Original article

Use of a novel porous hydroxyapatite bone graft substitute in postero-lateral and interbody spinal fusion: clinical and radiographic analysis at 4 year follow up

P. GIORGI, D. CAPITANI, G.R. SCHIRÒ

Department of Orthopaedic Surgery, "Niguarda Ca' Granda" Hospital, Milan, Italy

SUMMARY: ***Aims.*** *In the last years a variety of new synthetic bone graft substitutes have been developed for spinal applications, in order to avoid drawbacks related to autologous bone graft harvesting procedures. Aim of the present prospective clinical study was to evaluate the use of a novel ceramic-based hydroxyapatite bone graft substitute in form of chips, combined with autologous bone, to induce bony fusion in a series of patients undergoing posterolateral or interbody spinal fusion.*

Materials and methods. *Thirty-six patients were consecutively enrolled and prospectively evaluated. Patients underwent instrumented posterolateral or interbody spinal fusion using a porous hydroxyapatite bone graft substitute mixed with autologous bone in a 2:1 ratio. Radiological evaluations (X-Ray exams including Ferguson view or CT-scan) were performed and clinical parameters (Oswestry Disability Index and Visual Analogical Scale) were recorded at regular intervals up to 4 years follow-up. Age, gender, Body Mass Index, smoking habits, previous surgeries and post-operative complications were recorded and analyzed to find possible correlations with clinical and radiological outcomes.*

Results. *The percentage of bony fusion was around 90% in both treated groups after 1 year, and this data was confirmed at 4 years follow-up. Within each group, a statistically significant time-dependent improvement of the fusion rate ($p < 0.05$) was observed. Clinical outcomes showed statistically significant differences ($p < 0,05$) between pre-operative and post-operative time points up to 4 years follow-up. No correlations were found between age, gender, Body Mass Index, smoking habits, previous surgeries and the fusion rates.*

Conclusions. *The present study provides clinical evidences on the osteointegrative properties of the used hydroxyapatite bone graft substitute in spinal fusion applications, which use could represent a valid alternative to autologous bone harvesting procedures.*

KEY WORDS: *Bone graft substitute, Hydroxyapatite, Interbody spinal fusion, Osteointegration, Posterolateral fusion.*

INTRODUCTION

Instrumented spinal fusion is an effective treatment for symptomatic degenerative disc disease. Many studies have demonstrated an improvement of spinal fusion outcomes when performed by the use of instrumentations, compared with conservative treatments[13]. However, failure of bony fusion (also referred to as pseudoarthrosis) still represents a significant challenge in spinal surgery, occurring in 5-35% of patients[4,12]. Instrumentation systems (fixator devices, pedicle screws, rods, etc.) are employed to provide added

Correspondence: Dr. Giuseppe Rosario Schirò, Department of Orthopaedic Surgery, Niguarda Ca' Granda Hospital, piazza Ospedale Maggiore 3, 20162 Milan (MI), Italy, ph. +39-(0)2-6444789, e-mail: giusepper.schiro@gmail.com

Progress in Neuroscience 2015; 3 (1-4): 117-124. *ISSN: 2240-5127*

doi: 10.14588/PiN.2015.Giorgi.117

LIST OF ACRONYMS AND ABBREVIATIONS: **AB** = Autologous Bone; **ANOVA** = ANalysis Of VAriance; **BMI** = Body Mass Index; **HA** = Hydroxyapatite; **mos** = months; **ODI** = Oswestry Disease Index; **PEEK** = PolyEther Ether Ketone; **post-op.** = post-operative period; **pre-op.** = pre-operative period; **T-PAL** = Transforaminal Posterior Atraumatic Lumbar; **VAS** = Visual Analog Scale; **wks** = weeks; **yrs** = years.

stability and improve the fusion rates, however the use of bone graft material is required in order to fuse adjacent vertebrae together, thus improving instrumentation stability and providing long-term support[3,12,18]. Because of its osteoinductive, osteoconductive and osteogenic properties, autologous bone graft is still considered the "gold standard" approach for achieving a successful spinal fusion[3,12,16,18]. Autologous bone can be harvested from laminectomy, however a relatively limited quantity allow the need of other sources for autologous bone retrieval, i.e. from the iliac crest, with possible drawbacks related, such as donor-site morbidity, post-operative pain, haematoma and infections, longer operative periods, increased estimated blood loss and longer hospital stay, which may occur in as many as 25-30% of patients, thus limiting its use[16]. The alternative use of allograft bone (harvested from cadaveric donors) avoids donor site complications, however this procedure is often related to potential risks of serious disease transmissions, bacterial contaminations or host-related reactions[8]. In order to avoid all these issues, a variety of synthetic bone graft substitutes, with biochemical and mechanical properties comparable to the human bone components, have been developed and proposed on the market[18]. Among these, hydroxyapatite, a ceramic-based material with a porous structure, has been widely investigated for its biological features and biomechanical structure. Hydroxyapatite represents the most important constituent of the human bone component, being present in percentages ranging between 65% and 80%. The characteristic porosity of this material allows anchorage sites and mechanical stability for mesenchimal stem cells to differentiate into new bone tissue, thus providing a structural support for new bone ingrowth and tissue remodelling[3,12,16,18]. A number of clinical studies have been published reporting the beneficial effects of HA bone substitutes applications in posterolateral fusion for patients with scoliosis[7,17], as well as for anterior interbody fusion of the cervical spine[10,19]. However, no controlled prospective study has ever been conducted to evaluate the performance of these materials in instrumented posterolateral and interbody spinal fusion.

Aim of this clinical study was to analyse the osteointegrative properties of a novel biomimetic and porous ceramic-based HA bone graft substitute, with chemical and microstructure features which are very similar to the mineral component of human bones, in instrumented single or multi-level posterolateral or interbody spinal fusion in a patient population with degenerative disc disease. The study was set up as a prospective and controlled trial to determine the clinical and radiographic outcomes up to 4 years follow-up.

MATERIALS AND METHODS

Clinical study design. In this prospective controlled study we consecutively screened and enrolled patients who had indications for single or multi-level instrumented posterolateral or interbody spinal fusion due to symptomatic degenerative disc disease.

The study was approved by the Medical Ethic Committee of Niguarda Hospital (Milan, Italy) and informed consent was obtained from each patient (in conformity to the 1975 Declaration of Helsinkj). Specific inclusion variables included: skeletally mature subjects, at least 18 years of age at the time of surgery with symptomatic spinal degenerative disc disease, severe low back pain for at least 6 months, with sciatica and/or neurogenic claudication; subjects who had indication for posterolateral or interbody fusion as confirmed by plain radiography on antero-posterior and lateral view in the neutral standing position and dynamic views (flexion and extension lateral radiographs) and supplementary magnetic resonance with or without computed tomography imaging; one or more motion segment(s) to be fused between T12 and S1; subjects who were unresponding to previously administered conservative therapy (i.e. bed rest, bracing, anti-inflammatory medications, physical therapy); subjects who personally signed and dated informed consent document prior to any study-related procedures. Exclusion criteria were: alcohol or drugs abuse; subjects who were undergoing drug therapy resulting in impaired bone regeneration (use of corticosteroids, chemotherapeutic drugs, etc.);

active or systemic local infections, active malignancy, metabolic or haematic disorders; pregnancy; history of psychosocial disorders that could prevent accurate completion of self reporting assessment scales. All patients underwent decompression and spinal stabilization with the use of instrumented fixation supports (pedicle screws/rods) in addition to bone graft material, in at least 1 spinal level between T12 and S1. Bone graft material was prepared as a mixture of a commercially available HA bone graft substitute (EngiPore, provided by Fin-Ceramica Faenza SpA, Faenza, Italy) in form of chips (size 2.5-4.0 mm) and autologous bone (HA/AB ratio 2:1). All the patients were divided in 2 groups based on the type of arthrodesis performed: posterolateral (group A) or interbody fusion (group B) (with transforaminal approach). Patients were evaluated preoperatively: baseline characteristics (age, gender, Body Mass Index, smoking habits, previous surgical procedures undertaken) were recorded before surgery. The number of vertebral levels fused during surgery were also recorded. Patients were followed post-surgery until discharge. Follow-up visits were conducted at 6 weeks, 3, 6, 12 and 48 months.

❒ **Surgical Techniques.** All the surgical procedures were performed by the same senior surgeon using open posterior approach to the thoraco-lumbar spine. Patients were preoperatively treated with intravenous antibiotic treatment (Cefazolin 3 gr, total amount).
In both groups pedicle screw instrumentation (URS system, DePuy-Synthes) was used.
In group A, wide laminectomy combined with medial facetectomy was performed, obtaining a bleeding bone fusion bed through decortication of the posterolateral area from the transverse processes throughout the posterior aspect of facet joints. 5 cc of EngiPore (Fin-Ceramica Faenza SpA, Faenza, Italy) were mixed with morcelized bone (harvested during laminectomy) in a 2:1 ratio (Figure 1) and used for posterolateral fusion. In group B, after unilateral hemilaminectomy, discectomy was performed with transforaminal approach and intervertebral spaces were accurately prepared. Endplate preparation was performed using custom-designed down pushing curettes and endplate scrapers.
All of the cartilaginous endplates were removed, the bone endplates were decorticated but left structurally intact. 5 cc of EngiPore in form of chips (size 2.5-4.0 mm) were mixed with local bone (harvested during hemilaminectomy) in a 2:1 ratio. The mixture was placed 1) in the anterior portion of the interbody space and 2) used to fill the PEEK cage (with lordotic angle of 5°) (T-PAL spacer system, DePuy Synthes) prior to its placement (Figure 2). The PEEK cage was then placed in the interbody space to allow bony fusion. In all the cases, the screw instrumentation was compressed, in order to reproduce the normal inward lordotic curvature of the spine column. The wound was sutured in three layers over two suction drainage tubes. The patients were intravenously treated with prophylactic antibiotic therapy immediately after surgery (Cefazolin 3 g, total amount) and mobilized 2 to 3 days after surgery. Lumbar brace was used for

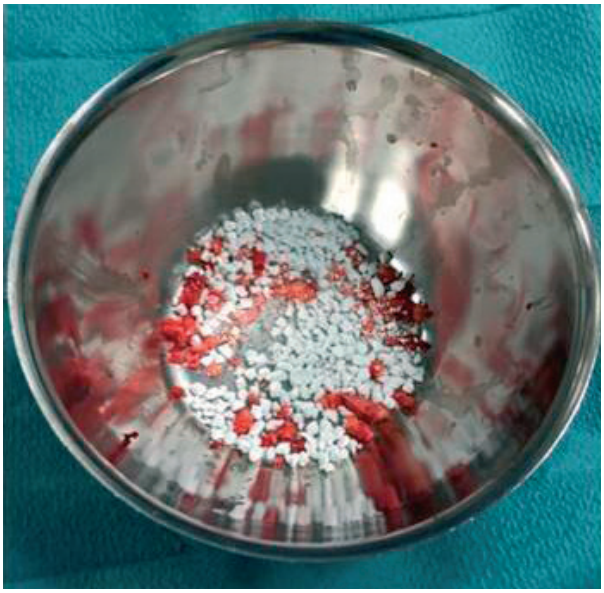


Figure 1. HA bone graft substitute Engipore in form of chips (*white*) mixed with morcelized autologous bone (*red*) (ratio 2:1). a1 a2 a3

Figure 2. Titanium cage filled with Engipore chips and autologous bone (ratio 2:1). b1 b2

Lenke classification of posterolateral fusion success	
• Grade A:	Definitely solid with bilateral trabeculated stout fusion masses present.
• Grade B:	Possibly solid with a unilateral large fusion mass and a contra-lateral small fusion mass.
• Grade C:	Probably not solid with a small fusion mass bilaterally.
• Grade D:	Definitely not solid with bone graft reabsorption or obvious pseudarthrosis bilaterally.

c1 **Table 1.** Lenke classification system.

Brantigan-Steffee classification for interbody fusion success	
• BSF-1	Radiographical pseudarthrosis is indicated by collapse of the construct, loss of disc height, vertebral slip, broken screws, displacement of the carbon cage, or significant resorption of the bone graft, or lucency visible around the periphery of the graft or cage.
• BSF-2	Radiographical locked pseudarthrosis is indicated by lucency visible in the middle of the cages with solid bone growing into the cage from each vertebral endplate.
• BSF-3	Radiographical fusion: bone bridges at least half of the fusion area with at least the density originally achieved at surgery. Radiographical fusion through one cage (half of the fusion area) is considered to be mechanically solid fusion even if there is lucency on the opposite side.

d1 **Table 2.** Brantingan-Steefe classification system.

Baseline characteristics	*Group A*	*Group B*
Patients number	19	17
Age	45-70	43-72
Gender (M/F)	8/11	7/10
BMI (kg/m^2)	22-30	19-31
Smoking subjects	7	6
Previous surgeries	1	6
Operated levels:		
- 4 levels	7	1
- 2 o 3 levels	10	7
- 1 level	2	9

e1 e2 e3 e4 **Table 3.** Baseline Characteristics of 36 patients with single or multi-level instrumented posterolateral and interbody spinal fusion for symptomatic degenerative disease. Values are expressed as min-max ranges or ratios, as appropriate.

about 1 month after surgery in all the patients. The average hospitalization period was 10 days.

❒ **Results assessment.** Clinical and radiological data were collected before and immediately after surgery, then at 6 weeks, 3 months, 6 months, 1 year and 4 years after surgery. The degree of fusion was determined by 2 independent observers using plain radiography, including antero-posterior, lateral, flexion/extension and Ferguson view or CT-scan. For group A, radiological assessment for posterolateral fusion was graded by the Lenke classification system[11] (Table 1), while Brantingan and Steefe classification[5] was used to grade interbody fusion in group B (Table 2). Fusions were considered to be successful when all the following criteria were satisfied: radiographic evidences of mature bony trabeculae bridging into the fusion area, no signs of pseudoarthrosis, no interspace between the cage and the vertebral body (Lenke A-B, Brantigan 3). Clinical evaluations were performed by an independent observer using the Oswestry Disability Index for the quantification of patient's disability for low back pain and the 10-point Visual Analog Scale for patient's pain intensity.

❒ **Statistical analysis.** Values are presented as mean values, minimum and maximum ranges, ratios or percentages, as appropriate. Analysis was performed with the use of the Friedman analysis of variance (ANOVA) test for comparisons among the two treatment groups. Differences between the two groups were analyzed by means of the Wilcoxon-matched pair test or the Mann-Whitney test, as appropriate. Correlations between clinical/radiological outcomes and the different time points were analyzed by means of the Kendall-Tau rank correlation test. The level of statistical significance was set at $p < 0.05$. Data were analyzed with the use of Statistica 6 software (StatSoft Inc, Tulsa, OK, USA).

□ RESULTS

A total of 36 patients satisfied the inclusion criteria and were enrolled in the study protocol (Table 3). 19 patients were included in group A and 17 patients in group B (range age: 45-70 in group A; 43-72 in group B). In total, there were 15 male and 21 female with a mean age of 58 years (range: 43 - 71), of which 8/11 in group A and 7/10 in group B. BMI, calculated

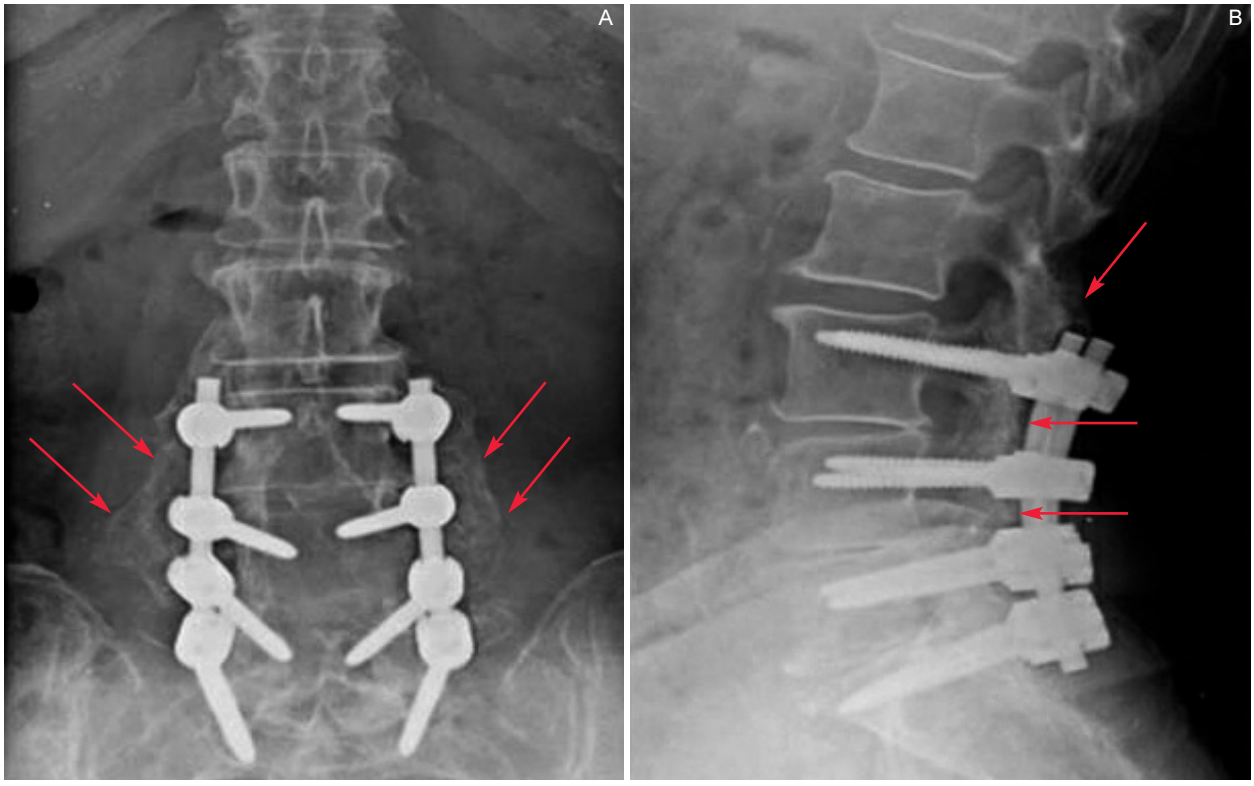
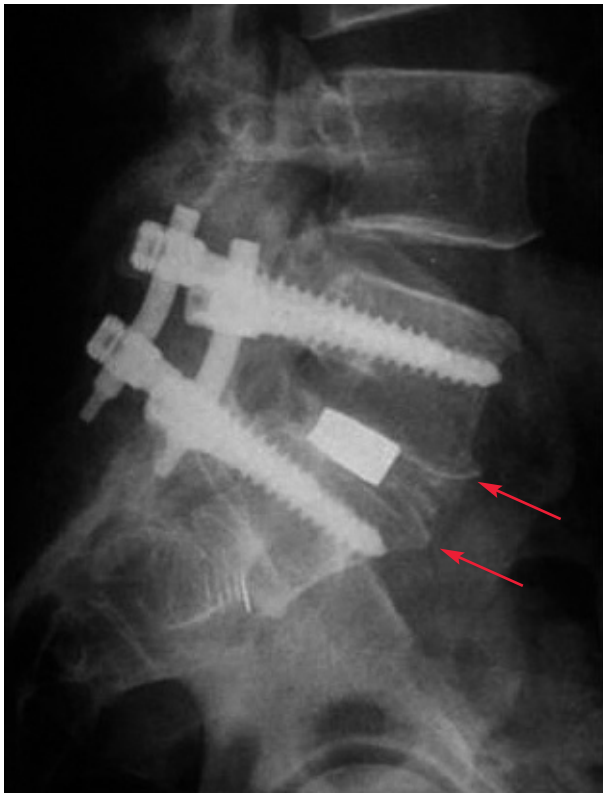


Figure 3. Example of posterior (A) and lateral (B) x-ray image showing successful posteroateral fusion as confirmed by the presence of mature bony trabeculae (*arrows*), equivalent to Lenke classification Grade A. f1 f2

dividing patient's weight in kilograms by the square of the height in meters, ranged between 22-30 in group A and 19-31 in group B, with a mean value of 25.3 kg/m^2. A total of 13 patients (7 in group A and 6 in group B) were smokers. Only one subject underwent previous surgery in group A, six in group B. 22 patients were surgically treated for lumbar stenosis and instability, 3 patients were treated for lumbar degenerative disc disease and disc herniation, 4 patients were treated for spondylolisthesis and 7 cases were treated for failed back surgery syndrome for previous spinal decompression surgery. In 8 cases long fixation (4 or more levels) was performed (7 in group A, 1 in group B), in 17 cases 2 or 3 levels were fixed (10 in group A, 7 in group B), only 11 cases (9 in group A, 9 in group B) underwent a single level of fusion. Statistical analysis performed showed no significant differences between the two groups in terms of age, gender, BMI, smoking habits, previous surgeries and successful fusions in both groups (data not shown). Radiographic images showed instrumented stability with no signs of flexion-extension, hyper-mobility and breakage in 35 out of 36 patients (one case of screw mobilization was recorded in group A and treated with surgical revision). Radiographic analysis evidenced the incorporation of EngiPore chips into the fusion mass with formation of mature bony trabeculae and no sign of pseudoarthrosis in 17 out of 19 patients in group A (Figure 3). Only 2 cases of non fusion were recorded (Table 4). In group B, successful fusion was outlined by the absence of interspaces between the cage and the vertebral bodies, no signs of pseudoarthrosis and new tissue formation in the interspaces between the vertebral bodies (Figure 4). Only 1 case of non fusion was recorded in group B (Table 4). No major complications related to the surgical procedures were recorded in both the

	Fusion	Non fusion	Fusion rate	Assessment at 4 years follow-up
Group A	17	2	89.4%	$p < 0.05$
Group B	16	1	94.1%	$p < 0.05$

Table 4. Fusion rate. g1



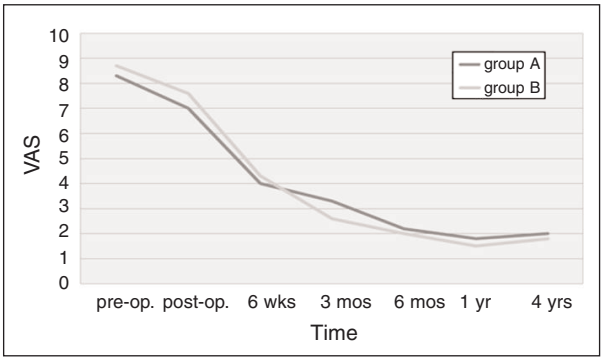
h1 **Figure 4.** X-ray image evidencing successful interbody fusion
h2 as confirmed by: absence of interspaces between the cage and
h3 the vertebral body, no signs of pseudoarthrosis and the presence
h4 of mature bony trabeculae (arrows) in the anterior intervertebral
h5 space (equivalent to Brantingan-Steffee classification level 3).

treatment groups. According to the Brantigan and Steffe or the Lenke classification systems used, the fusion rate was 89,4 % in group A and 94,1 % in group B at 4 years follow-up (Table 4). A statistically significant time-dependent fusion rate was observed within each group until 4 years follow-up ($p < 0.05$), however no differences were found between the two groups. No correlation was found among non fusion rates and the number of fused levels or the pathology treated (data not shown). ODI and VAS scores were recorded at pre-operative and post-operative intervals. In both groups, a time-dependent decrease was recorded within the first six months and this data was maintained up to 4 years follow-up (Figure 5 and 6). No statistically significant differences were recorded for ODI and VAS scores between group A and group B.

DISCUSSION

We have presented here the results of the first controlled prospective study concerning the performance of a novel ceramic-based HA bone graft substitute (EngiPore, provided by Fin-Ceramica Faenza S.p.A., Faenza, Italy), mixed with autologous bone, for applications in instrumented posterolateral and interbody spinal fusion for symptomatic degenerative disc disease. Our study demonstrate how, regardless the different surgical applications, similar radiographic fusion rates and equivalent variations of clinical outcomes have been recorded in all the patients up to 4 years follow-up.

In the last decades, a lot of new bone graft substitutes have been developed in order to reduce patient-related drawbacks due to the use of autologous or allograft bone. Several authors have supported the use of bone graft substitutes, in place of iliac crest bone harvesting, in spinal surgical procedures. In a study of Alsaleh et al.[1], comparable fusion rates, similar functional outcomes, lower complications and lower risks of donor site pain have been recorded in a number of patients undergoing posterolateral thoracolumbar



i1 **Figure 5.** Results of the VAS scores at 4 years follow up.

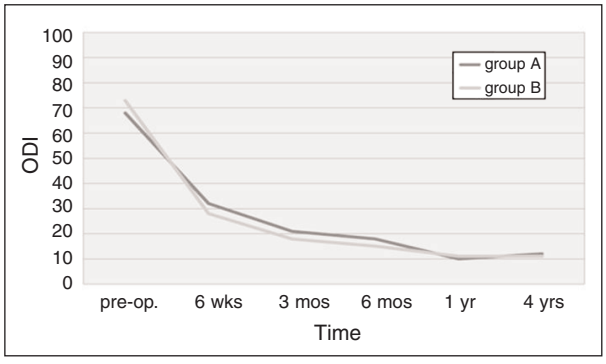


Figure 6. Results of the ODI scores at 4 years follow up. m1

spinal fusion with the use of osteoconductive bone graft extenders, compared to patients treated with autogenous iliac crest bone graft. Introduced for clinical use in the 1980s, the safety and efficacy of porous stoichiometric hydroxyapatite as bone graft substitute is nowadays supported by relevant literature data[6,9,14], which demonstrate that HA biochemical structure and mechanical properties are very similar to the human mineral component[2,15,18]. The material used in the current study (EngiPore, Fin-Ceramica SpA, Faenza, Italy) is a biomimetic and biocompatible porous stoichiometric hydroxyapatite composed of calcium ions, phosphate ions, and hydroxyl groups, which is very similar in microstructure and chemical composition to the mineral component of human vertebral bones. The trabecular structure, which resembles the mineralized phase of natural bone, is characterized of 90% porosity rate, allowing physiological fluids absorption, the promotion of cell migration and adhesion for mineral matrix synthesis and therefore offering an ideal environment for new bone formation[14]. The composition, shape and malleability properties of this material make this scaffold an ideal bone graft candidate for spinal fusion applications. Moreover, this material can be safely mixed with autologous bone, as demonstrated by no scaffold-related adverse events recorded. Demographic data (age, gender) and prognostic factors (BMI, smoking habits, previous surgeries) showed no correlations with clinical and radiological outcomes, therefore confirming the efficacy and safety of Ha mixed with autologous bone in both the surgical procedures tested.
There are some limitations in this study, which did not include a control group treated with autologous bone alone. However, these results suggest that patients receiving this treatment would have comparable clinical and radiological outcomes to patients treated with autologous bone alone, therefore representing a valid alternative to invasive procedures for autogenous bone harvesting.

□ CONCLUSIONS

This prospective and controlled study demonstrates that HA can be used as an ideal bone graft substitute in spinal applications and that it can be safely applied in combination with autologous bone. This would potentially avoid the need of autologous bone graft harvesting and, therefore, the risk of drawbacks-related side effects.

□ REFERENCES

1. Alsaleh KA, Tougas CA, Roffey DM, Wai EK. Osteoconductive bone graft extenders in posterolateral thoracolumbar spinal fusion: a systematic review. Spine 2012; 37 (16): E993-1000.
2. Baramki HG, Steffen T, Lander P, Chang M, Marchesi D. The efficacy of interconnected porous hydroxyapatite in achieving posterolateral lumbar fusion in sheep. Spine 2000; 25 (9): 1053-1060.
3. Boden SD. Overview of the biology of lumbar spine fusion and principles for selecting a bone graft substitute. Spine 2002; 27 (16 Suppl 1): S26-31.
4. Boden SD, Martin GJ Jr, Morone M, Ugbo JL, Titus L, Hutton WC. The use of coralline hydroxyapatite with bone marrow, autogenous bone graft, or osteoinductive bone protein extract for posterolateral lumbar spine fusion. Spine 1999; 24 (4): 320-327.
5. Brantigan JW, Steffee AD. A carbon fiber implant to aid interbody lumbar fusion. Two-year clinical results in the first 26 patients. Spine 1993; 18 (14): 2106-2107.
6. De Long WG, Jr., Einhorn TA, Koval K, McKee M, Smith W, Sanders R et al. Bone grafts and bone graft substitutes in orthopaedic trauma surgery. A critical analysis. J Bone Joint Surg Am 2007; 89 (3): 649-658.
7. Delécrin J, Takahashi S, Gouin F, Passuti N. A synthetic porous ceramic as a bone graft substitute in the surgical management of scoliosis: a prospective, randomized study. Spine 2000; 25 (5): 563-569.
8. Delloye C, Cornu O, Druez V, Barbier O. Bone allografts: what they can offer and what they cannot. J Bone Joint Surg Br 2007; 89 (5): 574-579.
9. Holmes RE, Bucholz RW, Mooney V. Porous hydroxyapatite as a bone graft substitute in diaphyseal defects: a histometric study. J Orthop Res 1987; 5 (1): 114-121.
10. Kim P, Wakai S, Matsuo S, Moriyama T, Kirino T. Bisegmental cervical interbody fusion using hydroxyapatite implants: surgical results and long-term observation in 70 cases. J Neurosurg. 1998; 88 (1): 21-27.
11. Lenke LG, Bridwell KH, Bullis D, Betz RR, Baldus C, Schoenecker PL. Results of in situ fusion for isthmic spondylolisthesis. J Spinal Disord 1992; 5 (4): 433-442.
12. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. Eur Spine J 2000; 9 (Suppl 1): S119-125.
13. Möller H, Hedlund R. Surgery versus conservative management in adult isthmic spondylolisthesis--a prospective randomized study: part 1. Spine 2000; 25 (13): 1711-1715.
14. Nandi SK, Roy S, Mukherjee P, Kundu B, De DK, Basu D. Orthopaedic applications of bone graft & graft substitutes: a review. Indian J Med Res 2010; 132 15-30.
15. Ohtsuki C, Kamitakahara M, Miyazaki T. Bioactive

ceramic-based materials with designed reactivity for bone tissue regeneration. J R Soc Interface 2009; 6 (Suppl 3): S349-360.

16. Park JJ, Hershman SH, Kim YH. Updates in the use of bone grafts in the lumbar spine. Bull Hosp Jt Dis 2013; 71 (1): 39-48.
17. Ransford AO, Morley T, Edgar MA, Webb P, Passuti N, Chopin D et al. Synthetic porous ceramic compared with autograft in scoliosis surgery. A prospective, randomized study of 341 patients. J Bone Joint Surg Br 1998; 80 (1): 13-18.
18. Spivak JM1, Hasharoni A. Use of hydroxyapatite in spine surgery. Eur Spine J 2001; 10 (Suppl 2): S197-204.
19. Thalgott JS, Fritts K, Giuffre JM, Timlin M. Anterior interbody fusion of the cervical spine with coralline hydroxyapatite. Spine 1999; 24 (13): 1295-1299.

Disclosure. *All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.*