion of patients with bilateral or unilateral bridging bone at each of their treated segments was calculated. The proportion of segments with bilateral or unilateral bridging bone was calculated. The proportion of individual treated sites with bridging bone was calculated as well. Patients were grouped by the number of segments treated (1-segment, 2-segment, and 3-segment procedures), sex, age (below 62 y or 62 y and above), BMI (< 30 or ≥ 30) [calculation of BMI using formula from CDC: weight (lb)/(height (in))$^2 \times 703$; http://www.cdc.gov/healthyweight/assessing/bmi] and smoking status and the proportion of individual sites with bridging bone was calculated for each group.

Clinical Documentation of Outcome

One-year postoperative clinical outcomes were assessed by the surgeon using the PROLO score. PROLO

TABLE 1. Demographic Information of the Patient Population

Variables	All Arthrodesis	1-Segment Arthrodesis	2-Segment Arthrodesis	3-Segment Arthrodesis
#Segments treated	70	29	20	21
#Patients treated	46	29	10	7
Average age (SD) (y)	58.6 (13.4)	60.0 (13.1)	55.6 (13.9)	57.3 (14.9)
Average [BMI (SD)]	30.0 (5.3)	29.3 (5.3)	29.6 (4.5)	33.5 (5.7)
#Male patients	20	10	5	5
#Female patients	26	19	5	2
Patient comorbidities				
Hypertension	4	2	0	2
Obesity (BMI $\geq$ 30)	19	12	2	5
Type II diabetes	2	1	0	1
Smoking	6	3	2	1
Chronic steroid use	1	0	1	0
Osteopenia	3	1	1	1

BMI indicates body mass index.

scores combined the patient's working and disability status. Work status was graded on a scale of 1 (completely disabled/unable to work) to 5 (working at previous occupation with no restriction). Disability status was graded on a scale of 1 (completely disabled) to 5 (able to perform all activities). A PROLO score of 9 to 10 was considered excellent; a score of 7 to 8 was considered good; a score of 5 to 6 was considered fair; and a score of 4 or less was considered poor.[27,28]

Complications

Medical and surgical complications were recorded using information from the retrospective chart review. Assessments of heterotopic bone formation, device disassembly, loosening or fracture, hardware condition, and screw fixation were performed by the independent radiologist. The independent radiologist also documented additional observations, such as bone lysis, lucency, or discontinuity within the graft or along the bone/implant interface, etc.

RESULTS

This level IV retrospective case series reports the results from a total of 46 patients, representing 70 treated segments (140 individual sites). The average age at the time of surgery was 58.6 years and the average BMI was 30.0. There were 20 males and 26 females. One-segment instrumented arthrodesis was performed in 29 patients, 2-segment instrumented arthrodesis was performed in 10 patients, and 3-segment instrumented arthrodesis was performed in 7 patients. Comorbidities for patients included hypertension, a BMI $\geq$ 30, type II diabetes, smoking, and osteopenia. Table 1 below further describes the patient demographics.

The most common diagnosis of the segments treated was degenerative disk disease. Two procedures included the removal of hardware from the previous fusion surgery at a level adjacent to the treated level. One procedure included the removal of hardware from previous fusion surgery at the treated level. Of the segments treated, L4–L5 was the most and L1–L2 the least common. Table 2 below further describes the segments treated.

Arthrodesis Rates

Posterolateral arthrodesis progression was documented approximately 1 year after surgery. Ninety-three percent (130/140) of the individually treated sites had bridging bone present (Table 3). Of the 70 treated segments, 64 (91%) exhibited bilateral bridging bone, 2 exhibited unilateral bridging bone, and 4 segments exhibited no bridging bone bilaterally. The 12 segments that were not treated with an IBF device exhibited bilateral bridging bone.

Of the 46 patients treated, 41 (89%) exhibited bilateral bone at their treated segments and 1 patient exhibited unilateral bridging bone. Three patients exhibited no bridging bone bilaterally, whereas 1 patient exhibited unilateral bridging bone at one treated segment and no bridging bone bilaterally at the second treated segment. Shown below is an example of bilateral bridging trabecular bone across the posterolateral gutters. Figures 1A and B show the coronal and sagittal views of the patient's 1-year postoperative CT scan.

There was an unexpected trend of increase in fusion rate with the increase in the number of segments fused, however this was not significant (Fisher exact test: $P = 0.813$). One-segment procedure had 88%, 2-segment

TABLE 2. Information of the Treated Segments

Variables	All Arthrodesis
Diagnosis by segment	
SPO	21
DDD	40
Stenosis w/DDD and transitional syndrome	1
Stenosis w/degenerative scoliosis	5
Stenosis w/facet arthrosis	1
Grade II SPO w/failed back syndrome	1
SPO w/adjacent level pseudoarthrosis	1
Prior surgery at treated segment	24
Treated segments	
#L1–L2	2
#L2–L3	6
#L3–L4	16
#L4–L5	29
#L5–S1	17

DDD indicates degenerative disk disease; SPO, spondylolisthesis.

TABLE 3. Independent Radiographic Assessment Results of Individual T-P Site

	#Individual Sites	#Individual Sites w/Bridging Bone
Right posterolateral gutter	70	64
Left posterolateral gutter	70	66
Total	140	130

procedures had 93%, and 3-segment procedures had 100% bridging bone for individual sites. Shown below is an example of bilateral bridging trabecular bone across the posterolateral gutters in a 3-segment procedure. Figures 2A and B show the coronal and sagittal views of the patient's 1-year postoperative CT scan.

The results of individual site arthrodesis rates of the patients grouped by sex, age, smoking, and BMI are shown in Table 4. Men had slightly higher rates of individual-site bridging bone compared with women and the rates of bridging bone were similar for patients regardless of age. Nonsmoking patients under the age of 62 had 96% of the individual sites with bridging bone. Patients with a BMI of at least 30, had bridging bone at 95% of the individual sites. Patients with comorbidities such as diabetes, chronic steroid use (with rheumatoid arthritis and lymphocytic leukemia), osteopenia, failed back syndrome, and pseudoarthrosis also had bilateral bridging bone on all segments treated. Smokers trended toward having a lower individual-site arthrodesis rate; however, this difference was not found to be significant ($P = 0.12$). Four of the 6 smokers showed bilateral bridging bone on all segments treated.

Clinical Outcomes

Of the 46 patients studied, 43 PROLO scores were recorded 12 months postoperatively. Thirty-three (77%) patients had an excellent or good PROLO score with up to 90% of the individual sites exhibiting bridging bone. As expected, the Fisher exact test revealed a decrease in PROLO scores with an increase in the number of treated segments ($P = 0.0034$); however, even with fair and poor PROLO scores, the proportion of individual sites with bridging bone was 100%. The decreased rates of bridging bone in the patients with excellent and good PROLO scores indicates that patients with pseudoarthrosis were asymptomatic 1 year after surgery. The patients with no bridging bone had excellent and good PROLO scores 1 year postoperatively.

Complications

There were 18 medical complications (Table 5). All medical complications were treated intraoperatively or before the patient's discharge from the hospital. One-year postoperative CT scans showed loose screws in 3 male patients older than 62 years at the time of surgery. Two of the men (both 3-level) had bridging bone bilaterally and the third had no bridging bone (2-level).

DISCUSSION

In this heterogenous population, independent assessment of CT scans demonstrated bilateral or unilateral bridging trabecular bone in 94% of the segments treated with nHA, BMA, and local autograft bone. There were no symptomatic nonunions and no surgical complications. Favorable clinical and functional results were observed regardless of the presence of bridging bone or the presence of comorbidities such as osteopenia, obesity, diabetes, or smoking.[29] All of the comorbidities statistically evaluated in this study failed to reject the null hypothesis showing no difference in arthrodesis rate.

The primary limitation of this study was the small sample size. The patient population did not have the power to determine statistically significant differences

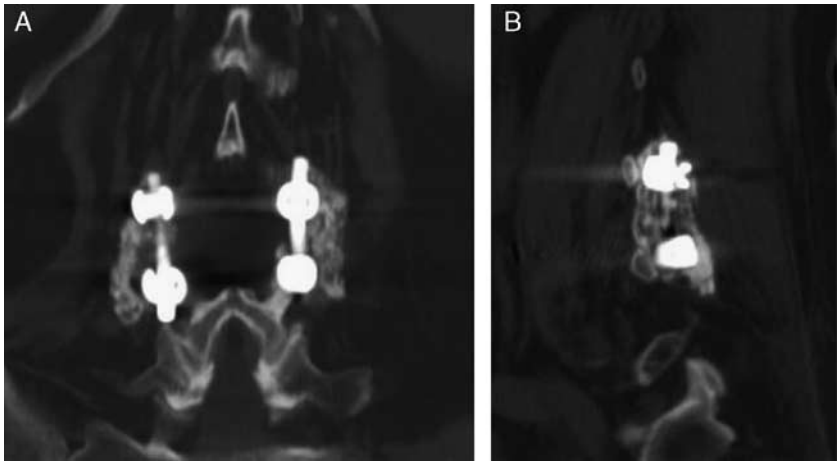

FIGURE 1. A, These images are representative of the results of a single-segment procedure. The images are from a 12-month postoperative computed tomographic scan of a 78-year-old, nonsmoking female who had a posterolateral fusion procedure at L3–L4. The independent radiologist determined that bridging bone was observed bilaterally, as seen in the coronal plane. B, The same patient from the sagittal plane.

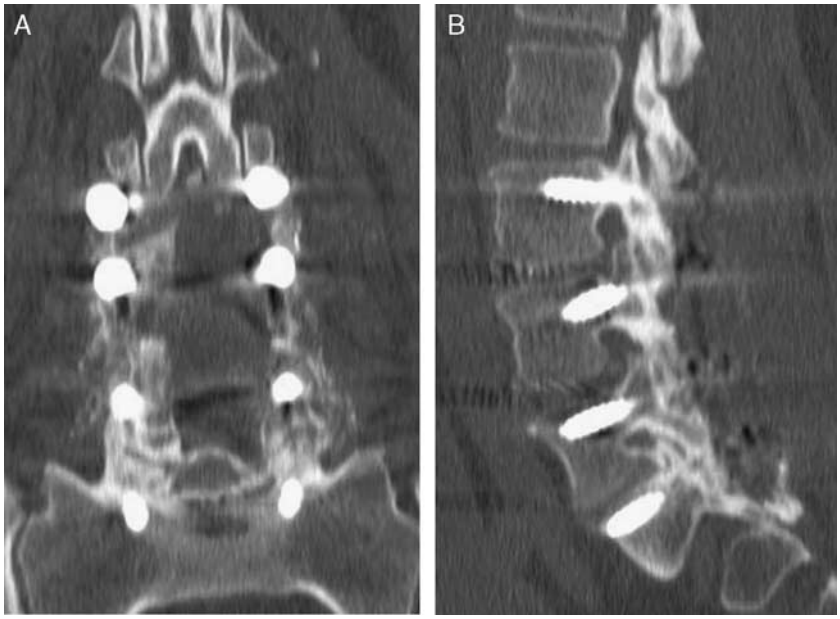

FIGURE 2. A, These images are representative of the results of a 3-segment procedure. The images are from a 16-month postoperative computed tomographic scan of a 38-year-old nonsmoking female with a body mass index of 42.9 and a history of hypertension that had a posterolateral fusion procedure at L3–S1. The independent radiologist determined that bridging bone was observed bilaterally, as seen in the coronal plane. B, The same patient from the sagittal plane.

between groups. This uncontrolled retrospective record review allows for the inclusion of many variables, such as surgical technique/instrumentation and varying medical histories, which further limits the objective analysis of each subgroup for significant differences. The independent radiographic assessment was also limited to the evaluation of the CT scans, which prevented angular and translational motion from being assessed.

Previous studies of autograft bone demonstrate varying success rates. Two years postoperatively, iliac crest autograft bone demonstrated a success rate of 84% in single-level instrumented PLF surgery.[30] In a study examining fusion results with local autograft bone in 2-level instrumented PLF surgeries, the success rate was 93% (bilateral or unilateral fusion) 2 years postoperatively.[31] Similarly, studies comparing fusion results of autograft to synthetic bone void fillers in the same patient in single-segment instrumented PLF surgeries have demonstrated success rates between 75.4% and 100% (Table 6).[32–35]

Posterolateral fusion represents the most challenging environment for bone healing in the spine. The results of this level IV retrospective case series are comparable with those seen with other synthetic bone void fillers on the market today[36] and suggest that the use of nanocrystalline hydroxyapatite with local bone and BMA leads to favorable clinical outcomes and excellent radiographic results 1 year postoperatively. These data support the use of this synthetic nHA (nanOss Bioactive; Pioneer Surgical Technology) as a bone graft extender for instrumented PLF.

TABLE 4. Independent Radiographic Assessment Results of Individual T-P Site by Group

Variables	#Individual Sites	% Individual Sites w/Bridging Bone (%)
Males	70	96
Females	70	90
1-segment arthrodesis	58	88
2-segment arthrodesis	40	93
3-segment arthrodesis	42	100
Under 62 y	74	93
Nonsmokers	54	96
<62 y		
62 y and older	66	92
Body mass index	62	95
≥ 30		
Smokers	20	85

TABLE 5. List of Medical Complications Experienced by Patients During Hospital Stay

Complications	#Patients
Intraoperative bleeding/acute anemia	7 (15%)
Intraoperative dural tear	4 (9%)
Intraoperative vascular tear	1 (2%)
Deep venous thrombosis—lower extremity	1
Infection	1
Pneumonia	1
Shortness of breath/chest pain	1
Tachycardia	1
Urinary tract infection	1

TABLE 6. Fusion Success Rates of Autograft Bone and Synthetic Bone Void Fillers

References	Procedure/Indication	F/U (y)	Fusion Success Rate Autograft	Fusion Success Rate Synthetic
Yamada et al[32]	1-segment instrumented PLF (within patient control)	1	LBG = 75.4%	Porous β-TCP ceramics + percutaneously harvested bone sticks + BMA = 83.6%
Bansal et al[33]	1-segment instrumented PLF (within patient control)	1	ICBG = 97%	90% HA + 10% β-TCP + saline + BMA = 100%
Dai et al[34]	1-segment instrumented PLF (randomized)	3	ICBG + LBG = 100%	β-TCP + LBG = 100%
Kitchel[35]	1-segment instrumented PLF with a posterior lumbar interbody fusion (within patient control)	2	ICBG = 84%	Mineralized collagen matrix + BMA = 80%

BMA indicates bone marrow aspirate; β-TCP, β tricalcium phosphate; F/U, follow-up; HA, hydroxyapatite; ICBG, iliac crest bone graft; LBG, local bone graft; PLF, posterolateral fusions.

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