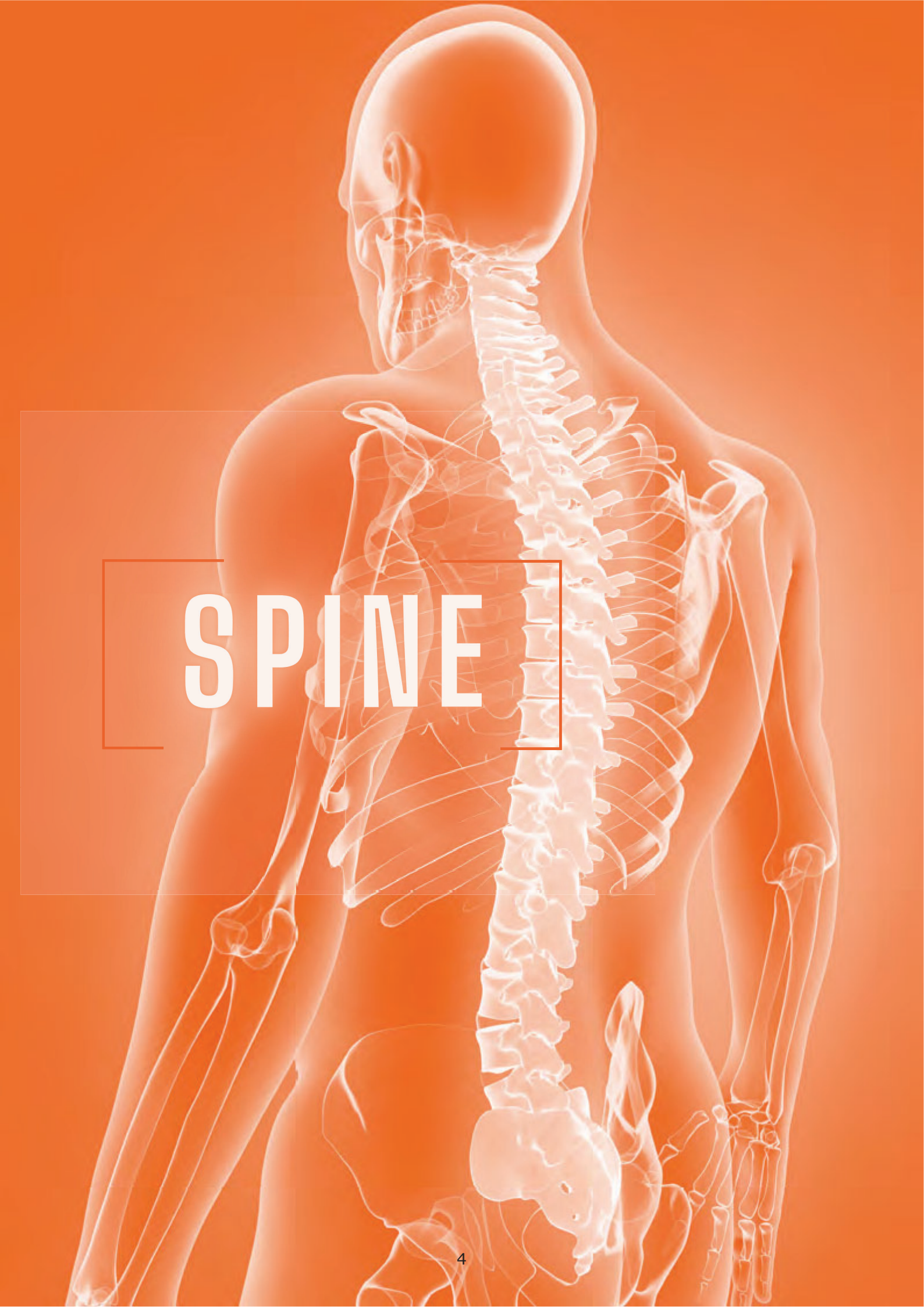
SPINE

Cervical or lumbar pain, also defined respectively as low back or neck pain, is the most common health problem among older adults that results in pain and disability. Low back or neck pain is sometimes associated with disc degeneration and injury occurring in the lumbar or cervical spine (the thoracic spine is less affected) or deformity (Frost et al., 2019; Nemani et al., 2016; Zhu et al., 2022). These pains could be associate with other symptoms as deformity, neurologic signs, radiculopathy, disability, mechanical instability, stiffness, sagittal and coronal imbalance, claudication, myelopathy etc. (Cho et al., 2014; Nemani et al., 2016; Passias et al., 2015; Vercoulen et al., 2021; Wewel et al., 2019; Zhu et al., 2022).

Various pathologies associated with these symptoms are diagnosed, such as degenerative disc disease (lumbar and cervical), vertebral spinal stenosis, spondylolisthesis, scoliosis (idiopathic adolescent or adult), cervical spondylosis myelopathy. Currently, the non-operative, also called conservative treatment is the first-line approach, for patients without severe neurologic deficits or the unique approach for contraindicated surgery patient.

When conservative treatment fails, that is to say when there are progressive and important neurological deficit, unacceptable deformity causing cosmetic or respiratory problems (scoliosis deformity), severe disability, and pain unresponsiveness to treatment after several months: surgery is indicated and necessary (Boer et al., 2021; Heemskerk et al., 2021; Olgun & Yazici, 2013; Ozyemisci Taskiran, 2020; Zigler et al., 2018). The goals of surgical treatment include improvement of the regional back or neck pain, correction of deformity and achievement of a balanced spine, prevent further deterioration of the curve (prevent progression of the disease) decompression of the neural elements, and spinal stabilization with solid bony fusion while avoiding complications. Major surgical procedures can be combined: arthrodesis (osteosynthesis +/- bone graft) and osteosynthesis alone.

Common options for bone grafting include: autograft; allograft; Bone morphogenetic protein and synthetic materials (Katsuura et al., 2020). Of all the grafts available clinically, autologous bone is still considered the absolute reference because all the properties necessary for bone regeneration in terms of osteoconduction, osteoinduction and osteogenesis are combined (Wang & Yeung, 2017).

However, the disadvantages of autografting have been widely reported: morbidity of the site of collection (risk of infection, complication, pain), a limited volume of available material as well as a prolonged operating time. For these reasons, health professionals will use other bone substitutes (HAS_2013; Wang & Yeung, 2017). The most common options for replacing autograft are: allografts; xenografts and synthetic bone substitutes. These alternatives eliminate the second operative site due to autologous sample. Regarding allografts and xenografts, they are not exempt from viral contamination and immune reaction and with a minimal risk of transmission of a pathogen (Ameri et al., 2009; Crawford et al., 2013; Delécrin et al., 2000; Ilharreborde et al., 2008). Synthetic bone substitutes allow a biocompatibility with no risk of contamination and an availability in quantity.

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children

MDPI

Brief Report

Safety and Efficacy of Stand-Alone Bioactive Glass Injectable Putty or Granules in Posterior Vertebral Fusion for Adolescent Idiopathic and Non-Idiopathic Scoliosis

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Abstract: Posterior spinal fusion (PSF) is the standard procedure for the treatment of severe scoliosis. PSF is a standard procedure that combines posterior instrumentation with bone grafting and/or bone substitutes to enhance fusion. The aim of this retrospective study was to evaluate and compare the post-operative safety and efficiency of stand-alone bioactive glass putty and granules in posterior spine fusion for scoliosis in a paediatric cohort. A total of 43 children and adolescents were included retrospectively. Each patient's last follow-up was performed at 24 months and included clinical and radiological evaluations. Pseudarthrosis was defined as a loss of correction measuring >10° of Cobb angle between the pre-operative and last follow-up measurements. There was no significant loss of correction between the immediate post-operative timepoint and the 24-month follow-up. There was no sign of non-union, implant displacement or rod breakage. Bioactive glass in the form of putty or granules is an easily handled biomaterial but still a newcomer on the market. This study shows that the massive use of bioactive glass in posterior fusion, when combined with proper surgical planning, hardware placement and correction, is effective in providing good clinical and radiological outcomes.

Keywords: scoliosis; biomaterials; spine; fusion; bioactive glass

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1. Introduction

Scoliosis is defined as three-dimensional structural deformity of the spine in the anterior-posterior, sagittal and transverse planes. The most common type is adolescent idiopathic scoliosis (AIS), but neurologic or muscular disorders may also lead to progressive spine deformities (non-idiopathic scoliosis, or NS) [1].

In the most severe cases, progression of the deformity necessitates surgery to correct the spinal curvature, rebalance the spine and, above all, stop progression [2,3]. Posterior spinal fusion (PSF) is the standard procedure for the treatment of scoliosis [4]. In paediatrics, this surgery improves self-esteem and general appearance [3]. PSF is a standard procedure that combines posterior instrumentation with bone grafting to enhance fusion [5]. Pseudoarthrosis or non-union diagnosed ≥1-year post-operatively is the main cause of fusion failure in spine surgery [4,6]. The rate of pseudarthrosis has been reported to be 0–3% with either allograft or autograft bone [4,7].

Autologous iliac crest bone grafts have long been the gold standard in posterior spine fusion [3,8,9]. However, iliac bone harvesting is associated with increased surgical time and may lead to donor site morbidity, with a risk of infection and loss of sensation or chronic pain [6,10,11]. In addition, the quantity and properties of available autologous grafts are limited. Different types of bone substitutes have been used as alternatives to autologous grafts, including allografts, ceramics, and synthetic bone substitutes [9,12]. Allografts are not free of viral contamination, and their availability is limited [10,13]. Synthetic bone

substitutes have variable results but are convenient for the surgeon, easily resourced and ready to use [6].

Different bone substitutes are available on the market, but the data are limited, and no compound has yet proven to be superior to others [14]. However, 45S5 bioactive glass is an innovative biomaterial composed of optimal proportions of silicon, calcium, sodium, and phosphorus minerals. Published reports have confirmed its safety and efficacy in various adult orthopaedic conditions and procedures. The use of novel biomaterials in paediatric patients is always a concern in terms of tolerance and efficacy, particularly in posterior spinal fusion, where a large amount of graft material is needed. A study conducted by Ilharreborde et al. in 2008 [9] suggested that bioactive glass can be used in place of autologous grafts as an effective bone substitute in AIS. The safety and efficacy of bioactive glass in paediatric spinal deformities have not yet been evaluated, but there was no significant loss of correction between the 1st erect radiograph and the 24-month post-operative radiograph. There was no sign of non-union, implant displacement or rod breakage.

In our clinical practice, we routinely use bioactive glass to enhance fusion in scoliosis patients. The aim of this retrospective study was to evaluate and compare the post-operative safety and efficiency of bioactive glass 45S5 putty and granules in posterior spine fusion for AIS and NS in a paediatric cohort.

2. Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki and the current regulations and reference methodology between July 2018 and December 2022 in a single institution. The study was approved by the Institutional Review Board CPP Ile de France 2 on 07/20/2020: No. ID RCB: 2020-A01071-38. An information letter was sent to all patients and their guardians. The present study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15].

2.1. Patient Selection

The inclusion criteria were as follows:

- paediatric patient < 20 years old (AIS or NS);
- scoliosis requiring posterior fusion posterior instrumentation;
- use of bioactive glass (Glassbone Granules or Glassbone Injectable Putty, NORAKER, Lyon-France) as adjuvant fusion;
- minimum of 2 years of follow-up.
- The exclusion criteria were as follows:
- surgical revision;
- patient opposition to data collection.

2.2. Surgical Technique

All procedures were performed by the same surgeon. A classic straight dorsal incision, centred on the patient's spinous processes, was performed. The posterior vertebral arch was then exposed. Hybrid constructs, which combine screws, sublaminar bands and hooks, were typically used in addition to cobalt-chrome 6 mm rods. A combination of different correction manoeuvres was performed, including rod rotation, postero-medial translation and in situ contouring. A typical construct is depicted in Figure 1.

In all patients, bioactive glass in the form of GlassBone Injectable Putty or Granules (NORAKER—Lyon/France) was applied to the spine after facetectomies and standard decortication of the laminae at the end of the procedure. GlassBone Granules are composed of 45S5 bioactive glass. GlassBone putty is an injectable paste composed of 45S5 bioactive glass granules mixed with an absorbable binder combining polyethylene glycol and glycerol. The choice between putty or granules relied only on the availability of the putty on

the market. Granules came first on the market and putty second. The bone harvested from the facetectomies, and the spinous processes was not used for additional grafts.

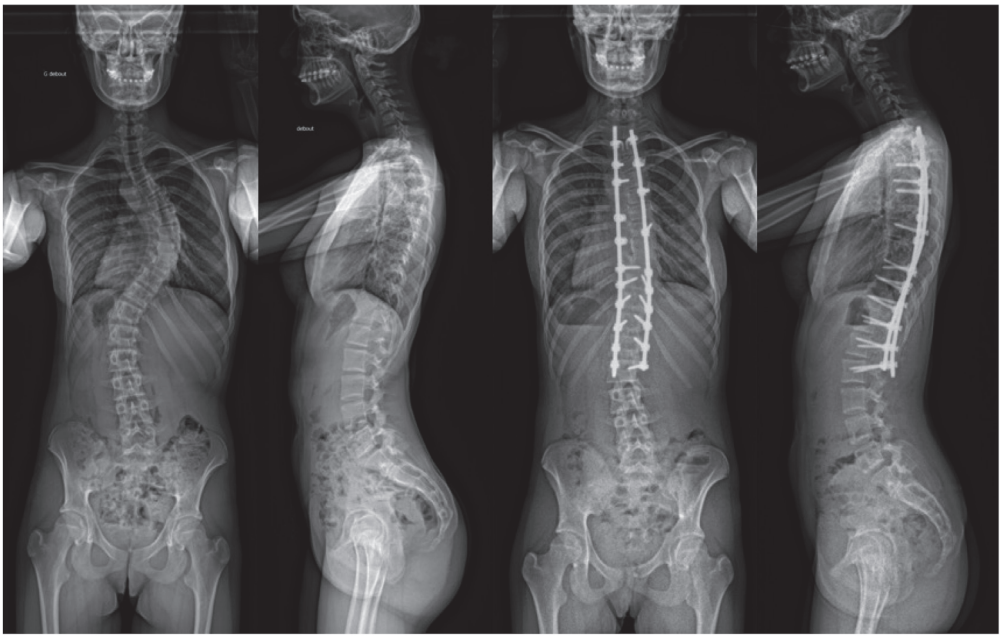

Figure 1. Pre- and post-operative full-spine coronal and sagittal X-rays illustrating a typical long construct for posterior fusion to correct a deformity.

2.3. Outcomes of Interest

Baseline demographic data such as gender, age at surgery, skeletal maturity (Risser grade) and Lenke curve type were collected.

The occurrence of any anomaly and/or complication was recorded at each post-operative visit (15 days, 6 months and 2 years). Postoperative radiographs were performed at each follow-up and were evaluated for instrumentation failure, bone fusion and Cobb angle. Bone fusion in the instrumented section was classified as acquired, in progress or not acquired. Cobb angle measurement was performed at post-operative discharge and at the final follow-up visit, and the results were compared [9]. Pseudarthrosis was defined as a loss of correction manifested as a difference of >10° between the immediate and final post-operative measurements [7,16]. As it is now accepted that loss of correction after fusion in AIS usually occurs within 2 years after the procedure [17], we used the same time interval for our study. Any screw loosening was also reported.

Pre- and post-operative radiological evaluations were performed using the EOS system (EOS-Imaging—Paris, France). EOS is a low-dose imaging system providing simultaneous AP and lateral views in a stand-up position [18,19]. Semiautomatic 3D reconstruction, using SterEOS software (EOS-Imaging—Paris, France), is based on identifiable anatomic points [20,21]. It provides a 3D image of the spine deformity, giving measurements of spine parameters in a stand-up position. The spine 3D geometry is limited between T1 and S1 since cervical spine is not routinely captured. Validation of the accuracy and reproducibility of the 3D reconstruction method has been reported in previous studies [20,22,23]: the 95% prediction limits for the intra- and inter-observer errors in measurement were computed. The 95% prediction limits indicate the difference between two successive replicate measurements that would exceed approximately 5% of the time due to an error of measurement. The inter-observer 95% prediction for the Cobb angle was 2.8°. The intra-observer 95% predication for the Cobb angle was 2°.

2.4. Statistical Analysis

All included patients were considered in the evaluation. A descriptive analysis of all variables of interest was performed. Ellistat (version 5.31; 2020/04, France) was used to perform t tests and other statistical tests. Continuous data are expressed as the mean and standard deviation, while categorical variables are expressed as percentages. Student's *t*-tests or Mann–Whitney U tests were used to compare the mean pre- and post-operative measurements. The qualitative variables are presented as counts and frequencies. The 95% confidence intervals and statistical significance are presented when relevant. The primary endpoint was the rate of adverse events at least 1 year after surgery.

3. Results

3.1. Patient Selection and Demographic Data

A total of 43 children and adolescents were included retrospectively (30 females, 69.8%, and 13 males, 30.2%); their mean age at the time of surgery was 15.4 years (range 11–19 years). A flowchart of the study is presented in Figure 2.

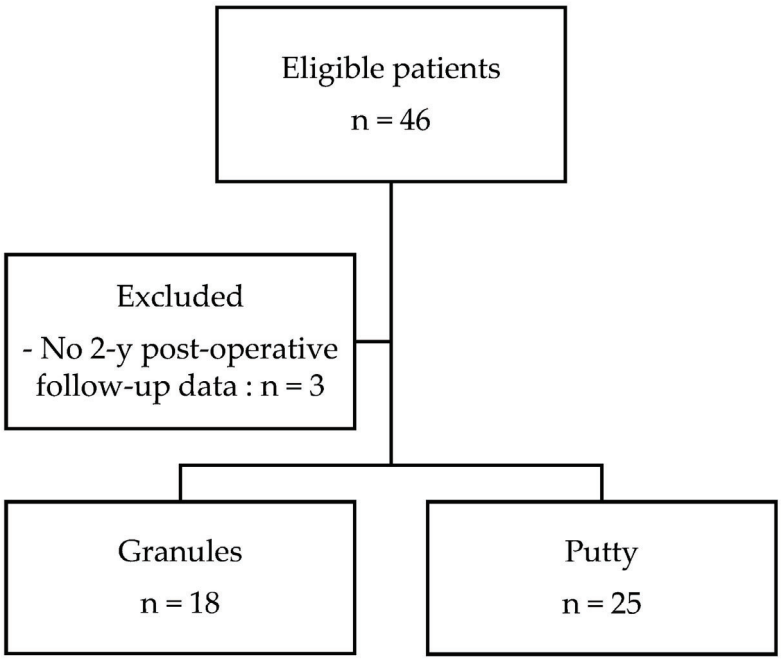

Figure 2. Flowchart of the study.

Patient demographic and clinical data are recorded in Table 1. Each patient's last follow-up was performed at 24 months after the surgery.

3.2. Peri-Operative Data

All patients underwent posterior thoracolumbar spinal fusion. The average number of instrumented vertebrae was 10 ± 3 [4–15], with 62.8% of patients having more than ten levels instrumented. Detailed peri-operative data are presented in Table 2. The mean operative time was 202 ± 66 [90–300] min. In the putty group, all patients received 20 cc of Glassbone injectable putty (NORAKER—Lyon/France); in the granule group, 14 (78%) patients received 10 cc and 4 (22%) received 20 cc of Glassbone granules (NORAKER—Lyon/France) without adjuvant. The mean hospital stay was 6 ± 3 days [4–15].

3.3. Safety

Four of the 43 operated patients experienced adverse events. Three complications appeared early during immediate post-operative follow-up. Two patients had surgical site infection (4.7%), which was treated with revision and cleaning, and one patient had

an extended stay in the intensive care unit (2.3%). All these adverse events were due to surgical intervention. No other causes were identified. One case (2.3%) of late mechanical complications was observed 24 months after surgery. The patient was diagnosed with proximal junctional kyphosis (PJK) with dislocation of the proximal hooks; surgical revision was performed, and the instrumentation was removed. No other complications were observed during follow-up.

Table 1. Patient characteristics. Comparisons were computed between the granule and putty groups. There was no significant difference between the 2 groups.

Characteristic	N = 43	Granules (n = 18)	Putty (n = 25)	p Value between Groups
Age (years), mean ± SD	15.4 ± 1.9 [11–19]	15.7 ± 1.7 [13–19]	15.2 ± 2.0 [11–19]	p = 0.466—NS
Female	30 (69.8%)	10 (55.6%)	20 (80%)	/
Male	13 (30.2%)	8 (44.4%)	5 (20%)	/
Weight (kg)	49.4 ± 9.9 [31–77]	47.9 ± 11.5 [31–71]	50.4 ± 8.7 [37–77]	p = 0.413—NS
Size	1.60 ± 0.06 [1.50–1.75]	1.58 ± 0.07 [1.50–1.70]	1.61 ± 0.06 [1.50–1.75]	p = 0.402—NS
BMI (kg/m^2)	19.9 ± 3.3 [15.8–29.7]	20.8 ± 3.6 [15.8–26.1]	19.5 ± 3.2 [16.0–29.7]	p = 0.290—NS
Smoking	None	/	/	/
Indication				
Adolescent idiopathic scoliosis	34 (79.1%)	9 (50%)	25 (100%)	/
Neurologic scoliosis	7 (16.3%)	7 (38.9%)	/	/
Neuromuscular scoliosis	2 (4.7%)	2 (11.1%)	/	/
Lenke classification	1A 20 (46.5%) 2A 2 (4.7%) 1B 3 (7.0%) 3C 1 (2.3%) 5C 16 (37.2%) 1C 1 (2.3%)	1A 6 (33.3%) 2A 0 (0%) 1B 2 (11.1%) 3C 0 (0%) 5C 9 (50%) 1C 1 (5.6%)	1A 14 (56%) 2A 2 (8.0%) 1B 1 (4.0%) 3C 1 (4.0%) 5C 7 (28%) 1C 0 (0%)	/
Risser classification	1 2 (4.7%) 2 3 (7.0%) 3 3 (7.0%) 4 30 (69.8%) 5 5 (11.6%)	1 2 (11.1%) 2 2 (11.1%) 3 2 (11.1%) 4 11 (61.1%) 5 1 (5.6%)	1 0 (0.0%) 2 1 (4%) 3 1 (4%) 4 19 (76%) 5 4 (16%)	/

Table 2. Distribution of the number of instrumented levels.

	N (%)	Granules (%)	Putty (%)
Mean number of levels	10 ± 3 [4–15]	12 ± 3 [5–15]	8 ± 3 [4–12]
Number of instrumented levels			
≥10	27 (62.8%)	16 (88.9%)	11 (44%)
8–9	7 (16.3%)	1 (5.6%)	6 (24%)
6–7	0 (0%)	0 (0%)	0 (0%)
≤5	9 (20.9%)	1 (5.6%)	8 (32%)

3.4. Radiographic Analysis

The results from the radiographic measurements are summarized in Table 3. At the latest follow-up, bony fusion was documented in all patients. The radiographic parameters of the two groups at each follow-up are presented in Table 3.

Table 3. Radiographic data (Cobb angle, correction rate, loss of correction). NS: Not Significant.

	N = 43		***p* Value**	**Granules (n = 18)**		***p* Value**	**Putty (n = 25)**		***p* Value**
	Mean (n)	Range		Mean	Range		Mean	Range	
Cobb angle									
Pre-op	62.7 ± 22.7 (43)	[30–130]	/	70.4 ± 24.9 (18)	[42–130]	/	57.2 ± 19.6 (25)	[30–120]	/
1st erect	26.5 ± 16.4 (43)	[0–68]	$p < 0.05$ from pre-op (7.10−13)	30.1 ± 17.9 (18)	[2–68]	$p < 0.05$ from pre-op (3.10−6)	23.9 ± 15.1 (25)	[0–50]	$p < 0.05$ from pre-op (2.10−8)
3–6 months	24.0 ± 13.9 (25)	[0–50]	$p < 0.05$ from pre-op (8.10−11)	23.0 ± 7.1 (2)	[18–28]	$p < 0.05$ from pre-op (0.02)	24.1 ± 14.5 (23)	[0–50]	$p < 0.05$ from pre-op (3.10−8)
24 months	27.1 ± 16.1 (42)	[0–70]	$p < 0.05$ from pre-op (10−12)	31.2 ± 18.6 (17)	[7–70]	$p < 0.05$ from pre-op (9.10−6)	24.1 ± 14.1 (25)	[0–52]	$p < 0.05$ from pre-op (10−8)
Correction rate									
Pre-op vs. 1st erect (°)	36.2 ± 12.0 (43)	[15–70]	/	40.3 ± 11.4 (18)	[24–70]	/	33.2 ± 11.7 (25)	[15–70]	/
Loss of correction									
1st erect vs. 3/6 months (°)	−0.55 ± 3.32 (25)	[−8.0–5.0]	$p = 0.874$—NS	0.00 ± 5.7 (2)	[−4.0–4.0]	$p = 0.950$—NS	−0.60 ± 3.25 (23)	[−8.0–5.0]	$p = 0.773$—NS
1st erect vs. 24 months (°)	−0.65 ± 3.24 (42)	[−7.0–7.0]	$p = 0.671$—NS	−1.12 ± 3.52 (17)	[−7.0–7.0]	$p = 0.685$—NS	−0.18 ± 2.97 (25)	[−6.5–6.0]	$p = 0.868$—NS

The mean pre-operative Cobb angle was 62.7° [30°–130°], and the mean Cobb angle at the 24-month follow-up was 27.1° [0°–70°]. There was a significant difference between the pre-operative and post-operative measurements (Figure 3. This change reflected a significant reduction in spinal deformity.

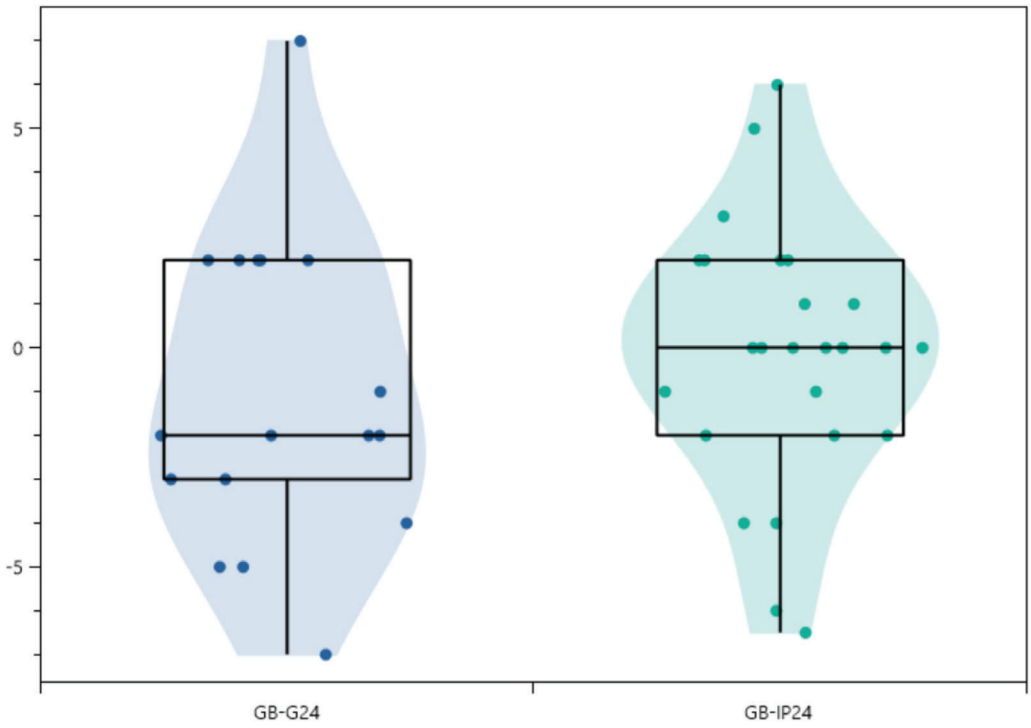

Figure 3. Box plots of loss of correction in the granule group (GB-G24) and the putty group (GB-IP24) groups, 24 months follow-up. There were no outliers. More than 50% of the data are included in the box plot for each material. The median is 0 for the putty group and −2 for the granule group. The results reflect little or no loss of correction.

The mean post-operative Cobb angle on the 1st X-ray (after hospitalization) was 26.5° [0°–68°]. No significant loss of correction occurred between the immediate post-operative examination and the 24-month follow-up. There was no sign of non-union, screw loosening, implant displacement or rod breakage.

4. Discussion

The main finding of the present study was that bioactive glass, both in putty and in granular form, is efficient and safe to use in association with proper instrumentation, facetectomies and posterior arch decortication to enhance posterior fusion in young patients with adolescent or neuromuscular scoliosis as evaluated 2 years after surgery.

The clinical and radiological characteristics of our cohort, along with the surgical procedure and the rate of revisions and complications, are in line with the results obtained in other recent studies [9,24,25]. None of the observed patients experienced a post-operative increase in the Cobb angle by >10°, indicating that bioglass alone is sufficient to promote fusion.

Iliac crest graft represented the gold standard for many years, but they are known to be associated with donor site morbidity [3,6,8,9,11,12]. Furthermore, the grafts may be harvested in insufficient quantity for patients requiring long fusion. At present, different synthetic options are available to surgeons, and many have proven to be as effective as iliac crest grafts [4]. These biologic materials allow solid fusion while reducing the surgical time and eliminating the donor site morbidity associated with iliac crest grafting. Ilharreborde et al. [9] reported that the use of bioactive glass in addition to local autologous bone grafts in AIS was as effective as autologous iliac crest bone alone. To the best of

our knowledge, the present study is the first to show that the use of bioglass alone also represents a viable and safe option for enhancing fusion in scoliosis surgery.

While CT scans would represent the most reliable tool to evaluate the fusion mass, this imaging technique is not routinely used at our institution to limit radiation exposure [26]. Therefore, we performed an indirect evaluation of the fusion rate using the definition of pseudarthrosis suggested by Price et al. [7]. A loss of correction measuring more than 10° of Cobb angle over the observation period was taken to define a non-fused spine [7]. The mean loss of correction was less than 2° in our series, which is within the accepted 3° measurement error (Figure 4).

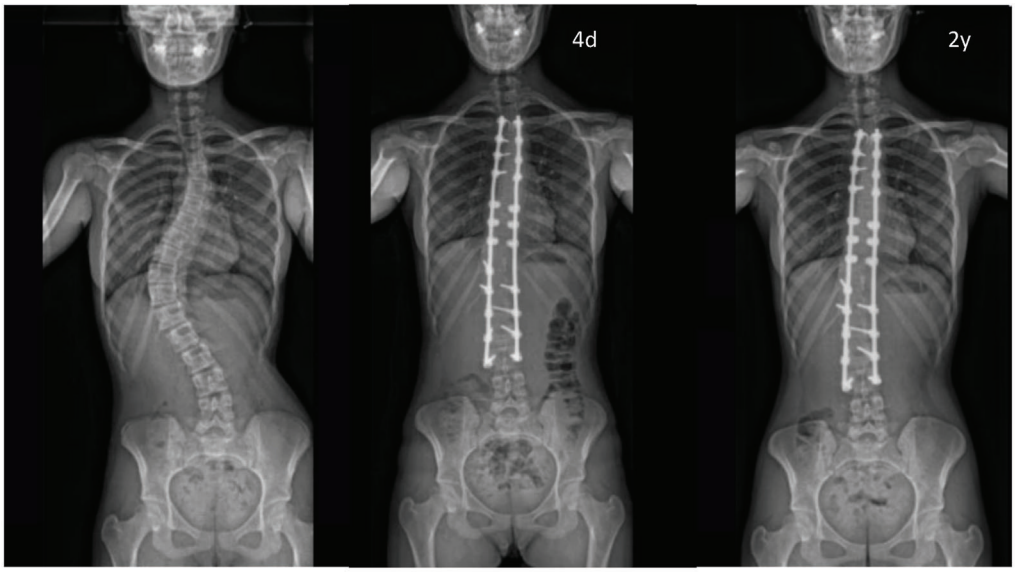

Figure 4. Pre- and post-operative full-spine coronal X-rays (1st erect and 2y po) illustrating the proper stabilisation of the main curve (<10°) without any screw loosening. (4d: Day 4 after surgery).

The need for a safety evaluation of the massive use of bioglass on the spine is evident from the issues experienced with high doses of bone morphogenetic proteins (BMPs) in spine surgery [27]. Bioactive glass is an osteoconductive bone substitute and not an osteoinductive agent as BMP is, meaning that bioglass merely acts as a scaffold to promote the settlement of osteoblasts arising from bone decortication. BMPs create bone in a bone-free environment and have a well-documented dose effect. As safety is a priority and a legitimate concern when applying newly developed biomaterials in the human body, we kept this concern in mind and examined safety as an outcome of this study. In the cohort that we observed, bioactive glass did not have the disadvantage of a dose effect. At least 20 cc of bioactive glass was applied in most of the patients without adverse effects. While a longer follow-up will be required to investigate possible long-term effects, we believe that, to the osteoconductive rather than osteoinductive nature of bioglass, there will not be long-term complications associated with the use of this material.

In studies on oral microorganisms in vitro, bioglass has demonstrated antibacterial properties, which may reduce the potential for bacterial colonization of the grafted sites [28,29]. The 4.7% infection rate in our study is equivalent to the values reported in the recent literature. Both patients who developed wound infections in this study were NS patients, and people with this condition are known to be more prone to infections than people with AIS. We were unable to evaluate the antibacterial properties owing to the design of the study and the small sample of patients, and we did not detect a trend in the rate of operating site infections in our patients to support these properties. However, in light of our data compared with the literature, it is highly unlikely that the observed wound infections were connected to the use of bioglass.

We did not observe a significant difference in outcomes between patients who received putty grafts and those who received granular grafts. The bioactive glass putty plays the same role as granules. There are no primary mechanical properties to consider when applying bioactive glass putty. This is not an issue in posterior spinal fusion because the instrumentation assures primary mechanical stabilization, but a putty graft may not be a suitable stand-alone solution for bone filling. However, the "wet sand" consistency and adhesive properties facilitate the accurate placement of the biomaterial. Once applied to the bone, it does not move, even in the event of irrigation or bleeding. It is also very useful in intersomatic cages. Hammering a cage during insertion does not dislodge the putty from the cage, as is usually experienced when small autologous bone fragments are used instead. For those reasons, bioactive glass putty has progressively replaced granules in most spine procedures.

The retrospective nature and uncontrolled design of this study are its main limitations. While these observations confirmed the efficacy and safety of stand-alone bioactive glass 45S5 as an alternative to autologous bone grafts, further studies will be required to compare the available materials and assess possible differences among the various compounds.

5. Conclusions

PSF is currently a common procedure that has a very low rate of complications, regardless of the type of biomaterial used. Bioactive glass in the form of putty or granules is an easily handled biomaterial but still a newcomer on the market. This study shows that its massive use in posterior fusion, when combined with proper surgical planning, hardware placement and correction, is effective in providing good clinical and radiological outcomes.

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Bioactive glass grants equivalent fusion compared to autologous iliac crest bone for ALIF: a within-patient comparative study

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Abstract

Purpose: To determine within-patient fusion rates of chambers filled with bioactive glass versus autologous iliac crest bone on computed tomography (CT) following anterior lumbar interbody fusion (ALIF).

Methods: A consecutive series of 40 patients (58 levels) that underwent single-level (L5-S1 only) or two-level (L5-S1 and L4-L5) ALIF were assessed. Indications for fusion were one or more of the following: degenerative disc disease with or without Modic changes, spondylolisthesis, and stenosis. Each intervertebral cage had a middle beam delimiting two chambers, one of which was filled with bioactive glass and the other with autologous iliac crest bone. CT scans were graded using the Bridwell classification (grade I, best; grade IV, worst). Patients were evaluated using the Oswestry Disability Index (ODI), and by rating pain in the lower back and legs on a Visual Analog Scale (pVAS); complications and reoperations were noted.

Results: At 15 ± 5 months follow-up, there were no significant differences in fusion across chambers filled with bioactive glass versus chambers filled with autologous bone ($p = 0.416$). Two patients with Bridwell grade III at both chambers of the L4-L5 cages required reoperation using posterior instrumentation. Clinical assessment of the 38 remaining patients (54 levels) at 25 ± 2 months, revealed ODI of 15 ± 12, lower back pVAS of 1.4 ± 1.5 and legs pVAS of 1.9 ± 1.6.

Conclusions: For ALIF at L5-S1 or L4-L5, within-patient fusion rates were equivalent for bioactive glass compared to autologous iliac crest bone; thus, bioactive glass can substitute autologous bone, avoiding increased operative time and blood loss, as well as donor site morbidity.

Keywords: Bioactive glass, ALIF, Bridwell grade, Fusion, Complications

Introduction

Spinal fusion is a common surgical procedure, with over 400,000 surgeries performed in the United States every year [23]. Fusion is used increasingly for the treatment of spondylolisthesis, scoliosis, disc degeneration, herniation and stenosis [12, 18]. Its main goal is to fuse two or more vertebrae by inducing bone growth between segments, though fusion is not always successful, with pseudarthrosis reported in up to 50% of cases [8]. In 2016, a meta-analysis reported that patients with successful fusion had better improvements in clinical outcomes compared to patients with pseudarthrosis [21].

Autologous iliac crest bone is the gold standard graft material used during spinal fusion [24]. Harvesting autologous iliac crest bone has been associated with increased operative time and blood loss, donor site pain and morbidity, as well as increased complication rates [14, 22, 25]. Therefore, synthetic alternatives to autologous iliac crest

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bone graft continue to be developed and evaluated [24], of which various formulations of bioactive glass have shown promising results, when used alone or in combination with autologous bone [8].

For the last five years, the authors have been performing anterior lumbar interbody fusion (ALIF) for a variety of indications, using intervertebral cages with one chamber filled with bioactive glass and the other chamber filled with autologous iliac crest bone, within the same patient. The aim of this study was to determine the fusion rates of chambers filled with bioactive glass versus autologous iliac crest bone, within the same patient, on computed tomography (CT) following ALIF. The hypothesis was that there would be no differences in fusion rates of chambers filled with bioactive glass compared to those filled with autologous iliac crest bone.

Materials and methods

The authors retrospectively assessed a consecutive series of 40 patients that underwent ALIF at L5-S1 between November 2017 and April 2019, operated on by 2 surgeons (BLINDED). Twenty-two patients had single-level ALIF (L5-S1 only), whereas 18 patients had two-level ALIF (L5-S1 and L4-L5). Each of the 58 intervertebral cages (L5-S1 and L4-L5) had a middle beam delimiting two chambers, one of which was filled with bioactive glass, and the other was filled with autologous iliac crest bone. Indications for ALIF surgery were one or more of the following: degenerative disc disease with or without Modic changes, spondylolisthesis, and stenosis. Posterior fixation was used in 24 patients (60%) that either had spondylolisthesis or required posterior spinal decompression (these patients required posterior incisions, so screws were added to increase stability). None of the patients had prior spine surgery, other than foraminotomy or lumbar discectomy, nor did any patients require fusion at other levels.

Standing lateral radiographs were performed to measure disc height and magnetic resonance images (MRI) were acquired to assess disc degeneration, considering modified Pfirmann grade ≥ 4 and/or Modic changes to indicate degenerative disc disease (DDD). Patients were managed conservatively for at least 1 year, and if pain persisted, surgical intervention was discussed with a physiatrist. All patients provided written informed consent to use their data and images for research and publication purposes. The study was approved in advance by

Table 1 Patient demographics and surgical data

	Initial cohort ($n=40$)		No posterior instrumentation ($n=16$)		Posterior instrumentation ($n=24$)	
	mean ± *SD*	(range)	mean ± *SD*	(range)	mean ± *SD*	(range)
	n (%)		n (%)		n (%)	
Age (years)	48.7 ± 9.8	(29 – 65)	47.3 ± 8.9	(34 – 65)	49.7 ± 10.4	(29 – 65)
BMI (kg/m^2)	25.8 ± 3.5	(18 – 39)	26.0 ± 4.6	(20 – 39)	25.6 ± 2.7	(18 – 30)
Female	26 (65%)		11 (69%)		15 (63%)	
Smokers	15 (38%)		6 (38%)		9 (38%)	
Diabetes	1 (3%)		0 (0%)		1 (4%)	
Indications at L5-S1*						
DDD	26 (65%)		15 (94%)		11 (46%)	
Modic changes	7 (18%)		4 (25%)		3 (13%)	
Spondylolisthesis	11 (28%)		0 (0%)		11 (46%)	
Stenosis	23 (58%)		11 (69%)		12 (50%)	
Levels fused						
L5-S1	22 (55%)		11 (69%)		11 (46%)	
Both	18 (45%)		5 (31%)		13 (54%)	
Type of cage at L4-L5						
Roi A (Zimmer Biomet)	12 (30%)		0 (0%)		12 (50%)	
Synfix (DePuy Synthes)	6 (15%)		5 (31%)		1 (4%)	
None	22 (55%)		11 (69%)		11 (46%)	
Type of cage at L5-S1						
Roi A (Zimmer Biomet)	7 (18%)		1 (6%)		6 (25%)	
Idys ALIF (Clariance)	33 (83%)		15 (94%)		18 (75%)	

Abbreviations: BMI Body Mass Index, *DDD* Degenerative Disc Disease, *SD* Standard Deviation, *n* number of patients

* Subgroups are not mutually exclusive

Table 2 Fusion measured on computed-tomography scans using the Bridwell grade

	Bioactive glass				Autologous bone				
	Initial cohort	No posterior instrumentation	Posterior instrumentation		Initial cohort	No posterior instrumentation	Posterior instrumentation		
	n (%)	n (%)	n (%)	*p-value**	n (%)	n (%)	n (%)	*p-value**	*p-value***
Bridwell grade at any level (*n* = 58)				*0.120*				*0.060*	*0.416*
I	30 (52%)	11 (19%)	19 (33%)		23 (40%)	11 (19%)	12 (21%)		
II	26 (45%)	8 (14%)	18 (31%)		33 (57%)	8 (14%)	25 (43%)		
III	2 (3%)	2 (3%)			2 (3%)	2 (3%)			
IV									
Bridwell grade at L5-S1 (*n* = 40)				*0.755*				*0.339*	*0.262*
I	21 (53%)	9 (23%)	12 (30%)		16 (40%)	8 (20%)	8 (20%)		
II	19 (48%)	7 (18%)	12 (30%)		24 (60%)	8 (20%)	16 (40%)		
III									
IV									
Bridwell grade at L4-L5 (*n* = 18)				*0.120*				*0.007*	*0.779*
I	9 (50%)	2 (11%)	7 (39%)		7 (39%)	3 (17%)	4 (22%)		
II	7 (39%)	1 (6%)	6 (33%)		9 (50%)		9 (50%)		
III	2 (11%)	2 (11%)			2 (11%)	2 (11%)			
IV									

Abbreviations: SD Standard Deviation, *n* Number of levels fused

* Comparison of patients with and without posterior instrumentation

** Comparison of chambers filled with bioactive glass and autologous bone

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Surgical technique

The same pre-operative protocol was used by both surgeons. Surgery was performed under general anesthesia with the patient in supine position, using a left retroperitoneal approach and implanting an ALIF intervertebral cage. Each ALIF cage had a middle beam delimiting two chambers. Grafting was performed as follows, systematically by the two surgeons: one chamber was filled with bioactive glass putty only (Glassbone®, Noraker, Lyon, France), and the other chamber was filled with autologous bone only (obtained from the patient's iliac crest). The bioactive glass putty had a composition of 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5. The implants used at L5-S1 included both Roi A cages ($n = 7$; Zimmer Biomet, Warsaw, IN, USA) and Idys ALIF cages ($n = 33$; Clariance, Beaurains, France), while at L4-L5 they included both Roi A cages ($n = 12$; Zimmer Biomet, Warsaw, IN, USA) and Synfix cages ($n = 6$; DePuy Synthes, Raynham, MA, USA).

Clinical and radiographic assessment

CT scans were routinely performed at 12 months, and two experienced readers (MS, SB) assessed fusion using the Bridwell classification (grades I-IV): grade I indicated fusion with remodeling and trabeculae present; grade II indicated an intact graft, not fully remodeled and incorporated, but without lucency present; grade III indicated an intact graft, with potential lucency present at the top and bottom of the graft; and grade IV indicated absence of fusion with collapse/resorption of the graft [6]. Only patients with persistent back pain after surgery or worsening clinical scores had further radiographic follow-up, to not re-expose all patients unnecessarily to additional radiation. Clinical assessment was performed preoperatively and at 3, 6, 12, and 24 months using the Oswestry

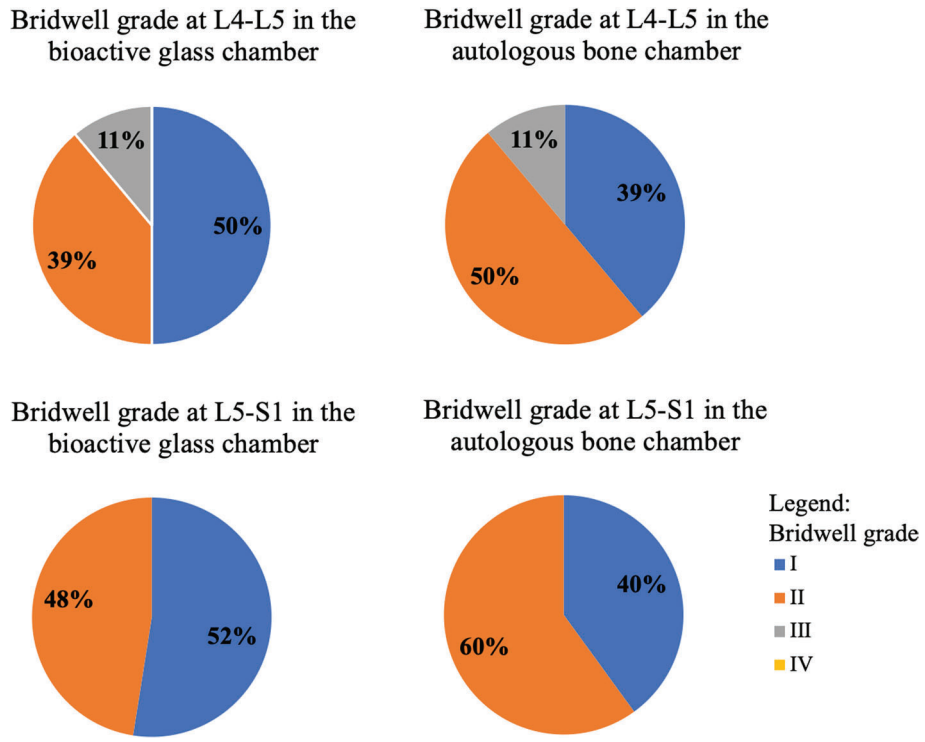

Fig. 1 Bar chart presenting the Bridwell grades in the chambers filled with bioactive glass and autologous bone, at L4-L5 and L5-S1

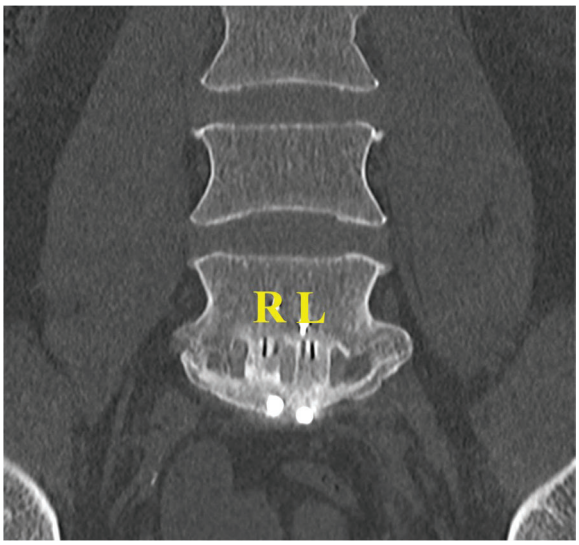

Fig. 2 Frontal CT scan of a patient with fusion of Bridwell grade I1 in both the chamber filled with bioactive glass (R) and the chamber filled with autologous bone (L)

Disability Index (ODI; 0–100%) and Short Form 12 (SF-12) questionnaires, and rating pain in the lower back and legs on a Visual Analog Scale (pVAS; 0–10). Only the latest follow-up of 24 months is shown in the present study. All complications, reoperations and revisions were noted.

Statistical analysis

Descriptive statistics were used to summarize the data. Comparisons of fusion rates between autologous bone and bioactive glass were performed using Chi-squared tests. Agreement on fusion rates between the two readers were calculated using Gwet's AC [9], and were found to be good to excellent (Gwet's AC > 0.691; $p < 0.001$) [7]. Patients were stratified to determine whether the addition of posterior instrumentation affected clinical outcomes. Statistical analyses were conducted using R version 3.6.1 (R Foundation for Statistical Computing). *P*-values < 0.05 were considered statistically significant.

Results

The initial cohort comprised 40 patients, 26 females and 14 males, with an age at index surgery of 49 ± 10 years and a BMI of 26 ± 3 kg/m^2 (Table 1). Fifteen patients (38%) were smokers, all of whom confirmed to have stopped smoking at least 8 weeks before surgery. There were two early postoperative complications (5%); one

Table 3 Pre- and post-operative clinical assessment

	Final cohort ($n=38$)		No posterior instrumentation ($n=14$)		Posterior instrumentation ($n=14$)		*p-value**
	mean ± *SD*	**(range)**	**mean ± *SD***	**(range)**	**mean ± *SD***	**(range)**	
Follow-up (months)	24.7 ± 2.4	(23 – 34)	25.4 ± 3.3	(23 – 34)	24.3 ± 1.6	(23 – 30)	*0.143*
Lower back pVAS							
Preoperative	4.9 ± 1.4	(2 – 8)	5.0 ± 1.2	(3 – 7)	4.9 ± 1.5	(2 – 8)	
Postoperative	1.4 ± 1.5	(0 – 6)	1.6 ± 1.8	(0 – 6)	1.3 ± 1.2	(0 – 4)	*0.742*
Net change	-3.5 ± 1.9	(-7 – 0)	-3.4 ± 2.0	(-7 – 0)	-3.6 ± 1.9	(-7 – 0)	*0.735*
Leg pVAS							
Preoperative	3.7 ± 2.0	(0 – 8)	3.5 ± 2.2	(0 – 7)	3.8 ± 2.0	(0 – 8)	
Postoperative	1.9 ± 1.6	(0 – 6)	2.4 ± 1.5	(1 – 6)	1.6 ± 1.6	(0 – 5)	*0.137*
Net change	-1.8 ± 2.8	(-8 – 5)	-1.1 ± 2.9	(-6 – 5)	-2.3 ± 2.7	(-8 – 2)	*0.207*
ODI							
Preoperative	47.9 ± 11.4	(32 – 72)	49.6 ± 12.1	(35 – 72)	46.9 ± 11.1	(32 – 72)	
Postoperative	14.8 ± 12.4	(0 – 54)	16.1 ± 14.0	(0 – 54)	14.0 ± 11.6	(0 – 42)	*0.647*
Net change	-33.1 ± 15.7	(-64 – 6)	-33.5 ± 16.7	(-64 -– 4)	-32.9 ± 15.4	(-62 – 6)	*0.910*
SF-12 physical							
Preoperative	27.5 ± 6.4	(16 – 44)	27.2 ± 7.0	(16 – 43)	27.7 ± 6.2	(17 – 44)	
Postoperative	45.4 ± 9.1	(20 – 59)	43.6 ± 9.7	(20 – 55)	46.5 ± 8.8	(24 – 59)	*0.340*
Net change	17.9 ± 9.4	(-9 – 36)	16.4 ± 9.0	(-1 – 32)	18.8 ± 9.7	(-9 – 36)	*0.214*
SF-12 mental							
Preoperative	35.8 ± 8.0	(22 – 53)	33.7 ± 8.0	(25 – 53)	37.0 ± 7.9	(22 – 50)	
Postoperative	46.4 ± 9.3	(21 – 59)	46.3 ± 11.2	(21 – 58)	46.5 ± 8.2	(27 – 59)	*0.705*
Net change	10.6 ± 13.2	(-32 – 37)	12.5 ± 15.9	(-32 – 28)	9.5 ± 11.6	(-8 – 37)	*0.203*

Abbreviations: SD Standard Deviation, *pVAS* pain on Visual Analogue Scale, *ODI* Oswestry Disability Index, *SF-12* Short-form 12

* Comparison of patients with and without posterior instrumentation

hematoma and one radiculopathy, neither of which required reoperation.

At a mean follow-up of 15 ± 5 months (range, 10–24), CT scans of the 40 patients (58 levels) indicated no significant differences in fusion across chambers filled with bioactive glass versus chambers filled with autologous bone ($p=0.416$), with Bridwell grade I at 30 levels (52%) in chambers with bioactive glass versus 23 levels (40%) in chambers with autologous bone, Bridwell grade II at 26 levels (45%) in chambers with bioactive glass versus 33 levels (57%) in chambers with autologous bone, and Bridwell grade III at 2 levels (3%) in chambers with bioactive glass versus 2 levels (3%) in chambers with autologous bone (Table 2, Figs. 1 and 2). The 4 chambers that had fusion of Bridwell grade III (graft intact, but a definite lucency at the top or bottom of the graft) were observed in the L4-L5 cages of 2 patients that had undergone two-level stand-alone ALIF. The first was a 38-year-old woman, non-smoker, that had Bridwell grade I fusion at the L5-S1 chamber filled with bioactive glass, but grade II fusion at the L5-S1 chamber filled with autologous bone; she was reoperated 10 months after the index ALIF procedure, using posterior instrumentation filled with autologous local bone and allograft. The second was a 44-year-old woman, also non-smoker, that had Bridwell grade II fusion at both L5-S1 chambers; she was reoperated 23 months after the index ALIF procedure, also using posterior instrumentation filled with autologous local bone and allograft. Both patients that required reoperations were excluded from clinical assessment. There were no cases of cage subsidence, cage displacement, metal-plate migration, metal-plate fracture or bony fracture. For chambers filled with bioactive glass, there were no statistically significant differences in fusion rates among patients with posterior instrumentation versus those without at either L5-S1 ($p=0.755$) or L4-L5 ($p=0.120$). For chambers filled with autologous bone, there were no statistically significant differences in fusion rates among patients with posterior instrumentation versus those without at L5-S1 ($p=0.399$), but fusion at L4-L5 was significantly better for patients with posterior instrumentation ($p=0.007$).

At a mean follow-up of 25 ± 2 months (range, 23–34), clinical assessment of the 38 remaining patients (54

Table 4 Previous clinical studies reporting on the use of bioactive glass during spinal surgery

First author	Year	Type of surgery	Indication	Name of bioactive glass	Combined w/ bone	Comparator	Levels	n	Follow-up	Fusion rate of bioglass	Fusion rate of comparator	Recommend Bioglass
Westerlund [27]	2020	ACDF	Neurocompressive disorders	Bioactive glass bone graft (BioSphere Putty)	Yes, cancellous allograft		1–4 (cervical)	115	> 1 year	100%		Yes
		TLIF	Neurocompressive disorders	Bioactive glass bone graft (BioSphere Putty)	Yes, cancellous allograft		1–3 (lumbar)	30	> 1 year	100%		
		ALIF	Neurocompressive disorders	Bioactive glass bone graft (BioSphere Putty)	Yes, autologous bone		1–3 (lumbar)	103	> 1 year	100%		
Barrey [4]	2019	Posterior fusion	Degenerative diseases, trauma or spinal deformities	45S5 bioactive glass (GlassBoneTM, Noraker)	Yes (50:50)		2–10 (lumbar)	27	> 1 year	82%		Yes
		Posterior fusion	Degenerative diseases, trauma or spinal deformities	45S5 bioactive glass (GlassBoneTM, Noraker)	Yes (50:50)		1–2 (cervical)	3	> 1 year	33%		
Rantakokko [22]	2012	Posterior fusion	Burst fractures	BAG-S54P4	Yes	Autologous iliac crest bone	1–2 (lumbar)	16	10 years	50%	100%	Yes
Frantzen [11]	2011	PLF	Degenerative spondylolisthesis	BAG-S53P4	No	Autologous bone	2–3 (lumbar)	17	11 years	71%	100%	Yes
Ameri [3]	2009	Posterior fusion	Adolescent Idiopathic scoliosis	Metal-derived bioactive glass (Novabone)	Yes, local bone	Autologous iliac crest bone and local bone	Average 10 (thoracoumbar)	40	> 2 years	90%	85%	Yes
Acharya [2]	2008	PLF	Spondylolisthesis or stenosis	Hydroxyapatite-bioactive glass ceramic composite (Chitra-HABg)	Yes, bone marrow	Autologous bone	1–3 (lumbar)	24	> 1 year	0%	73%	No
Kasai [16]	2003	PLF	Stenosis	2:1 of bone:AWGC	Yes, autologous bone		2 (lunbar)	35	> 2 years	83%		Yes
			Stenosis	1:1 of bone:AWGC	Yes, autologous bone		2 (lunbar)	35	> 2 years	83%		
			Stenosis	1:2 of bone:AWGC	Yes, autologous bone		2 (lunbar)	35	> 2 years	82%		
Hashimoto [13]	2002	PLIF	Lumbar degenerative pathologies with instability	Bioactive ceramic granules (AWGC)	Yes, autologous bone		1 (lumbar)	25	> 2 years	100%		Yes

Table 4 (continued)

First author	Year	Type of surgery	Indication	Name of bioactive glass	Combined w/ bone	Comparator	Levels	n	Follow-up	Fusion rate of bioglass	Fusion rate of comparator	Recommend Bioglass
Ido [15]	2000	PLIF	Spondylolisthesis	AWGC	Yes, autologous bone		L4-L5	5	1.5 years 2 years	20% 50%		Yes
		PLF	Spondylolisthesis or vertebral fracture	AWGC	Yes, autologous bone		Multi (lumbar)	6	1.5 years 2 years	17% 50%		

Abbreviations: AFPBP Autogenous Fine Particulate Bone Powder, *BMSC* Bone Marrow mesenchymal Stem Cells, *ACDF* Anterior Cervical Decompression and Fusion, *TLIF* Transforaminal Lumbar Interbody Fusion, *ALIF* Anterior Lumbar Interbody Fusion, *PLF* Postero-Lateral Fusion, *RCT* Randomised Controlled Trial, *PLIF* Posterior Lumbar Interbody Fusion, *ICBG* Iliac Crest Bone Graft, *BMA* Bone Marrow Aspirate, *(TCP)* Tri-calcium Phosphate, *AWGC* Apatite-Wollastonite Glass–Ceramics, *n* number of patients

levels) revealed that ODI improved from 48 ± 11 preoperatively to 15 ± 12 postoperatively (Table 3). Furthermore, lower back pVAS improved from 4.9 ± 1.4 to 1.4 ± 1.5 and legs pVAS improved from 3.7 ± 2.0 to 1.9 ± 1.6. Finally, the SF-12 physical component improved from 28 ± 6 to 45 ± 9 and the SF-12 mental component improved from 36 ± 8 to 46 ± 9. There were no statistically significant differences in postoperative clinical outcomes nor in the net change in clinical outcomes among the 24 patients with posterior instrumentation versus the 14 patients without.

Discussion

The most important finding of this study is that, for ALIF at L5-S1 or L4-L5, fusion rates were equivalent for bioactive glass compared to autologous iliac crest bone, within the same patient. As reported for other ALIF implants [17, 19, 26], the present study found significant improvements of clinical outcomes at a follow-up ≥ 2 years, including ODI, lower back pain and leg pain. Therefore, the findings of this study suggest that for patients undergoing ALIF, bioactive glass can be used as a substitute to autologous iliac crest bone; thus, avoiding increased operative time and blood loss, as well as donor site morbidity [14, 22, 25]. While the follow-up of two years may not be sufficient to ascertain long-term clinical outcomes, the fusion rates of chambers filled with bioactive glass were already equivalent or better than the fusion rates of chambers filled with autologous bone graft, which led the authors to hesitate regarding the acquisition of further CT scans at longer follow-up, due to both ethical (exposure to radiation) and logistical (travel to radiology centers during the pandemic) considerations.

Comparing Bridwell grades observed in the present study suggests that fusion was better in chambers filled with bioactive glass (grade I in 52%) than in those filled with autologous bone (grade I in 40%), though the difference was not statistically significant ($p = 0.416$). There are two possible explanations for this trend: the first is that bioactive glass may induce better or faster bone growth; the second is that bioactive glass may appear more consolidated because it has greater radiopacity (Fig. 2). Considering Bridwell grades I and II to be satisfactory, the present study suggests fusion rates of 97%, both for bioactive glass and for autologous bone. These findings are similar to the only other published study that assessed ALIF using bioactive glass (combined with autologous bone), which reported a fusion rate of 100% at 1 year follow-up, in patients with neuro-compressive disorders at one to three lumbar levels [27]. Previous published studies on posterior fusion have reported fusion rates of 0–100% for bioactive glass (with or without autologous bone) [2–4, 11, 13, 15, 16, 22, 27], with only one of nine studies not recommending the use of bioactive glass [2] (Table 4). Furthermore, our fusion rate of 97% and complication rate of 5% are consistent with those reported for other studies investigating ALIF [5, 20, 26]. Of the 40 patients included in the present study, there were 2 patients that had to be reoperated because of inadequate fusion at L4-L5. It is important to note that both patients had undergone two-level stand-alone ALIF, and neither had posterior instrumentation. These findings suggest that when performing ALIF at two levels, posterior fixation may be necessary to stabilize the spine.

The present study has several limitations. First, comparisons between bioactive glass and autologous bone have been made within the same patient, and thus fusion or lack thereof in one chamber may have affected fusion in the other chamber; additionally, it is not possible to measure the effect of each material on postoperative clinical scores. Second, patients were operated on for a variety of indications, which may result in some variability in outcomes; although, this can also be regarded as a strength of the study since similar fusion rates were found for both materials across a range of indications. Third, ALIF cages of different sizes were used depending on the intervertebral height of each patient, which could mean that different cage sizes were filled with different amounts of material; however, this effect was diminished because we investigasted within-patient fusion rates, and the amount of filler material was equal for both chambers of each patient. Finally, the follow-up of the present study may not be sufficient to ascertain long-term clinical outcomes, although it is sufficient to evaluate fusion rates. Previous studies on other types of spinal surgery have demonstrated that early outcomes, such as ODI and Core Outcome Measures Index, improve or remain stable after 12 months and up to 8 years [1, 10].

Conclusions

For ALIF at L5-S1 or L4-L5, within-patient fusion rates were equivalent for bioactive glass compared to autologous iliac crest bone. The findings of this study suggest that for patients undergoing ALIF, bioactive glass can be used as a substitute to autologous iliac crest bone; thus, avoiding increased operative time and blood loss, as well as donor site morbidity.

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Authors' contributions
MSz study design, data collection, manuscript editing. SB study design, data collection and analysis, manuscript editing. IA study design, data collection, manuscript editing. MVK study design, data collection, manuscript editing. SRP literature review, data analysis and interpretation, manuscript writing. MSa literature review, data analysis and interpretation, manuscript writing. VF study design, data collection, manuscript editing. HA study design, data collection, manuscript editing. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee ('GCS Ramsay Santé pour l'Enseignement et la Recherche', IRB#: COS-RGDS-2021–05-004-SZADKOWSKI-M) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients provided written informed consent to use their data and images for research and publication purposes.

Consent for publication
Not applicable.

Competing interests
MSz consultancy fees and royalties from Clariance, and consultancy fees from Zimmer.
SB no conflicts of interest.
IA no conflicts of interest.
MVK no conflicts of interest.
SRP no conflicts of interest.
MSa no conflicts of interest.
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ORIGINAL ARTICLE • SPINE - BIOMATERIALS

Clinical and radiographic evaluation of bioactive glass in posterior cervical and lumbar spinal fusion

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Abstract

Introduction Spinal surgery of degenerative painful segments is a valuable treatment option in the management of chronic cervical and low back pain. The surgery consists in stabilizing and fusing painful vertebral segment(s). The objective of the study was to report our experience with 45S5 bioactive glass (BAG) to obtain inter-vertebral fusion in the context of posterior spine surgery.

Material and method In this retrospective study, 30 patients with a wide range of degenerative and traumatic conditions of the cervical or lumbar spine underwent spinal fusion utilizing a synthetic bone graft substitute of BAG (GlassBone™, Noraker, Lyon-Villeurbanne, France). The pain was evaluated by VAS score, and graft consolidation was assessed on according radiographic images at 1-year post-op.

Results All patients underwent posterior spinal fusion either in the cervical or the thoraco-lumbar spine. Multi-level fusions represented the majority of the cohort (43% of patients with more than seven levels treated). Radiographic imaging demonstrated excellent fusion rates (93%) at final follow-up, equivalent to the outcomes reported in the literature for autogenous bone, with excellent bone bridging and no spinal implant loosening. Only two cases of non-union were encountered. Additionally, 90% of the patients demonstrated recovery at 1 year after surgery with a pain reduction of 60%.

Conclusion The results of this retrospective study suggest that the 45S5 BAG may be an interesting alternative option to autologous graft, in terms of safety and bone fusion efficiency.

Level of evidence IV Retrospective study

Keywords Spinal surgery · Bone graft · Bioactive glass · Spinal fusion

Introduction

Cervical or low back pain represents the second leading cause of office visit, after respiratory infections, and the third leading cause of disability between the age of 45 and 65. Overall, 80% of the population experiences one or more episodes of back pain at some point in their life [1, 2]. Spinal fusion is commonly performed when treating degenerative, traumatic and scoliotic conditions. The surgery consists in joining two or more vertebrae into one single structure. The goal is to stabilize and fuse painful vertebral segment(s), reducing back pain. Although it is a subject of debate in the community, most surgeons consider that a successful outcome of fusion is characterized by a solid bridge of bone across the spinal segment instrumented.

Bone graft material can be taken from the patient's iliac crest (autograft bone) during the spine fusion surgery, harvested from cadaver bone (allograft bone), or manufactured (synthetic bone graft substitute). Autogenous bone graft is still considered as the gold standard for spinal fusion with confirmed effectiveness for more than 50 years [3]. The effectiveness of autogenous bone is generally attributed to two inherent properties: osteoconduction, as autogenous bone gives the adequate biological environment for new bone to grow; and osteoinduction, which is the ability to promote bone formation at a site where bone formation does not "naturally" occur. The harvested bone graft provides both a physical support for bone ingrowth and a biological reservoir of osteogenic cells, growth factors, cytokines and other naturally present substances that induce bone formation.

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However, graft harvested on the iliac crest (primary source of autologous bone) may lead to site morbidity such as increased blood loss and operative time, and post-surgery residual chronic pain, infection, fracture, loss of sensation or haematoma [4–6]. Alternative bone substitutes can be used to replace autograft, such as allograft or synthetic bone substitute, which are known to be osteoconductive. However, in the synthetic category, only bioactive glasses can potentially match the osteoinductive properties of autogenous bone due to their osteostimulative properties [7–9]. The latter is given by the ability of bioactive glasses to resorb, delivering silicic acid, calcium and phosphate ions to the surrounding osteoprogenetic cells, due to their very unique structure. Soluble silicate has notably demonstrated its role in up-regulating collagen synthesis [8, 9], osteoblastic metabolism [10], promoting osteoinductive gene expression, which in turns translates into faster bone formation. [9–11].

A comparative study of 45S5 bioactive glass (in wt %, 45% SiO_2, 24.5% CaO, 24.5% Na_2O and 6.0% P_2O_5, Particle size: 90 to 710 µm) versus iliac crest autograft for spinal fusion in adolescent idiopathic scoliosis has already been reported with a group of 88 patients. The results showed fewer infections and fewer mechanical failures in the bioactive glass group. [16] While this study was an elegant proof of concept, the efficacy of 45S5 bioactive glass remains to be proven with other indications. To our knowledge, this retrospective study is the first clinical report on utilization of bioactive glass in posterior spinal surgery for various conditions (degenerative, trauma, deformities, cervical disorders, etc.) in an adult population. The primary outcome was the graft consolidation after 1-year post-surgery with radiographic imaging. The pain was also evaluated with patients who have completed the visual analogue scale (VAS) score before and after the surgery. Complications were also recorded (general, infectious, neurological and mechanical).

It was hypothesized that 45S5 bioactive glass could be an alternative to autogenous bone with comparable fusion rates than the other bone substitutes for any indication in spine fusion.

Materials and methods

Research protocols

Medical records were reviewed for all patients consecutively treated with GlassBone™ (45S5 bioactive glass (BAG) with a particle size from 1 to 3 mm manufactured by Noraker, France) from January 2015 to October 2015 and confirmed from operating room records. Patients were operated for degenerative diseases, trauma or spinal deformities in the lumbar or cervical spine. All patients that underwent posterior fusion needed instrumentation. Indications for surgery are summarized in Table 1 for all patients. Demographic data, co-morbidities, pre- and post-operative pain levels and neurological status were recorded. Operative data included location and quantity of graft, intraoperative complications, blood loss and duration of operation. Pre- and post-operative data included clinical evaluation (pain evaluation, presence of complication), CT scans with sagittal and coronal reconstructions, at 6 and 12 months.

Table 1 Demographic data and indications for posterior spinal fusion for 30 patients from 22 to 85 years old (mean 63 years old)

Entry	Value (*n*)	Percentage (%)
Demographic		
Male	11	37
Female	19	63
Indication for spinal fusion		
Trauma	5	17
Degenerative	16	53
Deformity	6	20
Cervical spine	3	10
Number of levels		
1 or 2	5	17
3 to 6	12	40
> 6	13	13
Nicotine use		
Smoker	3	10
Non-smoker	27	90

Surgical technique

All patients from January to October 2015 with indications for a posterior spinal fusion procedure were operated by the author and consecutively included in the study. Appropriate decompressive surgery was performed as the clinical pathology dictated, with subsequent fixation using posterior instrumentation as appropriate. The blister packaging was opened in sterile conditions, and at the time of the surgery, the 45S5 BAG granules were then put in a stainless steel sterile container to be moistened with saline serum and mixed with local autologous bone at a 50:50 volume ratio (see Fig. 1).

The composite mixture was used for the posterior fusion and after adequate decortication, placed between adjacent facets and lamina along all the constructs (Fig. 1b to e). A drain was placed, and the wound was closed in a standard way.

Results

Thirty patients have been enroled in the study. Average age at the time of surgery was 63 years old (22 to 85 years old, 11 males, 19 females). Five patients underwent one or two

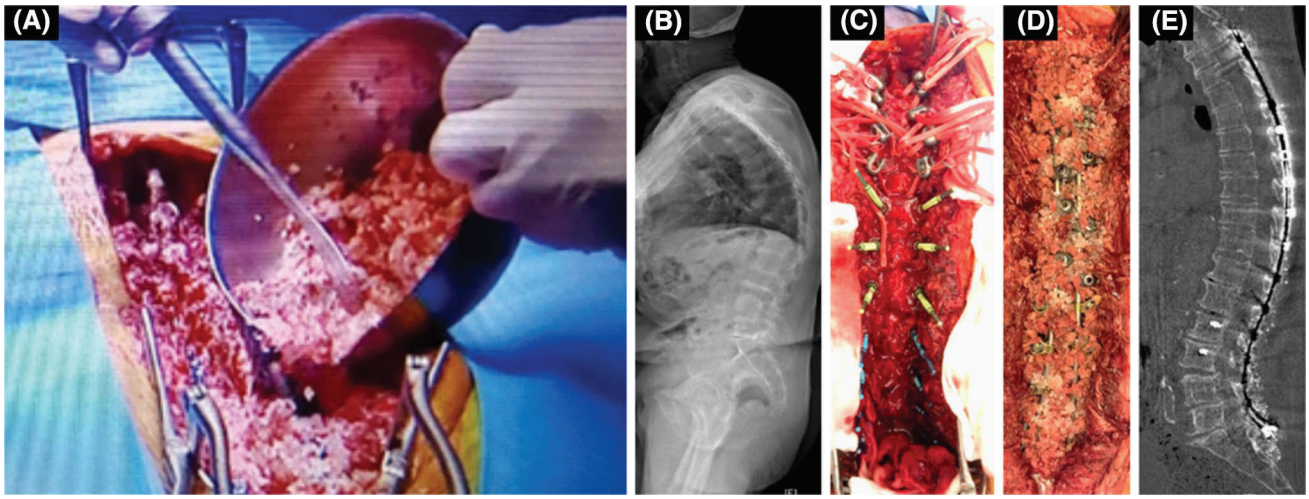

Fig. 1 **a** Mix of GlassBone with local autologous bone and saline serum place on the decorticated posterior elements of the spine; followed by an illustration of the surgery steps where a long instrumentation to treat thoraco-lumbar spinal deformity with sagittal imbalance. The composite bone graft/autologous bone was placed along the construct from T3 to pelvis. **b** Pre-operation X-ray; **c** positioning of the instrumentation; **d** composite placed between facets and lamina; and **e** post-operation X-ray

Table 2 Operative data recorded during surgery given with their standard deviation

# of levels (*n*)	# of patients (*n*)	Graft volume (cc)	Blood loss (mL)	Surgical time (min)
1 or 2	5 (17%)	12.4 ± 3.5	368 ± 181	182 ± 53
3 to 6	12 (40%)	15.1 ± 6.2	654 ± 496	174 ± 68
> 6	13 (43%)	22.2 ± 8.0	1112 ± 597	259 ± 62

levels fusions, 12 patients underwent three to six levels fusions, and 12 patients underwent more than seven levels fusion. Two patients were smokers (Table 1).

Operative data, such as the duration of operation, blood loss and GlassBone™ volume, are highly dependent of the number of levels treated, as shown in Table 2.

After surgery, four complications and one death were reported (see Table 3): 1 mechanical complication (3.8%), 3 infections after surgery (staphylococcus, 10%). There are no serious adverse events relating specifically to the use of 45S5 BAG. These four patients were re-operated successfully (graft consolidation and patient recovery).

For cervical procedures (three patients, one or two levels), fusion was evaluated using CT scans at 6 and 12-months post-surgery (case report Fig. 2). Fusion was acquired for one patient (33%) and is in good progress for two patients (67%). No patient showed average fusion nor pseudarthrosis. After few months, one patient died (for cardiac event) and the two other patients, who were in good progress, acquired complete fusion 1 year after surgery. Patient recovery is good for the two patients (100%) (Table 4).

For lumbar procedures (27 patients, two to ten levels), fusion was evaluated using CT scans at a minimum of 12-month post-op (Figs. 3 and 4). Fusion was acquired for 22 patients (82%) and in good progress for three patients

Table 3 Details of the type of complications encountered post-surgery

Complication	# of patient	Percentage (%)
General	0	0.0
Mechanical	1	3.3
Infection	3	10.0
Neurological	0	0.0
Mortality	1	3.3
Total	5	16.7

(11%) (Table 4). Two patients presented with pseudarthrosis (7%). These patients exhibited material failure after operation, necessitating the replacement of the hardware because of persistent pain. After the revisions, residual pain was not significant. Recovery was observed for all patients except for two patients. (7%: Two described above with pseudarthrosis, one of whom CT scans demonstrated a good bone consolidation, and one of whom where the pain experienced did not seem to be linked with the surgery.)

VAS scores were collected preoperatively and postoperatively at 1 year for 20 patients. One-year post-surgery

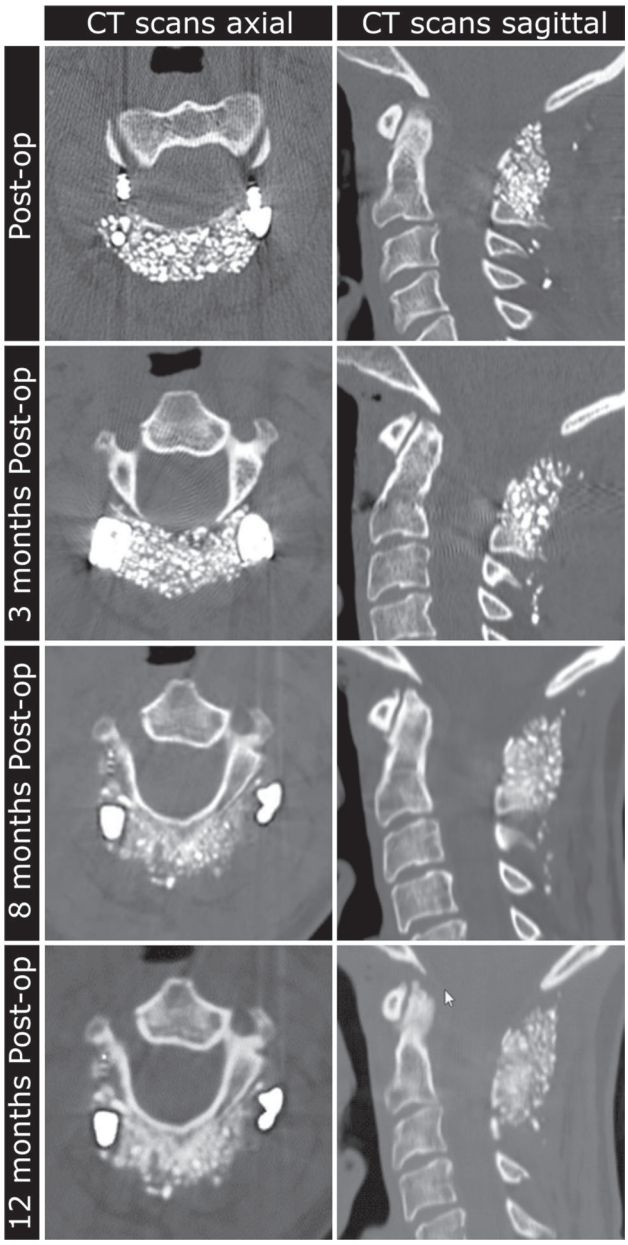

Fig. 2 Post-surgery CT scans of laminectomy with C1–C2 posterior fusion using a mixed of local bone and GlassBone

Table 4 Graft consolidation for 29 patients. One patient was excluded for this study (see Table 3)

Graft consolidation	12 m post-op cervical (*n*)	1 y post-op for T-L-S (*n*)
Acquired	2 (100%)	22 (82%)
In progress	0	3 (11%)
Pseudarthrosis	0	2 (7%)
Mediocre	0	0

T-L-S thoraco-lumbar-sacral

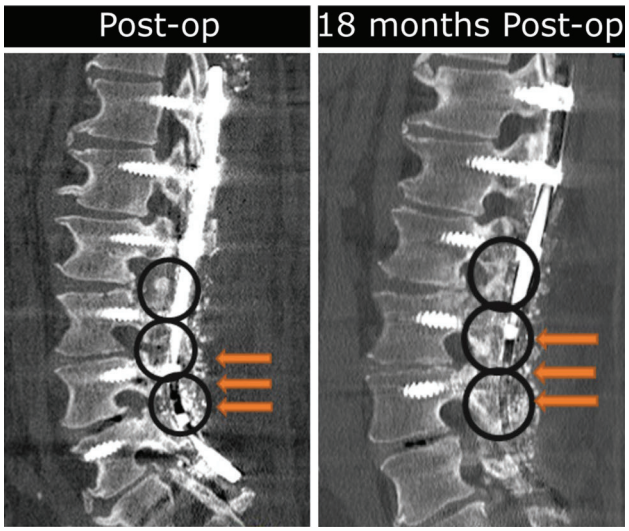

Fig. 3 Granules of bioactive glass are well-visible (orange arrow) immediately just after operation, and gap between posterior arches is visible (black circle). After 18 months, granules are less visible, and a bone bridging has formed with remodelling of the graft (color figure online)

pain decreased by 60% according to the score. The mean pre-operative score was 7.5 [4–10], and the mean post-operative score was 3 [0–7].

Case report (see Fig. 2)

This case consisted of a 47-year-old female, with major osteophytic arthritis at C1–C2 joint, confirmed by CT scan. She is a smoker with a 50 packs a year history.

The patient underwent posterior C1–C2 laminectomy with posterior fusion. Bone substitute GlassBone (16 cc) was mixed with patient's local bone and then placed between C1 and C2 posterior arches.

As early as 3-month post-op, cervical pain decreased by 80%. CT scans demonstrated early fusion with formation of a bone bridge between posteral C1 and C2 vertebras.

At 8- and 12-month post-op, a bone bridge of excellent quality was observed with a decreasing of the radio-opacity of GlassBone granules and progressive creation of a bony bridge. No complication was reported.

Discussion

The ideal bone graft substitute should be osteoconductive and osteoinductive potential similar to autologous graft. It would also need to be readily available, easy to apply, cost-effective and non-immunogenic, with no risk of viral or bacterial contamination [12]. 45S5 BAG is a synthetic bone graft that supports bone formation with its osteoconductive

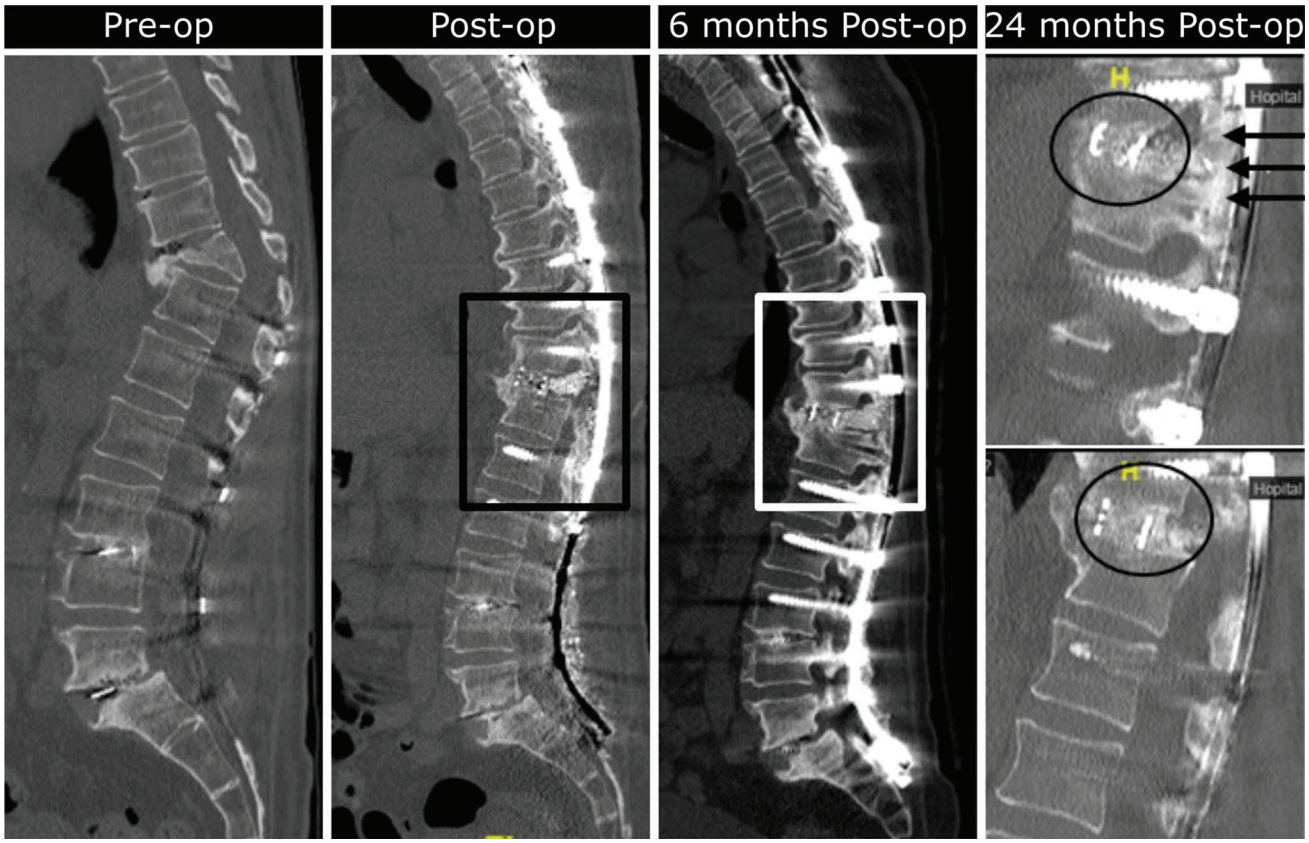

Fig. 4 Patient was operated by VCR (vertebral column resection) to treat PJK (proximal junctional kyphosis). The granules are visible immediately after surgery along the instrumentation. At 2 years after surgery, a bone bridging is clearly visible inside the vertebral cage and through the disc space

properties, while also being osteostimulative, showing higher osteoblastic activity than with calcium–phosphate ceramics [7–11]. In animal studies, mix of autograft and 45S5 BAG produced results comparable to those of autograft alone for non-healing calvarial defects and spinal fusion [13, 14]. This synthetic bone graft therefore presents characteristic close to an ideal bone graft.

To our knowledge, this is the first clinical report on utilization of 45S5 BAG in posterior spinal surgery for various conditions (degenerative, trauma, deformities, cervical disorders) in an adult population. The only adult study was reported by Frantzen et al. but in a strict indication (degenerative spondylolisthesis) using another bioactive glass composition with a higher silica content than 45S5 BAG (53.9 versus 46.1 mol % for 45S5), which in turn could potentially translate into a lower bioactivity and a lack of long-term resorption [15, 26].

The use of 45S5 BAG, with a particle size ranging from 90 to 710 µm, has been clinically reported for spine surgery [16–18]. Ilharreborde et al. and Ameri et al. reported separate studies of multi-level spinal fusion in adolescent patient suffering from idiopathic scoliosis. Complete fusion was observed 32-month post-surgery with 45S5 BAG used alone in both cases (no local autologous bone used). Seddighi et al. reported the anterior fusion of cervical spine in patients with degenerative cervical disc disease using PEEK cages filled with 45S5 BAG and autologous bone harvested locally during discectomy. A rate of spine fusion of 91.3% for single level and 80% for multi-level was observed after 6 months.

Even though the present report is looking at a larger particle size range of 45S5 BAG, above 1 mm, rate of fusion at 1 year was in between these reported for the idiopathic scoliosis, 32-month post-surgery and the anterior fusion of cervical spine, 6-month post-surgery. CT imaging provided objective confirmation that good clinical outcome was achieved, with evidence of good fusion by bridging bone (93% of bone fusion) and no sign of spinal implant loosening. In addition, fusion rates reported here are comparable with reports evaluating instrumented lumbar fusions using autologous graft, with fusion rates between 40 to 90% [19–23]. It is noteworthy to mention that the success rate for fusion above seven levels (46% of the patient treated) was high, with regard to conventional methods of treatment [24].

Two patients suffered from post-surgical infection (7.6%), rate in agreement with the literature, and were successfully re-operated [25].

Despite the fact that this cohort is retrospective, including a limited number of patients with a wide range of degenerative and traumatic conditions of the cervical and lumbar spine, conclusion can be drawn, with regard to the literature, with the following claims: (1) the particle size of 45S5 BAG when above 90 µm has little effect on the rate of fusion and that it is solely due to the inherent property of the glass; (2) the rate of fusion using 45S5 BAG is independent to the indication, if the site is free of pathogen prior to surgery.

Additional prospective studies are needed to confirm these preliminary findings, but our findings are encouraging for use of bioactive glass in posterior spinal fusion.

Conclusion

This study confirms that the use of 45S5 BAG mixed with local autograft represents, potentially, an alternative to autologous graft harvested in the iliac crest region, or other bone substitutes that are solely osteoconductive for posterior spinal fusion. No changes were required to the standard surgical techniques, and results at 6 and 12 months from the treatment of degenerative or trauma spine disorders were highly encouraging, with respect to pain, neurological status and function. At 12-month follow-up, high levels of bony fusion using 45S5 BAG were observed, in combination with various surgical spinal techniques. Imaging results supported clinical pictures of solid fusions. Additional prospective studies are ongoing to confirm these preliminary results.

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Compliance with ethical standards

Conflict of interest The author would like to declare a conflict of interest as he is a consultant for Noraker.

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