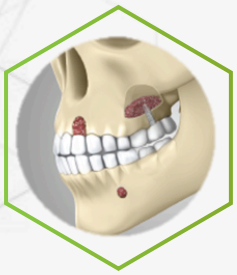
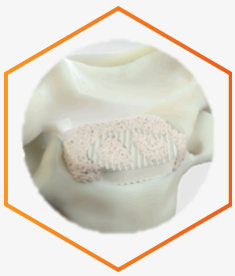
NORAKER®

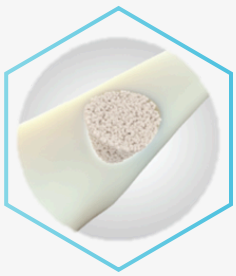
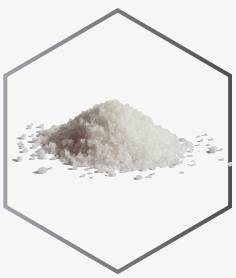
THE BIOGLASS® COMPANY

CLINICAL GUIDELINES

BIOGLASS BONE REGENERATION SOLUTIONS



1-NORA-Clinical guidelines-EN-1.0 07/2023

This document presents clinical data with some publications and patient cases.

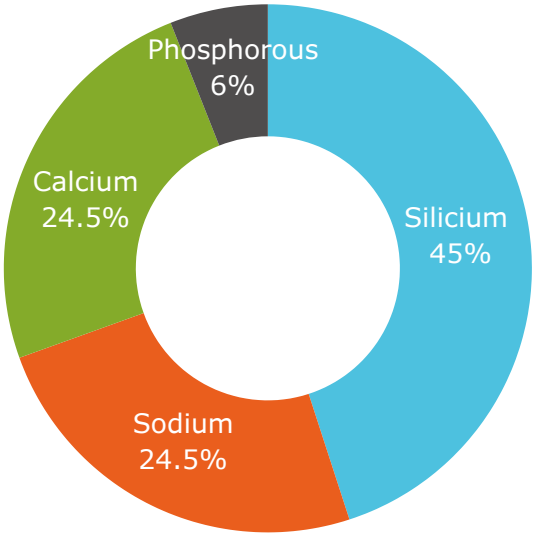
To note, cases reports were not subjected to clinical investigation protocols and are not sufficient proof to validate performance and safety of the device.

Please, consult our clinical studies.

BIOACTIVE GLASS

The bone substitute is made of Bioactive Glass 45S5, a revolutionary ceramic, composed of minerals naturally present in the human body.

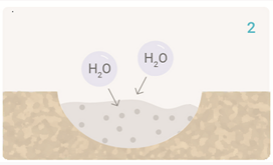
COMPOSITION



- Osteoconductive
- Improves the bone regeneration: natural matrix for cells to attach, differentiate and make new bone:
  - Bone Bonding
  - Soft tissue bonding
- 100 % synthetic
- Bioabsorbable
- Excellent biocompatibility

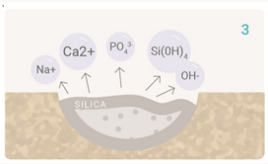
MECHANISM OF ACTION

1. Implantation of bioactive glass in a bone defect.
2. Rapid exchange of Na^+ and / or Ca^{2+} cations with H^+ of the solution, creating silanol (Si-OH) bonds at the glass surface: $SiO{-}Na^+ + H_2O \rightarrow Si{-}OH + Na^+_{(aq)} + HO^-$



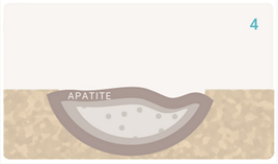
3. The pH of the solution increases and a silica-rich region forms near the surface of the glass. The high local pH drives the silica-glass network through HO^-, breaking the Si-O-Si bonds. The soluble silica is lost as $Si(OH)_4$ in the solution, leaving more than SiOH (silanols) at the glass / solution interface:

$$Si - O - Si + H_2O \rightarrow Si - OH + HO - Si$$

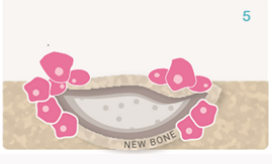


Then condensation of the Si-OH groups near the glass surface will allow to repolymerize the silica-rich layer.

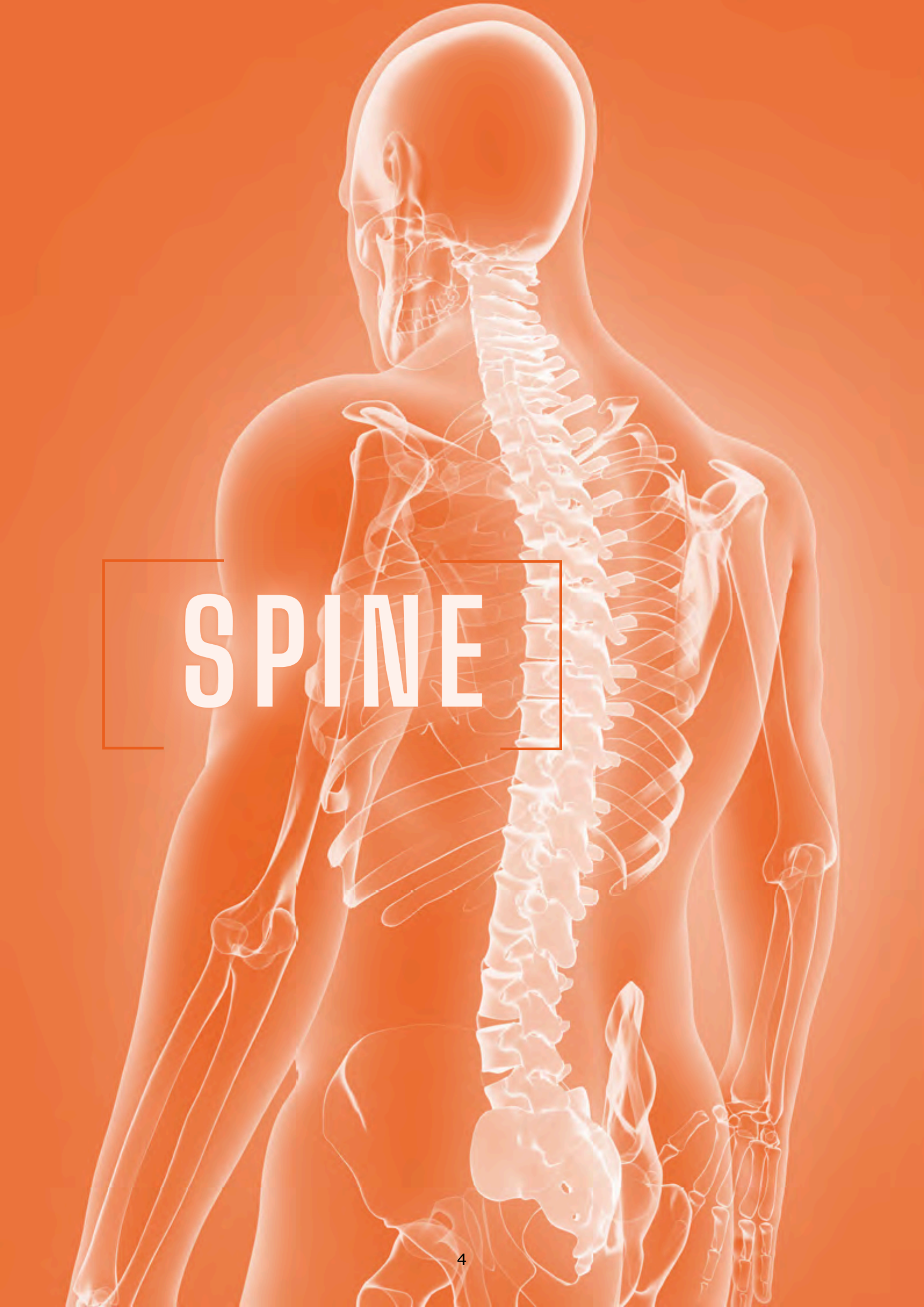
4. Migration of Ca^{2+} and PO_4^{3-} groups to the surface through the silica-rich layer and from the solution, thereby forming a film rich in amorphous calcium phosphate on the silica-rich layer. Finally, the incorporation of hydroxyls and carbonates in the solution and the crystallization of the calcium phosphate film will produce a carbonate hydroxy-apatite (CHA) layer. Therefore, this layer of hydroxyapatite formed is recognized as atural bone. This apatite will bind to native bone and soft tissues and release calcium and silicon ions, which promote bone formation by serving as a support for bone reconstruction (osteoconduction).



5-6. Following these reactions, bone growth continues, and bioactive glass continues to degrade and serves as a scaffold for bone regeneration.



SUMMARY


SPINE

SPINE

ORTHOPEDICS

CRANIO MAXILLO FACIAL - EAR NOSE THROAT

DENTAL

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.

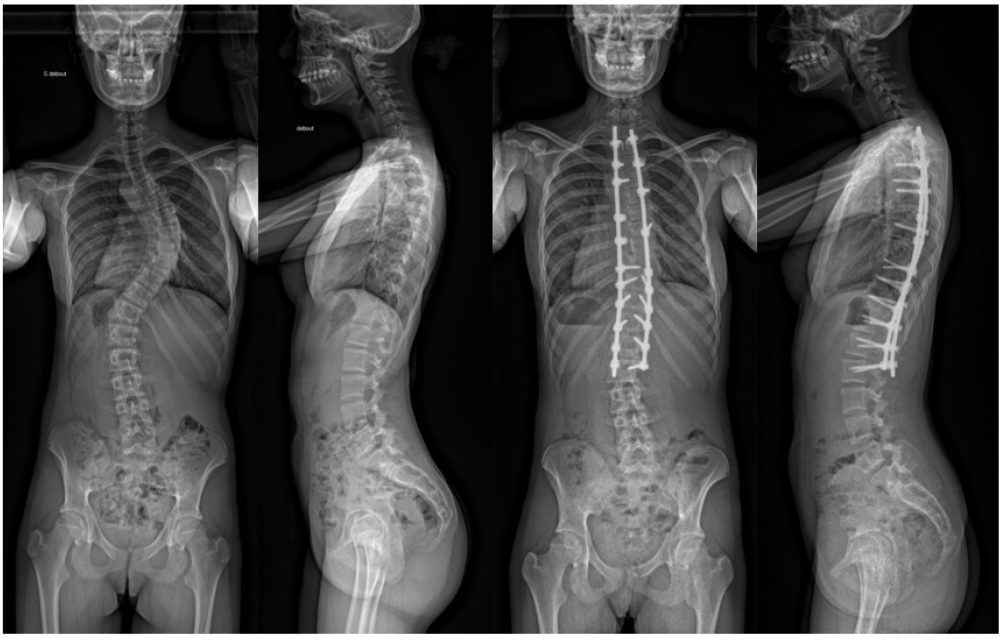

Figure 1. Pre- and post-operative full-spine coronal and sagittal X-rays illustrating a typical long construct for posterior fusion to correct a deformity.

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.

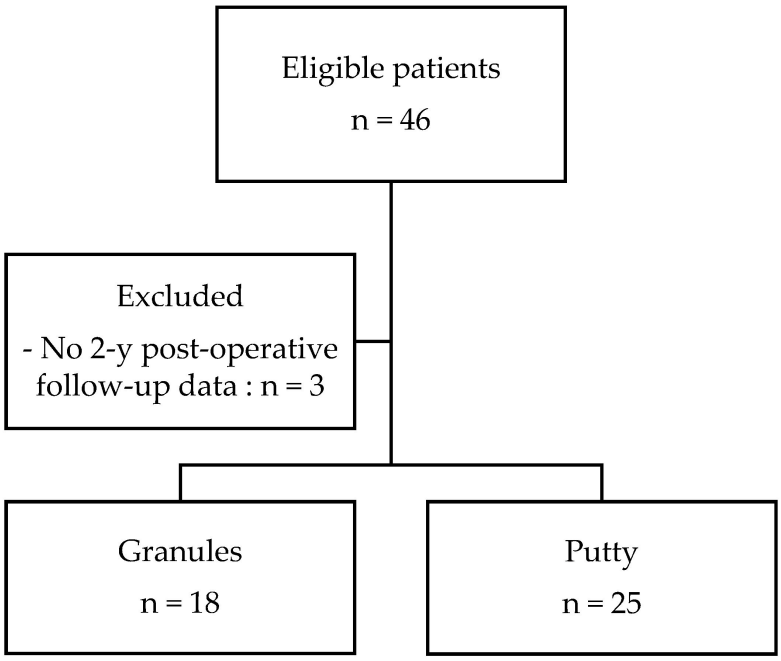

Figure 2. Flowchart of the study.

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.

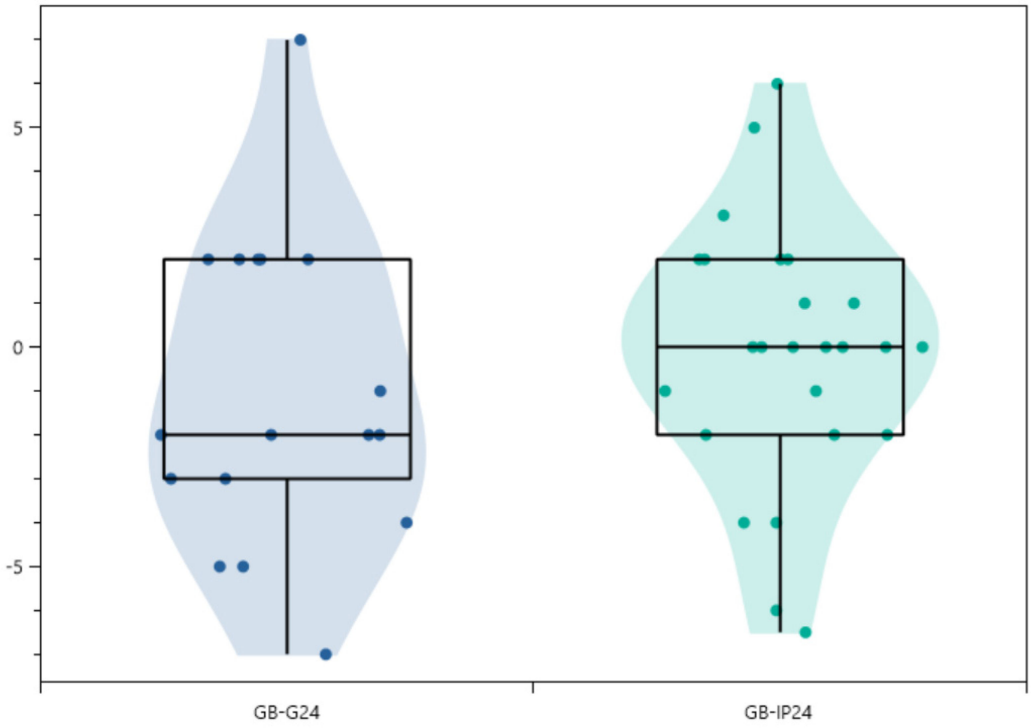

Figure 3. Box plots of loss of correction in the granule group (GB-G24) and the putty group (GB-IP24) groups, 24 months follow-up. There were no outliers. More than 50% of the data are included in the box plot for each material. The median is 0 for the putty group and −2 for the granule group. The results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

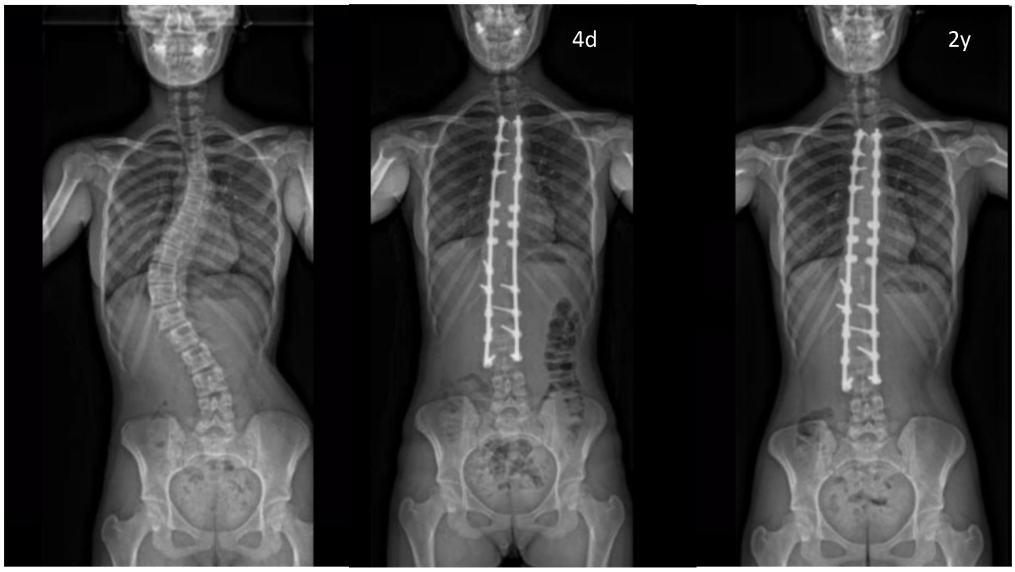

Figure 4. Pre- and post-operative full-spine coronal X-rays (1st erect and 2y po) illustrating the proper stabilisation of the main curve (<10°) without any screw loosening. (4d: Day 4 after surgery).

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

'GCS Ramsay Santé pour l'Enseignement et la Recherche' (IRB#: COS-RGDS-2021-05-004-SZADKOWSKI-M).

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

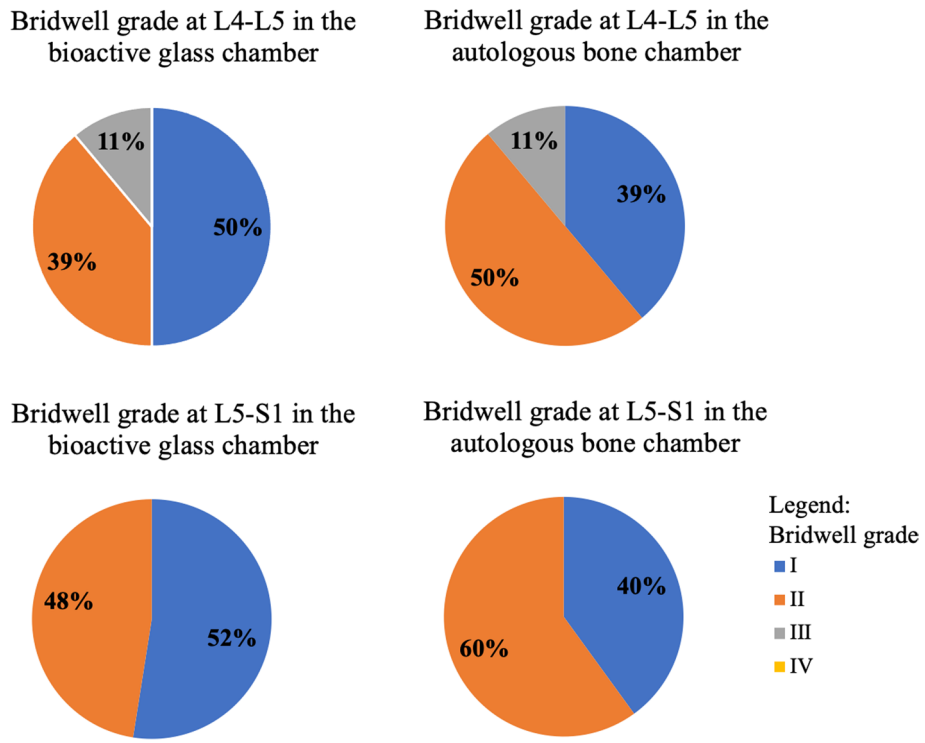

Fig. 1 Bar chart presenting the Bridwell grades in the chambers filled with bioactive glass and autologous bone, at L4-L5 and L5-S1

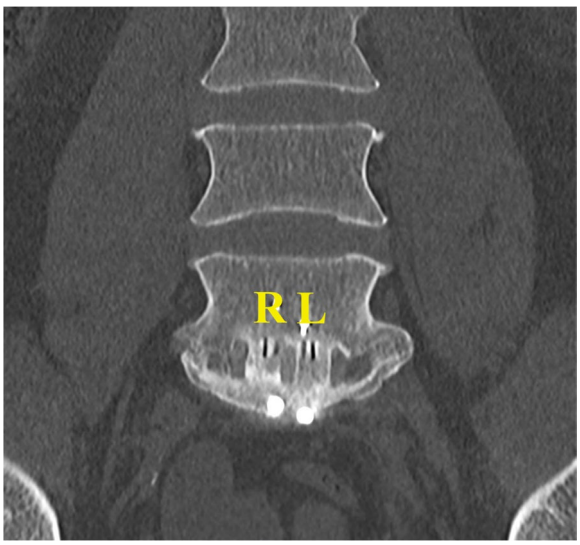

Fig. 2 Frontal CT scan of a patient with fusion of Bridwell grade I1 in both the chamber filled with bioactive glass (R) and the chamber filled with autologous bone (L)

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

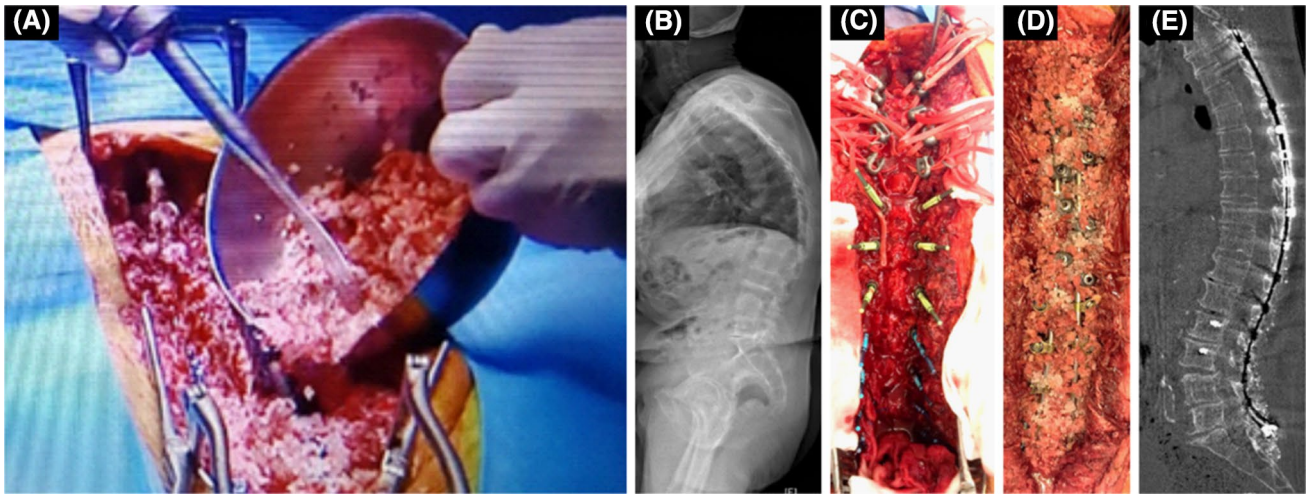

Fig. 1 **a** Mix of GlassBone with local autologous bone and saline serum place on the decorticated posterior elements of the spine; followed by an illustration of the surgery steps where a long instrumentation to treat thoraco-lumbar spinal deformity with sagittal imbalance. The composite bone graft/autologous 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

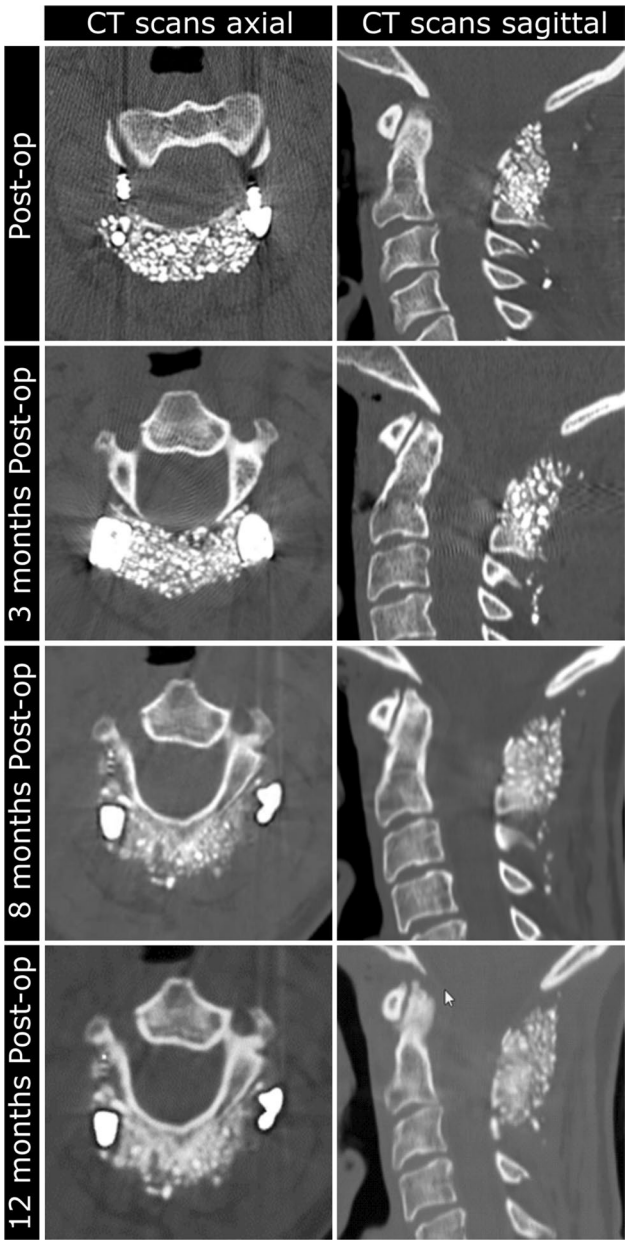

Fig. 2 Post-surgery CT scans of laminectomy with C1–C2 posterior fusion using a mixed of local bone and GlassBone

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

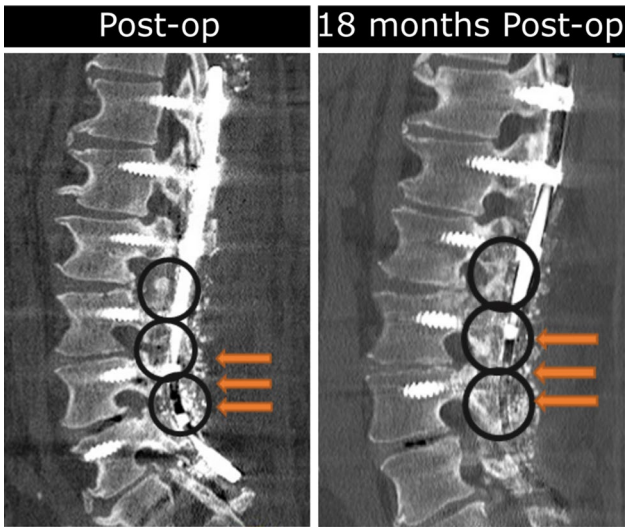

Fig. 3 Granules of bioactive glass are well-visible (orange arrow) immediately just after operation, and gap between posterior arches is visible (black circle). After 18 months, granules are less visible, and a bone bridging has formed with remodelling of the graft (color figure online)

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

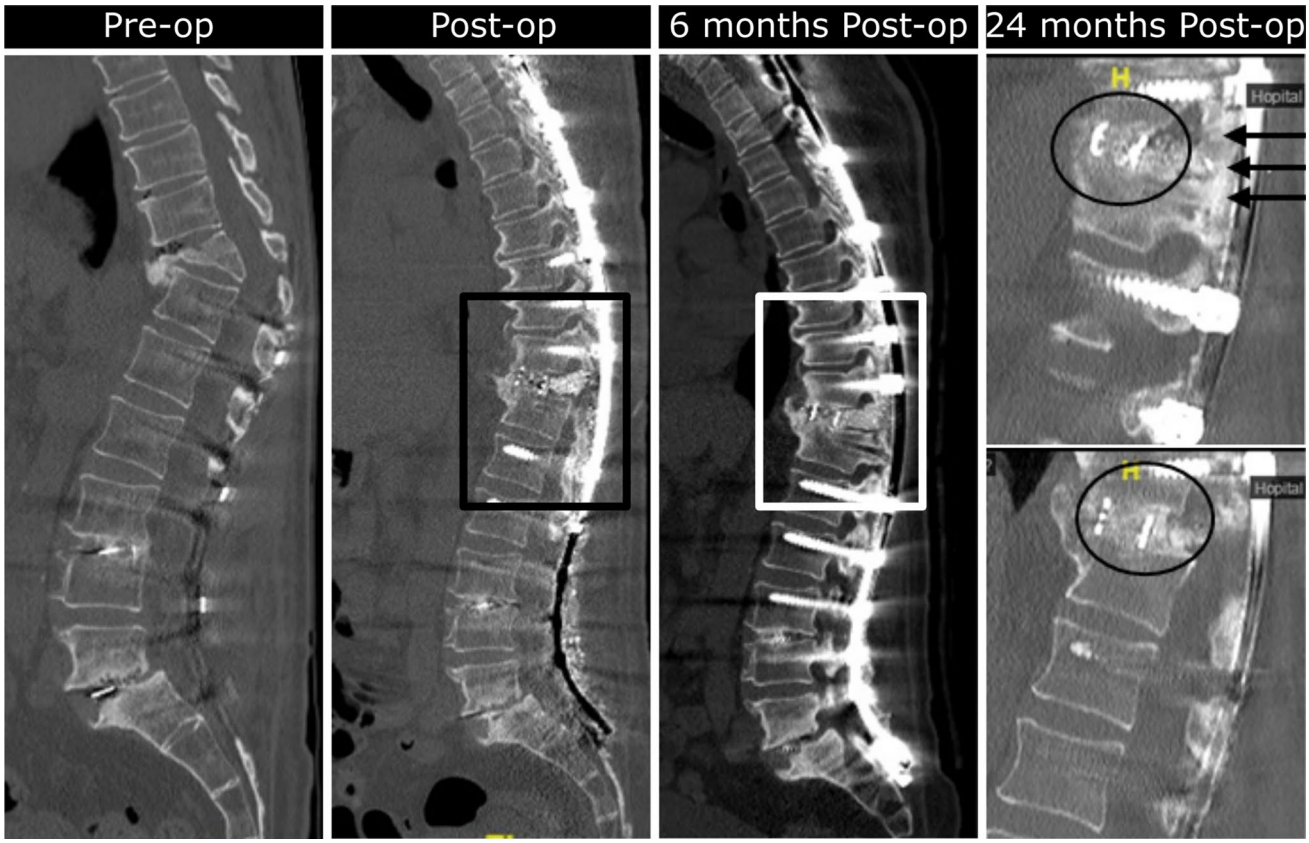

Fig. 4 Patient was operated by VCR (vertebral column resection) to treat PJK (proximal junctional kyphosis). The granules are visible immediately after surgery along the instrumentation. At 2 years after surgery, a bone bridging is clearly visible inside the vertebral cage and through the disc space

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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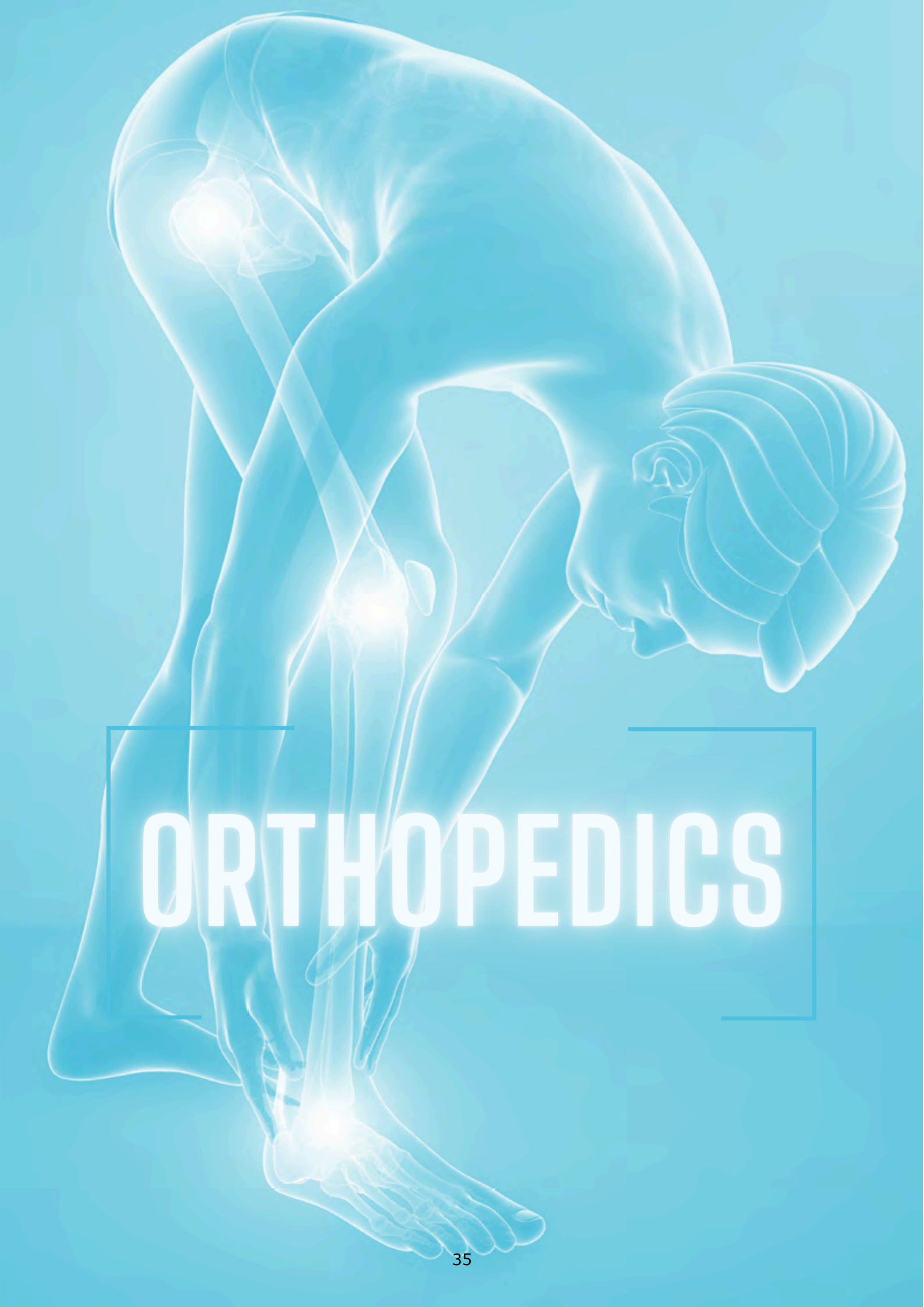
ORTHOPEDICS

SPINE

ORTHOPEDICS

CRANIO MAXILLO FACIAL - EAR NOSE THROAT

DENTAL

Orthopedic surgeries are performed daily to repair bone tissue due to traumatic injuries, disease as ntumors, deformity, and degeneration. It is intended to correct the osteoarticular deformations and to treat the painful joints/defect mainly due to the cysts, the tumors of the limbs and, finally, to correct the after-effects of the traumatisms (Andreasson et al., 2020; D'Elia et al., 2010; Dhanakodi et al., 2019; Dragosloveanu et al., 2020; Ferguson et al., 2019; Gaiarsa et al., 2019; Heikkila et al., 2011; Lindfors et al., 2009; Lindfors et al., 2010; Loveland et al., 2021; Pan et al., 2018; Pernaa et al., 2011; Shrouder-Henry et al., 2019; Thordarson & Kuehn, 2003; Wang & Yeung, 2017; Zhao et al., 2020) with or without infections.

Bone is one of the most common organs affected by metastases. Metastatic bone disease (MBD) can be caused by different primary tumors, with the highest prevalence being from breast and prostate cancer (Phull et al., 2021; Sebghati et al., 2021). Also, bone loss can be caused by the presence of a cyst or bone tumour that enlarge over time, resulting in thinning of the bone. Cysts are described as cavities filled with a benign fluid. Usually, these cysts are reported in the metaphyseal regions of long bones (50-70%) and 85% of unicameral bone cysts occur almost exclusively in children and adolescents (Dong et al., 2020; Noordin et al. 2018).

The treatment of tumors, cysts or even treatment-resistant infections often requires removing bone fragments that are too large for the natural self-repair process to be effective. Currently recommended treatment options include:

- curettage and bone-grafting
- intralesional injections with corticosteroids, bone marrow, demineralized bone matrix
- or bone ceramic filling, PMMA bone cement, decompression, not filling
- internal fixation
- and also combinations of these (Dong et al., 2020; Deventer et al., 2021; Gava & Engel, 2021).

After a fracture, the dead bone must be resorbed, and the new bone reformed. Bone resorption is performed mainly by osteoclasts and new bone formation is performed by osteoblasts. Osteoblasts line the outer surface of bones and are also present in most bone cavities. These cells secrete a very strong protein matrix, consisting mainly of collagen fibres. The matrix is then mineralized, and the osteoblasts become osteocytes. Blood vessels containing mineral elements are key contributors to the process of osteogenesis. Most bone fractures occur as a result of inconvenient or incompetent bone regeneration.

But sometimes segmental bone fractures did not repair instinctively and require orthopedic
operation (Ansari, 2019). Depending on the case, a repair of the fracture (osteosynthesis) by nail, plate, screw will be carried out with or without graft. In some cases (complex fracture of the elderly, risk of bone necrosis of the head, etc.) replacement by partial or total shoulder prosthesis will be chosen (Marongiu et al., 2020; Martin et al., 2021).

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ORIGINAL ARTICLE

The impact of bone graft type used to fill bone defects in patients undergoing ACL reconstruction with bone–patellar tendon–bone (BPTB) autograft on kneeling, anterior knee pain and knee functional outcomes

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Abstract

Purpose Multiple different materials are used for filling bone defects following bone–patellar tendon–bone (BPTB) graft ACL reconstruction surgery. The theoretical objective being to minimize kneeling pain, improve clinical outcomes and reduce anterior knee pain following surgery. The impact of these materials is assessed in this study.

Methods A prospective monocentric cohort study was conducted from January 2018 to March 2020. There were 128 skeletally mature athletic patients who underwent ACL reconstruction using the same arthroscopic-assisted BPTB technique, with a minimum follow-up of two years identified in our database. After obtaining approval from the local ethics committee, 102 patients were included in the study. Patients were divided into three groups based on type of bone substitute. The Bioactive glass 45S5 ceramic Glassbone™ (GB), collagen and hydroxyapatite bone void filler in sponge form Collapat® II (CP), and treated human bone graft Osteopure®(OP) bone substitutes were used according to availability. Clinical evaluation of patients at follow-up was performed using the WebSurvey software. A questionnaire completed in the 2nd post-operative year included three items: The ability to kneel, the presence of donor site pain, and the palpation of a defect. Another assessment tool included the IKDC subjective score and Lysholm score. These two tools were completed by patients preoperatively, and postoperatively on three occasions (6 months, 1 year, and 2 years).

Results A total of 102 patients were included in this study. In terms of Kneeling pain, the percentage of GB and CP patients' who kneel with ease were much higher than that of OP patients (77.78%, 76.5% vs 65.6%, respectively). All three groups experienced an important increase in IKDC and Lysholm scores. There was no difference in anterior knee pain between the groups.

Conclusion The use of Glassbone® and Collapat II® bone substitutes reduced the incidence of kneeling pain compared to Osteopure®. There was no influence of the bone substitute type on the functional outcome of the knee or on the anterior knee pain at two years of follow.

Keywords BTPT graft · ACL · Glassbone · Collapat · Osteopure · Kneeling pain

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Introduction

Anterior cruciate ligament (ACL) injuries are among the most common knee injuries, and ACL reconstruction (ACLR) is a widely performed operation [1, 2]. The bone–patellar tendon–bone (BPTB) and hamstring tendon autografts are two of the most commonly used autografts for ACLR [3, 4]. Furthermore, BPTB autograft has long been the gold standard for treatment, as its bone blocks at both ends of the graft provide high fixation strength [5, 6]. Nevertheless, 15–60% of patients may complain of long-term post-operative anterior knee pain during daily living or physical activities. Kneeling pain and donor site defects are also frequently observed [7–12].

It has been argued that patellar and tibial bone defects following graft harvesting are a risk factor impacting anterior knee pain in BPTB patients. Other claims are that infrapatellar nerve damage during graft harvesting is responsible for this morbidity [13, 14]. Recently, a systematic review showed that BTBP ACLR patients, whose bone defects were filled, have fewer post-operative knee complaints and better knee functional outcomes than patients treated without defect filling [8]. The most common bone grafts used are either autologous bone grafts, allogeneic bone grafts or synthetic substitutes [15–17]. Nonetheless, no study has compared the outcomes of different types of bone graft in terms of kneeling and functional outcomes in BTBP ACLR patients.

Such bone grafting options include the Bioactive glass 45S5 ceramic, such as Glassbone® (GB); collagen and hydroxyapatite bone void filler in sponge form, such as Collapat II® (CP), and treated human bone graft, such as Osteopure® (OP).

This cohort study aimed to investigate the influence of these bone graft types on kneeling and knee functional outcomes. The hypothesis was that there was no superiority of one substitute over another.

Materials and methods

A prospective single-center cohort study of the French prospective ACL Study [FAST] (NCT02511158) was performed, including all patients who performed ACLR using BPTB autograft between 2018 and 2020 by 4 senior surgeons. The study was approved by the local ethics committee (Comité de Protection des Personnes IDF VI), and informed consent was obtained from all patients. A retrospective analysis of the prospectively filled data, with a minimum follow-up of two years was performed. One hundred and two patients undergoing ACL reconstruction using BPTB autograft were assessed. Clinical evaluation of patients at follow-up was performed by the surgeons and data was entered in the WebSurvey software. The inclusion criteria were ACL reconstruction using the BTBP technique, athletes, a minimum of two years of post-operative follow-up and an age over 18 years. Exclusion criteria were associated knee ligament injury requiring surgical treatment, chondropathy of grade III or higher involving the trochlea or the patella, immune rheumatologic pathologies, preexisting anterior knee pain, and prior surgery on the same knee. Patients were divided into three groups according to bone substitute type. Three different bone substitutes were used according to availability at the time of surgery: Glassbone™, Collapat® II, and Osteopure®. The timeline is detailed in Fig. 1.

Bone substitutes

Osteopure® is a bone allograft harvested from a resected live human femoral head, and treated by sterilization at 25 kGy.

Glassbone® is a bioactive glass which is 100% synthetic, biocompatible, and osteoconductive and can integrate with the bone and soft tissue as a defect filler (Fig. 2). It is composed of a mixture of oxides (45% SiO_2, 24.5% CaO, 25.5%, Na_2O, and 6% P_2O_5 in weight %) [18–25].

Collapat® II is a bone void filler presented in spongy form. It is composed of a collagen structure in which hydroxyapatite granules are dispersed. The granules of hydroxyapatite give the material its osteoconductive properties [23].

Patient follow-up and data collection

Three tools were used for data collection at various time points. First, a questionnaire assessed the international knee documentation committee (IKDC) [24] subjective score and Lysholm score [25]. These two tools were completed by patients at four time points: first pre-operatively, and at 6 months, one year and two years postoperatively. Another standardized questionnaire was sent by email to the participants 4 months postoperatively. This was repeated at the 6 months, one year and two years marks following surgery. This questionnaire was made available online via a link to the WebSurvey software (websurvey.fr). If patients failed to answer, a first reminder was made via email, and a second by telephone call. Finally, a questionnaire was sent at the second post-operative year. It evaluated 3 items: The ability to kneel assessed by the subsection of Hacken's questionnaire [26], the presence of donor site pain during sports or daily activities assessed by the Numerical Rating Scales (NRS) [27], and the sensation of a defect at the donor site.

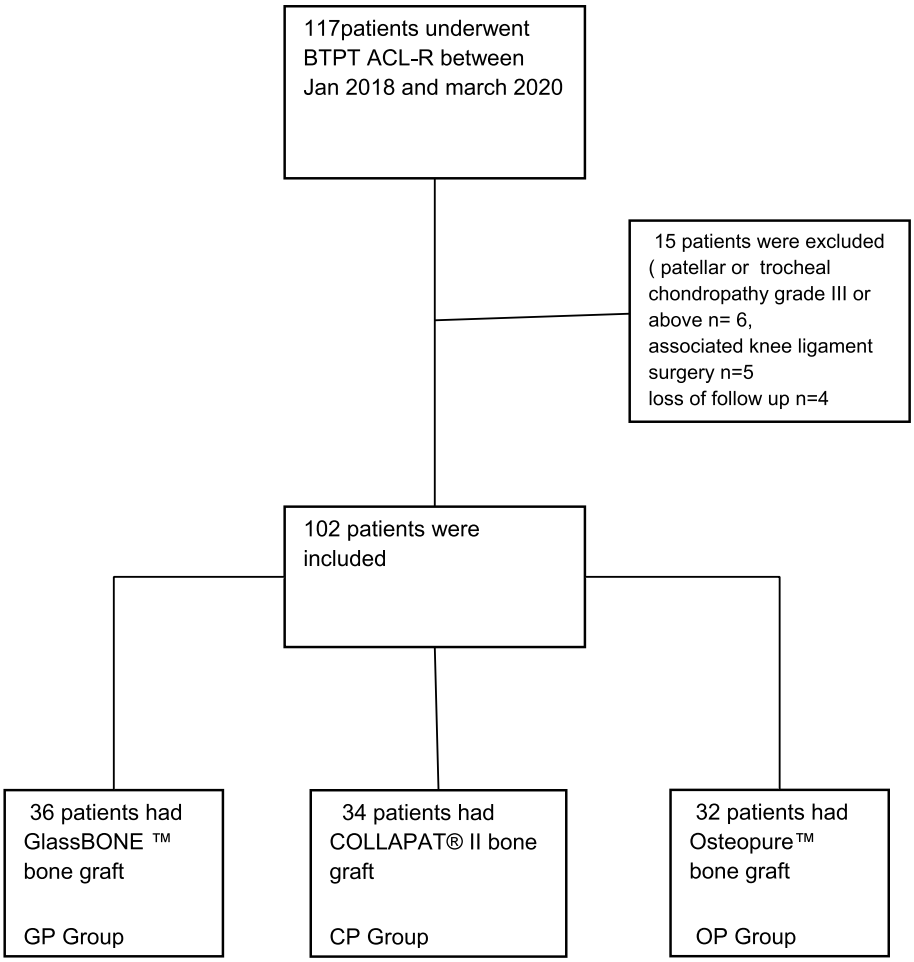

Fig. 1 Flowchart showing the distribution of patients into three groups

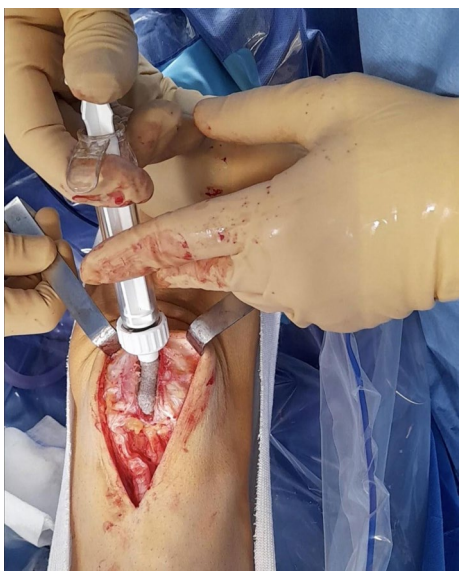

Fig. 2 Intra-operative photograph showing the patellar defect being filled with Glassbone allograft

No formal sample size calculation was done. All eligible patients who underwent ACLR BPTB graft between 2018 and 2020 at our institution were included in the study.

Surgical protocol

Under spinal anesthesia, BPTB autografts were used to reconstruct the ACL. A 9 cm para median incision was performed, the paratenon was dissected carefully, and the a middle third of the patellar tendon was harvested with approximately 10 × 10 × 20 mm bone blocks from the patella and tibia. The ACL remnant was preserved. The tibial bone tunnel was prepared to be 10 mm in diameter. The tibial tunnel was created with a specific guide (*Acufex; Smith & Nephew*). The femoral tunnel was 10 mm in diameter and placed at the origin of the native ACL, on the medial surface of the lateral femoral condyle using an inside-out technique. The BTB autograft was fixed in the femoral tunnel with a non-absorbable interference screw (*Softsilk; Smith & Nephew*) or absorbable pins using the RigidFix system (*DePuy Synthes, Mitek rigid fix*), depending on surgeon preference. After tensioning the graft, the patellar bone block

was stabilized in the tibial tunnel with another interference bioabsorbable screw (*Smith & Nephew*). Finally, the bony defects were filled with the corresponding bone graft and the paratenon was sutured over the bone substitutes.

Post-operative rehabilitation protocol

All patients underwent the same rehabilitation protocol. Immediate full weight-bearing with an articulated brace was allowed using crutches for the first 3 weeks to avoid unexpected falls. Physiotherapy for analgesia, patella mobilization, progressive full range-of-motion exercises, and isometric quadriceps contraction exercises were allowed, with the expectation that at one-month postoperatively, the patient would have a normal gait, full extension and 110° of flexion. In the case of meniscal suture, knee flexion while weight-bearing was limited to 120° for two months postoperatively.

Statistical analysis

All statistical analyses were performed using the IBM SPSS statistics software. Categorical variables were summarized as frequencies and percentages. Continuous variables were presented as means, standard deviations and ranges. One-way ANOVA was used to compare the mean IKDC and Lysholm scores, as well as the change in these scores between the three groups. Repeated measures ANOVA was used to compare the IKDC and Lysholm scores at different time points within each group. Pearson's Chi-square test or Fisher exact test were used to assess the association of gender, ability to kneel, and internal pain between the three groups. All tests were two-sided and a $p < 0.05$ was considered statistically significant.

Results

One hundred and seventeen patients underwent ACLR using BPTB autograft. Of those, 102 (87.17%) were included in this study, and 15 (12.83%) were excluded. Among the 102 patients, 36 (35.29%) patients were placed in the Glassbone® group (group 1), 34 (33.33%) in the Collapat II® group (group 2), and the remaining 32 (31.37%) in the Osteopure® group (group 3). The three groups had no significant differences in terms of age ($p = 0.127$) and gender ($p = 0.511$). The mean age was 32.17 ± 8.20 years. Men represented 78.43% of the studied population. Detailed demographic characteristics are described in Table 1.

Among the 102 patients studied, 27 (26.47%) complained of Kneeling pain. There was a significant difference between the three groups ($p = 0.045$), the percentage of Glassbone and Collapat patients' who kneel comfortably was significantly higher than that of osteobank patients (77.78%, 76,5% vs 65.6%, respectively). Moreover, the percentage of osteobank patients who were unable to kneel on hard surfaces was higher than that of Glassbone and Collapat patients (8% vs 2,78; 2.94%, respectively).

In the study population, 31 (30.39%) patients had anterior knee pain with an average of 3.77 ± 1.50 on the NRS scale. The percentage of patients experiencing anterior knee pain was 30.56% (mean 3.64 ± 1.03), 29.41% (mean 3.80 ± 1.69), and 31.25% (mean 3.90 ± 1.85) in groups 1, 2 and 3, respectively (p value 0.987).

The clinical characteristics are described in Table 2.

The IKDC score was significantly improved in the three groups compared to the pre-operative status ($P < 0.01$), as detailed in Table 3.

In group 1, the mean IKDC score increased from 56.67 ± 14.43 (range 26–84) pre-operatively to 69.22 ± 9.54 (range 36–86), 76.42 ± 9.26 (range 54–89) and 81.17 ± 10.61 (range 55–97) at 6 months, 1 year and 2 years postoperatively respectively, with a statistically significant mean change of 24.50 ± 15.64 (range (− 4)–60) ($p < 0.001$).

In group 2, the mean IKDC score increased from 60.35 ± 15.28 (range 32–90) at pre-operative to 66.65 ± 14.14 (range 20–83), 74.82 ± 16.58 (range 26–99) and 81.18 ± 15.97 (range 26–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 20.52 ± 15.55 (range (− 8)–55) ($p < 0.001$).

In group 3, the mean IKDC score increased from 53.63 ± 18.38 (range 13–84) at pre-operative to 66.31 ± 16.15 (range 33–95), 74.16 ± 15.89 (range 39–98) and 77.69 ± 16.79 (range 40–98) at 6 months, 1 year and

Table 1 Patients demographic characteristics

		Overall ($n = 102$)	GlassBone Group ($n = 36$)	Collapat II Group ($n = 34$)	Osteobank Group ($n = 32$)	P value
Age (years)	Mean ± SD (range)	32.17 ± 8.20 (18–56)	30.36 ± 8.38 (18–48)	34.32 ± 7.57 (21–54)	31.91 ± 8.36 (20–56)	0.127*
Gender n (%)	Male	80 (78.43)	30 (83.33)	27 (79.41)	23 (71.88)	0.511‡
	Female	22 (21.57)	6 (16.67)	7 (20.59)	9 (28.13)	

SD: Standard deviation. *p value was calculated using one-way ANOVA. ‡p value was calculated using Chi-square test or Fisher exact test. $P < 0.05$ was considered as statistically significant

Table 2 Patient clinical characteristics

		Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	P value
Kneeling n (%)	No pain with kneeling	75 (73.53)	28 (77.78)	26 (76.5)	21 (65.63)	0.045‡
	Mild pain with kneeling	13 (12.75)	6 (16.66)	5 (14.71)	2 (6.25)	
	Inability to kneel on hard surfaces	10 (9.80)	1 (2.78)	1 (2.94)	8 (25.0)	
	Completely, unable to kneel	4 (3.92)	1 (2.78)	2 (5.88)	1 (3.12)	
Anterior knee pain n (%)	No	71 (69.61)	25 (69.44)	24 (70.59)	22 (68.75)	0.987‡
	Yes	31 (30.39)	11 (30.56)	10 (29.41)	10 (31.25)	
If yes, NRS score ($n=31$)	Mean ± SD (range)	3.77 ± 1.50 (1–7)	3.64 ± 1.03 (2–5)	3.80 ± 1.69 (2–7)	3.90 ± 1.85 (1–6)	0.925*
Defect sensation	Yes	0	0	0	0	NA
	No	102 (100%)	36 (100%)	34 (100%)	32 (100%)	

SD: Standard deviation. *p value was calculated using one-way ANOVA. ‡p value was calculated using Chi-square test or Fisher exact test. $P<0.05$ was considered as statistically significant

Table 3 IKDC score at each time point by type of the bone substitute groups

	Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	P value*
Pre-operative	56.94 ± 16.11 (13–90)	56.67 ± 14.43 (26–84)	60.35 ± 15.28 (32–90)	53.63 ± 18.38 (13–84)	0.238
6 months post-op	67.45 ± 13.37 (20–95)	69.22 ± 9.54 (36–86)	66.65 ± 14.14 (20–83)	66.31 ± 16.15 (33–95)	0.615
1 year post-op	75.18 ± 14.07 (26–99)	76.42 ± 9.26 (54–89)	74.82 ± 16.58 (26–99)	74.16 ± 15.89 (39–98)	0.794
2 years post-op	80.08 ± 14.54 (26–100)	81.17 ± 10.61 (55–97)	81.18 ± 15.97 (26–100)	77.69 ± 16.79 (40–98)	0.537
Pre-op to 2-year post-op change	23.14 ± 16.99 (− 15–73)	24.50 ± 15.64 ((− 4)–60)	20.52 ± 15.55 ((− 8)–55)	24.06 ± 19.94 ((− 15.0)–73)	0.624
P value†		< 0.001			

SD: Standard Deviation; IKDC: International Knee Documentation Committee. Data were expressed as mean ± SD (range). *P value was calculated using one-way ANOVA. †P value was calculated using repeated measure ANOVA. $P<0.05$ was considered as statistically significant

2 years post-operative respectively, with a statistically significant mean change of 24.06 ± 19.94 (range (− 15.0)–73) ($p<0.001$).

There was no statistically significant difference in the mean IKDC score between the three groups ($p>0.05$).

The evolution of IKDC score by time in the three groups is shown in Fig. 3.

The Lysholm score was significantly improved in the three groups compared to the pre-operative status ($p<0.01$) as detailed in Table 4.

In group 1, the mean Lysholm score increased from 67.53 ± 15.18 (range 28–95) at pre-operative to 81.33 ± 11.26 (range 44–95), 86.53 ± 10.24 (range 60–99) and 89.78 ± 9.90 (range 52–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 22.25 ± 15.21 (range (− 6)–66) ($p<0.001$).

In group 2, the mean Lysholm score increased from 67.88 ± 18.06 (range 15–95) at pre-operative to 81.41 ± 16.02 (range 22–99), 85.68 ± 13.43 (31–100) and 87.18 ± 13.78 (range 30–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 19.29 ± 14.18 (range (− 1)–80.0) ($p<0.001$).

In group 3, the mean Lysholm score increased from 60.84 ± 20.61 (range 2–99) at pre-operative to 76.09 ± 13.32 (range 49–100), 80.78 ± 11.82 (range 56–98) and 85.16 ± 12.37 (range 56–100) at 6 months, 1 year and 2 years post-operative respectively, with a statistically significant mean change of 24.31 ± 21.93 (range (− 11)–80) ($p<0.001$).

Similarly, to the IKDC score, no statistically significant difference in the mean Lysholm score between the three groups was detected ($p>0.05$).

The evolution of Lysholm score by time in the three groups is shown in Fig. 4.

All patients in the study, having subjectively assessed their knees, found no sensation of a bony defect at 2 years

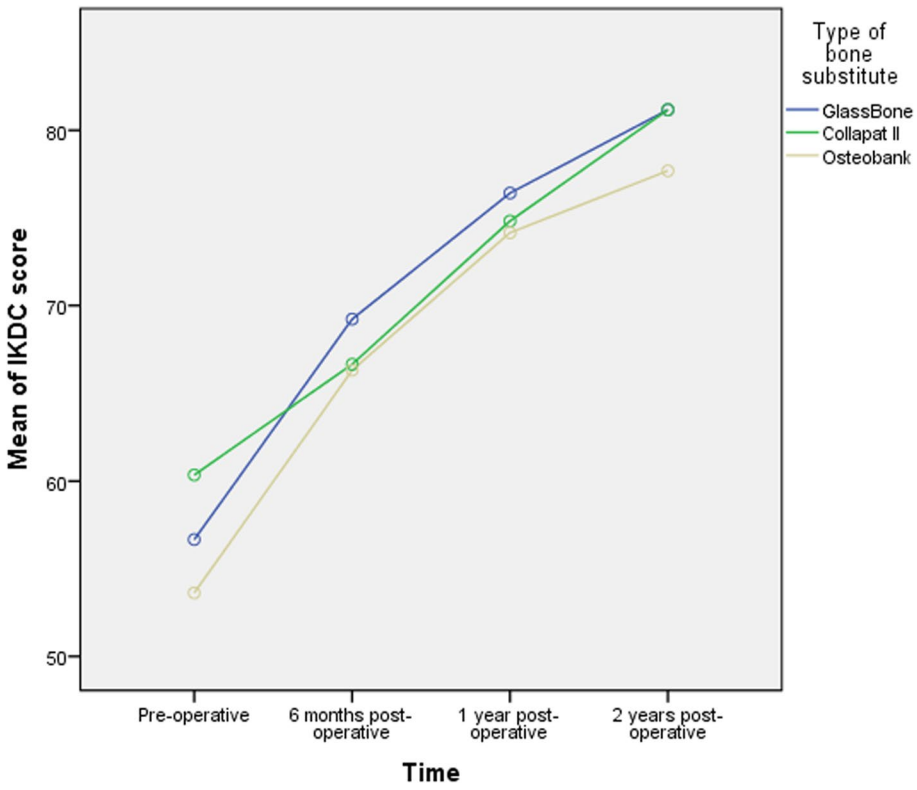

Fig. 3 Evolution of the IKDC score over time

Table 4 Lysholm score at each time point by type of the bone substitute groups

	Overall ($n=102$)	GlassBone group ($n=36$)	Collapat II group ($n=34$)	Osteobank group ($n=32$)	P value*
Pre-operative	65.55 ± 18.09 (2–99)	67.53 ± 15.18 (28–95)	67.88 ± 18.06 (15–95)	60.84 ± 20.61 (2–99)	0.207
6 months postoperative	79.72 ± 13.72 (22–100)	81.33 ± 11.26 (44–95)	81.41 ± 16.02 (22–99)	76.09 ± 13.32 (49–100)	0.198
1 year postoperative	84.44 ± 12.02 (31–100)	86.53 ± 10.24 (60–99)	85.68 ± 13.43 (31–100)	80.78 ± 11.82 (56–98)	0.110
2 years postoperative	87.46 ± 12.11 (30–100)	89.78 ± 9.90 (52–100)	87.18 ± 13.78 (30–100)	85.16 ± 12.37 (56–100)	0.290
Pre-operative to 2-year change	21.91 ± 17.26 (− 11–80)	22.25 ± 15.21 ((− 6)–66)	19.29 ± 14.18 ((− 1)–80.0)	24.31 ± 21.93 ((− 11)–80)	0.497
P value†		< 0.001			

Data were expressed as mean ± SD (range). *p value was calculated using one-way ANOVA. †p value was calculated using repeated measure ANOVA. $P < 0.05$ was considered as statistically significant

follow-up (Table 2). One incidence of a superficial abscess at the surgical site was observed in group 2. In this patient, the substitute was excized and an extra-articular debridement was needed to manage the complication.

Discussion

This study was designed to compare outcomes of ACL reconstruction with a BPTB autograft using one of three bone substitutes to fill the harvested zone. The primary finding was that the patients who received synthetic bone grafts, (Glassbone or Collapat II) had a higher percentage of painless kneeling compared to those who had Osteopure allograft filling. However, there was no significant difference between the three groups in terms of IKDC, Lysholm, and anterior knee pain.

Kneeling pain was evaluated using one item of Hacken's questionnaire [26]. The higher incidence of kneeling pain of patients of group 3 compared to patients from other groups might be due to the persistent inflammatory response or suboptimal bone consolidation caused by the Osteopure allograft [28]. The incidence of painless kneeling in this study was 73.53% overall, with 77.78% of the Glassbone patients reporting no pain. After reviewing the literature, it was found that this was higher than the study by Taylor et al. (62%) [29] and lower than the study by Hacken et al. (90.4%) [26]. In both of those studies, cancellous autograft

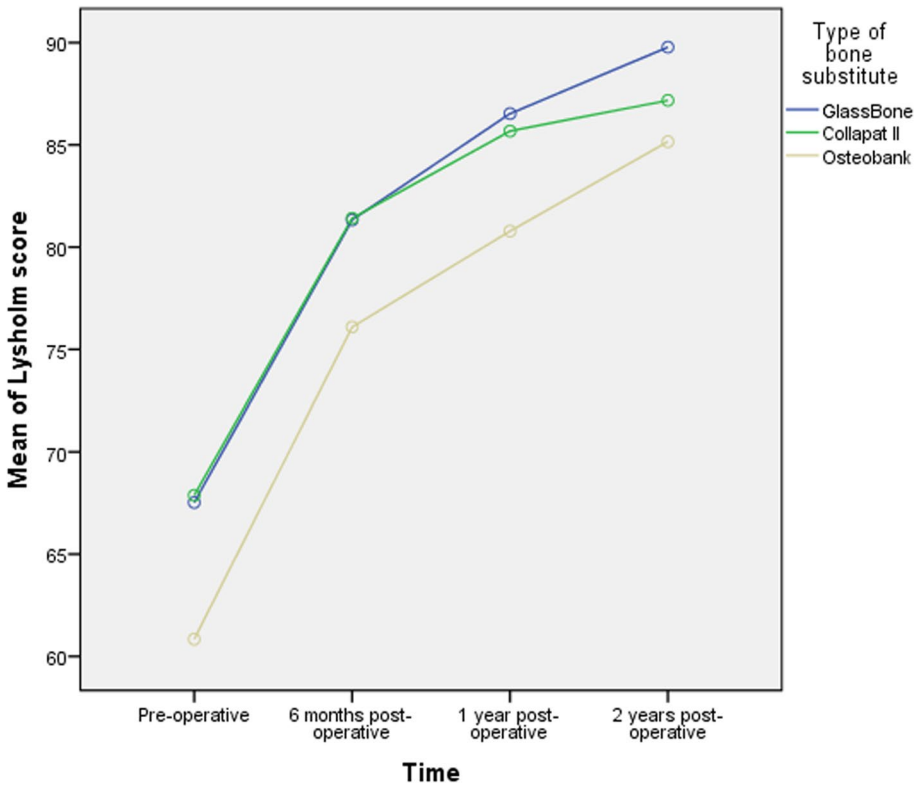

Fig. 4 Evolution of the Lysholm score over time

had been used for filling the bone defects. On the other hand Barrenius [30], Leitge [31] and Liden [32] who did not fill the bone defects registered a higher incidence of kneeling pain than the findings of the present study.

From a cosmetic standpoint, filling the defect with allograft improves appearance, a common patient concern, and abolishes the sensation of a bone gap or defect at the donor site. This allows avoidance of a further patient complaint during follow-up visits [33].

A major concern with using BPTB autograft for ACLR is donor site morbidity, specifically anterior knee pain [26]. Surgeons have attempted to change the harvesting technique in order to decrease this complication [12, 34], others have elected to change the graft type, like Schande et al. who used serum albumin-coated bone allograft [35]. Cervelline et al. filled the donor sites with PRP gel [36]. Nelson et al. also described a new technique for filling the defect [37]. Naresh et al. elected to fill the defects with ceramic bone graft but the results were non-satisfactory [38]. Our study aimed to identify the influence of different types of bone substitutes on anterior knee pain and found similar results in all three groups. The results are comparable to the findings of a systematic review by Lameire et al. who showed that filling defects decreased anterior knee pain, kneeling pain and extension loss [8].

No study evaluated and compared the functional outcome and donor site morbidity between Glassbone, Collapat II, or Osteopure bone substitutes in the BPTB ACLR population. Although there are numerous scoring tools to quantify ACLR patients' results [39], IKDC and Lysholm scores were chosen for this study, as they are standard instruments for evaluating patients postoperatively and two of the most commonly reported functional outcome scores [8, 26, 40]. Both scores in the present study showed satisfactory recovery in all three groups without significant difference between groups. Subjective IKDC ranged from 77 to 81 after two years following ACLR, and the Lysholm score ranged from 85 to 90. Comparing our results to the systematic review by Lameire et al., it is observed that the IKDC scores are similar, but the Lysholm scores are inferior [8]. Overall, however, it was determined that the type of bone substitute did not affect the functional knee outcome.

There was no complication reported in terms of wound healing except for a patient from group 2 who exhibited an extrusion of part of the bone substitute and needed surgical intervention. This case might be a coincidence, and conclusions cannot be drawn based on a single exceptional case. It is important to mention that this is the first study that showed the tolerance of donor sites to Glassbone in BPTB ACLR patients. There were no complications detected which might be due to its bacteriostatic activity [22]. No patellar fracture occurred in any patient of the three groups. This is similar to the results of Alexander et al. [41].

This study shows that the kneeling pain was higher in Osteopure group. We can only speculate about this discrepancy. Osteopure is a natural bone block which needs to be cut into shape to fill a defect. As a rigid substitute, it is more difficult to fully fill the defect with it compared to the other softer substitutes (Glassbone and Collapat). Furthermore, it is composed of cancellous bone. Perhaps the replacement of cortical bone from the patella and tibia with spongy bone from the bone substitute affects rigidity and therefore leads to more pain in this patient population. Bone graft healing is a sequential process involving inflammation revascularization, osteogenesis remodeling, and incorporation into the host skeleton to form a mechanically efficient structure so this process might be different between the three allograft types. Further studies would be needed to possibly give a more accurate response in the future.

The strengths of this study were the high response rate, the 2-year follow-up period and the prospective administration of questionnaires.

There were, however, several limitations. First, this was not a randomized trial, and it was not a blinded study. Although patients may have been blinded, the surgeons would not have been. Furthermore, the bone substitute used was done so based on availability, rather than random assignment. Secondly, although the operations were all performed in the same institution, different surgeons participated in the study and performed surgery. Moreover, concomitant meniscus injury was not part of the exclusion criteria. This likely affects standardization of the procedure and may cause variability in patient outcomes.

Conclusion

This study finds that there is a reduced incidence of kneeling pain and discomfort when using bone substitutes such as Glassbone® and Collapat II® compared to allografts such as Osteopure® at a 2-year follow-up. However, the choice of bone-filling material influences neither functional knee outcomes, nor anterior knee pain at 2 years postoperatively.

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Declarations

Conflict of interests All authors have declared and signed that they have no conflict of interests.

Ethical approval Animals are not involved.

Informed consent Humans were involved, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The Institutional review board CPP (comité pour la protection des personnes) CPP-Ile-de-France VI reviewed and approved the study protocol on 07/02/2013, see the certificate in the supplemental materials.

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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Is a Bioceramic Glass Bone Graft Superior to Spongious Allografts in Femoral and Tibial Benign Bone Lesions?

Femoral ve Tibial Benign Kemik Lezyonlarında Biyoseramik Cam Greftler Spongioz Allogreftlerden Üstün müdür?

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Abstract

Objective: this study aimed to examine the results of spongious and bioceramic bone graft applications in benign lesions of the lower extremity long bones.

Methods: Forty-seven patients, who applied to our hospital between the years 2007 and 2013; who received curettage-grafting for benign bone lesions in the long bones carrying lower extremity weight were examined retrospectively.

Results: In the bioceramic glass bone graft group, an increased average consolidation ratio, which is statistically significant compared to the spongious allograft group (p=0.002), was observed. When the fibrous dysplasia patients were considered a subgroup, the consolidation ratio in the bioceramic glass bone graft group was found to be significantly high compared to the spongious allograft group (p=0.029).

Conclusion: Bioceramic glass bone grafts are bone filler materials that hold radiologically superior and clinically similar results compared to spongious allografts. Having a statistically significant radiological consolidation success in fibrous dysplasia, which is a benign aggressive tumor, bioceramic glass bone grafts may be thought to be capable of being an advantage option for benign aggressive tumors.

Keywords: Bioceramic glass bone graft, spongious allograft, femur, tibia, benign bone lesion

Öz

Amaç: Bu çalışmanın amacı, alt ekstremite uzun kemiklerindeki benign lezyonlarda uygulanmış spongioz ve biyoseramik cam greftin sonuçlarının incelenmesidir.

Yöntem: 2007 ile 2013 yılları arasında hastanemize başvuru yapmış, alt ekstremite yük taşıyan uzun kemiklerindeki iyi huylu kemik lezyonlarına yönelik küretaj-greftleme operasyonu yapılan kırk-yedi hasta retrospektif olarak incelendi.

Bulgular: Biyoseramik cam greft grubunda, insan kaynaklı spongioz allogreft grubuna kıyasla, istatistiksel olarak anlamlı, artmış ortalama konsolidasyon oranı görülmüştür (p=0,002). Fibröz displazi hastaları sub-grup olarak değerlendirildiğinde; biyoseramik cam greft grubundaki konsolidasyon oranı, insan kaynaklı spongioz allogreft grubuna kıyasla anlamlı olarak yüksek bulunmuştur (p=0,029).

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Öz

Sonuç: Biyoseramik cam greftler, insan kaynaklı spongioz allogreftlerle karşılaştırıldığında radyolojik olarak üstün, klinik olarak benzer sonuçlara sahip kemik dolgu materyalleridir. Biyoseramik cam greftlerin; benign agresif tümör olan fibröz displazideki radyolojik konsolidasyon başarısının istatistiksel olarak anlamlı olmasından dolayı, benign agresif tümörlerde avantajlı bir seçenek olarak düşünülebilir.

Anahtar Kelimeler: Biyoseramik cam greft, spongioz allogreft, femur, tibia, benign kemik lezyonları

Introduction

The gold standard is autogenous bone graft applications while there are several graft material usages for treating bone defects resulting from congenital anomalies, diseases, tumoral lesions, atrophy, or surgical excisions. An autogenous graft holds some difficulties such as generating a second surgery region, risk of having a tumor, increase in patient morbidity, and the possibility of being incapable of obtaining the desired amount of bone graft. These situations led researchers to seek an ideal bone graft material that can substitute autogenous bone grafts. MacEwen first implemented allograft in humans with the purpose of child humerus reconstruction in 1881[1]. Until quite recently, orthopedic surgeons possessed only autologous bones and allografts as bone resources. Today, several different options have been improved using tissue engineering applications. Bioactive glass grafts are the products of this technology. The recent research has served for increasing the osteo-conductive, osteo-inductive, and osteogenic features of bone grafts obtained via synthetic ways.

The aim of treatment in benign bone lesions is to provide an osteo-conductive effect rather than a biological effect. Therefore, autograft or bioceramic grafts can be used for these lesions. The current study seeks a solution to partial healing on spongious allografts and to shed light on the literature. There is no previous study on this issue in our knowledge.

Materials and Methods

In this study, patients, who applied to our hospital between the years 2007 and 2013 and who were given curettage-grafting for benign bone lesions in their long bones carrying lower extremity weight were examined retrospectively after the approval of the İzmir Tepecik Education and Research Hospital Research Ethics Committee (date: 24.11.2015, decision no: 22).

Inclusion criteria were that the tumor was located in the femur or tibia and was treated with curettage and grafting using a bioceramic glass bone graft or spongious allograft. The criteria of exclusion from the study have been determined as lesions located were not femur and tibia; malign bone tumor, non-ossifying fibroma (NOF), fibrous cortical defect (FCD), and osteoid osteoma cases, severe systematic diseases, nonattendance for follow-up.

During this period, 123 patients underwent curettage and grafting operations. Seventy-six (62%) patients were excluded because the tumor was outside the femur or tibia (n=63), two patients had malignant bone tumors, eight patients had NOF-FCD or osteoid osteoma, one patient had advanced systemic disease, and two patients had nonattendance for follow-up.

Forty-seven (38%) patients who did not meet the exclusion criteria were included in the study. There were 29 patients (62%) treated with spongious allograft in group 1, and 18 patients (38%) treated with bioceramic glass bone grafts in group 2.

Physical examination findings, surgery records, and radiological findings were evaluated.

X-rays of affected bones were taken preoperatively; and the second week, the first month, the third month, the sixth month, the first year, and following years postoperatively for a checkup, and their visual analogue scale (VAS)[2] and lower extremity functional scale (LEFS)[3] scores were calculated and evaluated.

Preoperative lesion volume and the amount of graft used in the operation were calculated in cm^3. The lesion volume was calculated in a computer environment on magnetic resonance images. Additionally, patients with fibrous dysplasia were evaluated as a subgroup.

The groups were evaluated among each other following the staging of the tumors[4].

All patients in the study received the same surgical technique, opening a cap on the bone, curettage of the mass, the application of chemical cauterization with 1% formaldehyde and 70% alcohol, respectively, each for five minutes, a lot

of irrigation with physiological saline solution and filling with bone graft materials. The operation was performed by a single surgeon.

Cefazolin was given to all patients on the day of the operation and the day after the operation in 3 equal doses of 50 mg/kg for 2 days with the purpose of prophylaxis.

The spongious bone graft used in this study has crushed and freeze-dried primer form (Tranzgraft by Aziyo Biologics) while bioceramic glass bone graft has granule and bioglass primer form. A bioceramic glass bone graft is composed of silicon dioxide (45%), calcium oxide (24.5%), disodium oxide (24.5%) and pyrophosphate (6%) (GlassBoneR by Noraker).

Statistical Analysis

Statistical Package for Social Sciences version 17 was used for statistical analysis. The normality of continuous data was evaluated with the Shapiro-Wilk test. If the distribution of data was evaluated as normal, a t-test was used for statistical comparison. In the case of non-normally distribution, the Mann-Whitney U test was used. Categorical data were compared with the Fisher exact test. A p-value <0.05 was set as statistically significant.

Results

The study included 47 patients, 19 (40%) of whom were males. The average age was found to be 23.08 (7-57) (Table 1). Twenty-three of the patients had lesions located on femurs and twenty-four located on tibias. No statistically significant differences were found between the graft materials used when considered in terms of age, gender, and location (p>0.05).

Radiological consolidation success is achieved by proportioning the volume of the consolidated region on average 16.36 months (6-48) after curettage and grafting was evaluated.

The average pain score (out of 10, according to VAS) at the end of the follow-up period in the spongious graft group was 1.07±0.96 (0-3) while it was 1.0±0.84 (0-3) in the bioceramic glass bone graft group (p=0.898).

The average lower extremity function score percentage (out of 100, according to LEFS) at the end of the follow-up period in the spongious graft group was 93.75±3.67% (86.25-100) whereas it was 94.51±3% (88.75-100) in the bioceramic glass bone graft group (p=0.581).

The preoperative volume of tumors of the 47 patients was 43.15 (7-150) cm^3 on average and the average amount of graft applied to all the patients was 58.21 (8-180) cm^3 (Table 2). The average tumor volume was 45.79 cm^3 and the average amount of graft used was 67.93 cm^3 in the spongious allograft group, whereas the average tumor volume was 38.89 cm^3 and the average amount of graft used was 42.55 cm^3 in the bioceramic glass bone graft group (Figure 1). The rate of average tumor volume and the average amount of grafts used were calculated as 62.14±17.38% (33-92) in the spongious allograft group while they were calculated as 89.11±7.07% (70-100) in the bioceramic glass bone graft group (p<0.001).

When we examine the consolidation ratio according to the graft material used, 15 (52%) of the patients who received spongious bone graft were greater than 90%; 7 (24%) were between 80 and 90; 7 (24%) were below 80% [2 (7%) were 50%>], and 15 (83%) of the patients who received bioceramic glass bone graft were above 90%, and 3 (17%) were between 80 and 90% (Figure 2). The average consolidation ratio at the end of the follow-up period was 82.58±15.55% (35-98) in the spongious graft group while it was 93.78±3.67% (87-99) in the bioceramic glass bone group (p=0.002).

The average consolidation ratio in fibrous dysplasia, which is a tumoral lesion with a benign aggressive course, was identified as 71.5±7.76% (62-81) in the spongious allograft group (n=4) whereas it was found to be 96.75±1.50% (95-98) in the bioceramic glass bone graft group (n=4) (p=0.029).

Ten of the tumors were interpreted as stage 1; 29 were stage 2, and eight were stage 3 according to Enneking benign tumor staging (Figure 3). In the spongious allograft group, the statistical results between stage 1 and stage 2 were non-significant (p=0.097); the statistical result was significant between stages 1 and 3 (p=0.032); the statistical result was non-significant between stages 2 and 3 (p=0.129). In the bioceramic glass bone graft group, the statistical result was significant between stages 1 and 2 (p=0.01); the statistical result was non-significant between stages 1 and 3 (p=0.167), the statistical result was significant between stages 2 and 3 (p=0.009) (Table 3).

Examples from several cases in the study are shown in Figures 4, 5.

The graphics of the patients with the lowest consolidation ratio identified in both groups are demonstrated in Figures 6, 7.

Table 1. Demografic characteristics and scoring

Case	Age	Sex	Pathology	Stage	Follow-up (month)	LEFS %	VAS
1	8	M	FD	2	24	95.0	0
2	7	F	FD	3	12	92.5	1
3	20	M	SBC	1	6	93.75	1
4	28	F	GSBT	2	6	88.75	3
5	51	F	PS	3	6	91.25	2
6	56	F	SBC	1	7	92.5	1
7	15	F	FD	1	11	95.0	1
8	20	F	KB	2	36	95.0	0
9	14	F	ABC	3	36	91.25	2
10	47	F	FD	2	6	95.0	1
11	9	M	ABC	1	36	98.75	0
12	28	F	SBC	2	6	93.75	1
13	18	F	SBC	1	12	97.5	0
14	26	M	SBC	1	11	93.75	1
15	16	F	ABC	2	12	97.5	0
16	9	F	FD	2	12	100.0	0
17	27	F	FD	2	16	88.75	3
18	17	F	SBC	1	6	95.0	1
19	24	F	ABC+GSBT	2	36	93.75	1
20	11	M	ABC	3	24	86.25	3
21	31	F	ABC	2	6	93.75	1
22	8	F	ABC	2	6	90.00	2
23	57	M	GSBT	2	6	91.25	2
24	11	F	SBC	2	24	96.25	1
25	16	M	ABC	2	12	97.5	0
26	11	M	ABC	2	12	96.25	1
27	45	M	H	2	12	93.75	1
28	14	M	FD	2	18	97.5	0
29	15	F	L	1	7	98.75	0
30	16	F	ABC	1	18	93.75	1
31	10	F	ABC	2	36	92.5	1
32	18	M	OB	2	12	96.25	0
33	9	M	FD	2	24	95.0	1
34	20	M	ABC+GSBT	2	18	90.0	2
35	30	F	L	2	48	96.25	1
36	46	F	HS	2	12	93.75	1
37	19	F	ABC	2	18	100.0	0

Table 1. Continued

Case	Age	Sex	Pathology	Stage	Follow-up (month)	LEFS %	VAS
38	16	M	SBC	3	48	88.75	2
39	15	M	EG	1	18	98.75	0
40	26	F	GSBT	3	6	86.25	3
41	52	M	EC	2	24	91.25	2
42	18	M	FD+ABC	3	6	91.25	1
43	26	F	EC	2	6	93.75	1
44	28	F	L	2	6	95.0	0
45	47	F	FA	2	9	91.25	2
46	13	M	ABC	2	24	98.75	0
47	17	M	OB	3	12	97.5	1

LEFS: Lower extremity functional scale, VAS: Visuel analogue scale, F: Female, M: Male

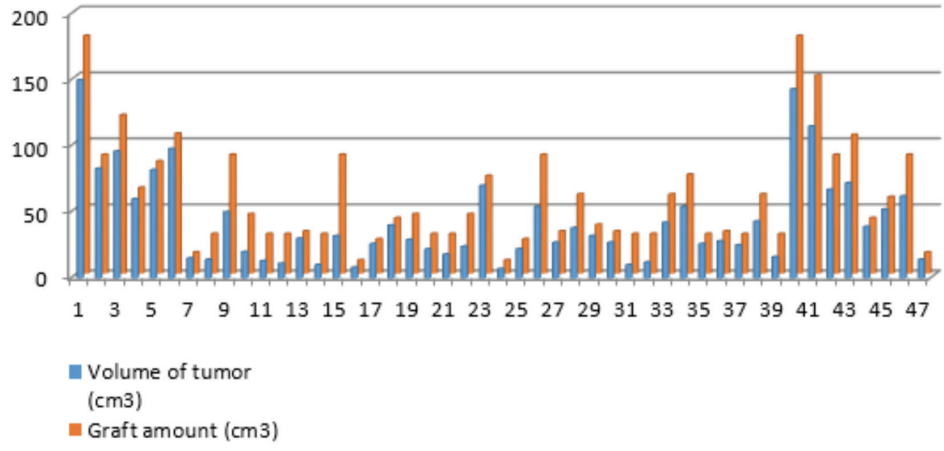

Figure 1. Volume of tumor and graft amount

Discussion

Bioceramic bone glass and spongious allografts are bone-filling materials that can be used in bone tumor. In this study, it was observed that consolidation rates were statistically significantly higher in the bioceramic bone graft group especially in the fibrous dysplasia group.

The ratio of the mean tumor volume and the amount of graft applied was higher in the bioceramic glass bone graft group compared to the other groups. This situation is thought to be developing out of the structural features of bioceramic glass bone graft.

In a randomized prospective study; Lindfors et al.[5] evaluated twenty-five patients in a total of two groups with benign bone lesions, in one that they used bioceramic glass bone graft and autograft after curettage. No difference in cavity volume was identified between the two groups after thirty-six months. In the following period, an increase in cortical thickness was observed to be higher in the bioceramic glass bone graft group compared to the autograft group. In our study, spongious allograft was implemented instead of autograft, and the consolidation ratio was found to be higher in bioceramic glass bone graft compared to the spongious allograft.

In their study, Sponer et al.[6] used bioceramic glass bone graft in a population of one hundred six patients with benign bone lesions, tibial plateau fractures, total hip replacement, and bone infections. The average length of follow-up was 3.2 years.

Table 2. Graft materials, volume and consolidation ratio				
Case	**Graft material: Sg: 1 Bg: 2**	**Volume of the tumor (cm^3)**	**Graft amount (cm^3)**	**Consolidation ratio (%)**
1	1.0	150	180	81
2	2.0	83	90	98
3	1.0	96	120	92
4	1.0	60	65	95
5	2.0	82	85	99
6	2.0	98	106	96
7	2.0	15	16	98
8	1.0	14	30	82
9	1.0	50	90	35
10	1.0	20	45	72
11	1.0	13	30	92
12	1.0	11	30	93
13	2.0	30	32	98
14	1.0	10	30	94
15	1.0	32	90	93
16	2.0	8	10	95
17	2.0	26	26	96
18	2.0	40	42	94
19	1.0	29	45	88
20	1.0	22	30	72
21	1.0	18	30	92
22	1.0	24	45	66
23	2.0	70	74	87
24	2.0	7	10	92
25	2.0	22	26	88
26	1.0	54	90	82
27	2.0	27	32	91
28	1.0	38	60	71
29	2.0	32	37	93
30	2.0	27	32	95
31	1.0	10	30	97
32	1.0	12	30	96
33	1.0	42	60	62
34	1.0	54	75	83
35	1.0	26	30	74
36	2.0	28	32	92
37	1.0	25	30	98
38	1.0	43	60	44
39	1.0	16	30	97
40	1.0	143	180	92
41	1.0	115	150	91
42	1.0	67	90	88
43	1.0	72	105	82
44	2.0	39	42	92
45	2.0	52	58	88
46	1.0	62	90	91
47	2.0	14	16	96
Sg: Spongious allogreft, Bg: Bioceramic glass bone graft				

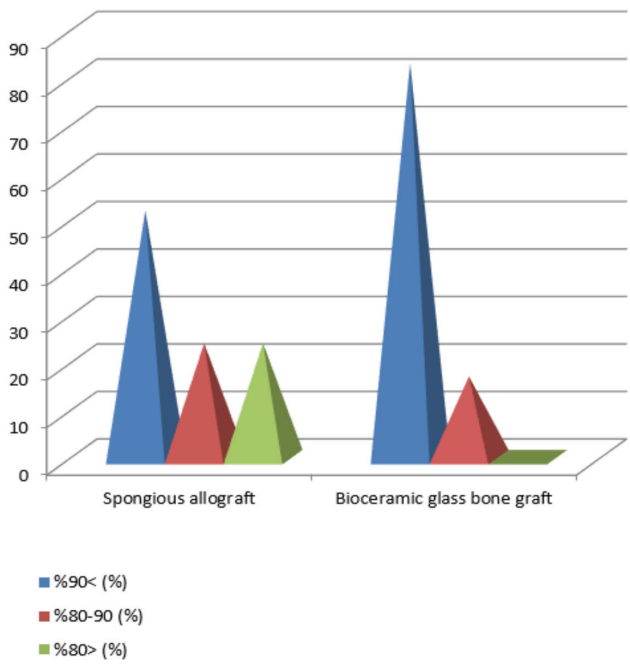

Figure 2. Consolidation range by graft materials

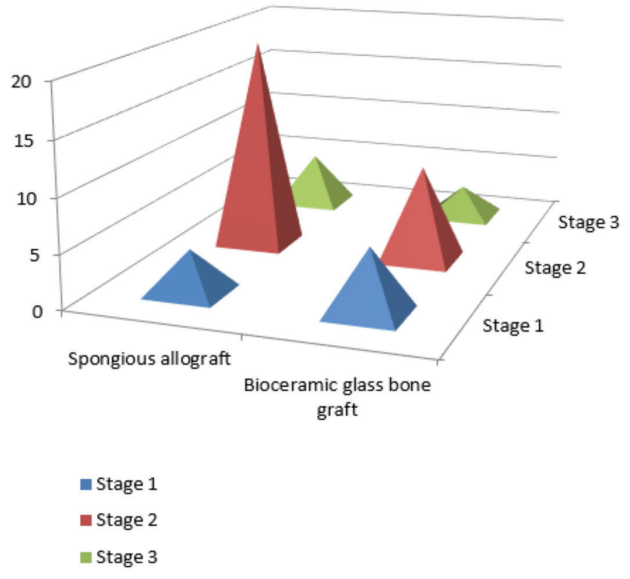

Figure 3. Enneking staging

Table 3. Comparison of consolidation rate		
	Consolidation rate	
Stage	Spongious allograft	Bioceramic glass bone graft
1	93.75±2.36% (92-97)	95.67±2.06% (93-98)
2	84.45±10.78% (62-98)	91.22±3.11% (87-96)
3	66.2±25.69% (35-92)	97.67±1.53% (96-99)

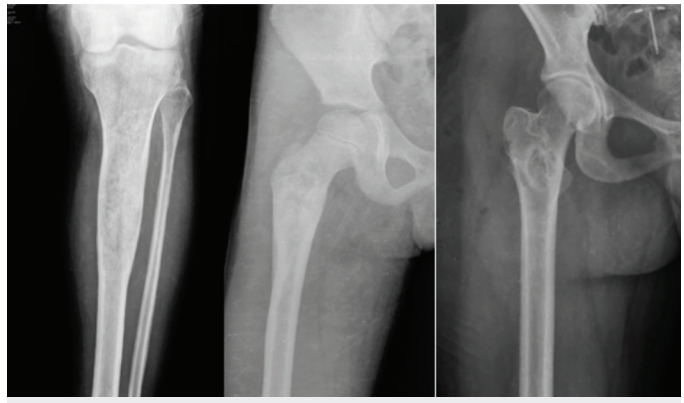

Figure 4. Spongious allograft samples

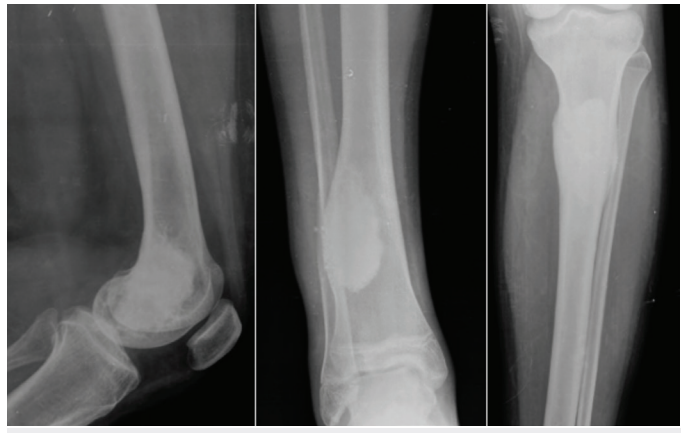

Figure 5. Bioceramic bone graft samples

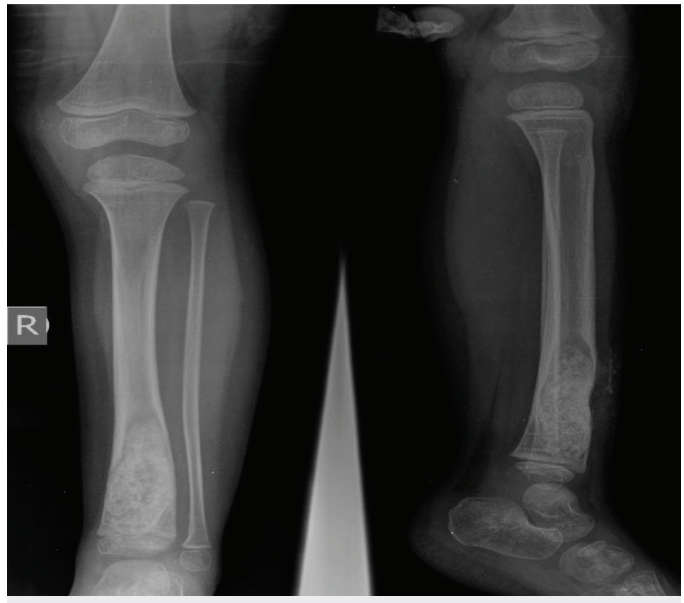

Figure 6. Patient sample with lowest consolidation rate of spongious allograft

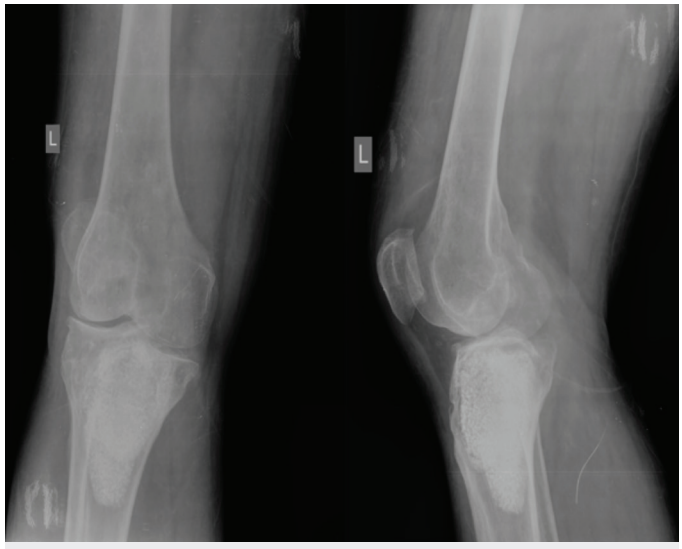

Figure 7. Patient sample with lowest

No a patient possessed radiological findings revealing a soft tissue reaction, periosteal reaction or irritation, or bone loss. Radiographs displayed that trabecula persisted on bioactive glass. In our study, as well, bioceramic glass bone graft was used only on benign bone lesions; and there was no radiological evidence of soft tissue reaction, periosteal reaction or irritation, or bone loss, which shows consistency with this study.

Sponer et al.[7] followed seventeen patients with long bone diaphyseal defects for 7 years and ascertained that bioceramic glass bone grafts are impractical in diaphyseal defects but they can be convenient bone filler materials in metaphyseal defects. In our study, 8 of the patients who were given bioceramic glass bone graft had mass located in the diaphyseal region and ten had the mass in the metaphyseal region. No significant difference was identified when the average consolidation ratios were statistically compared as diaphyseal and metaphyseal regions (p=0.972).

In one of their research, Sponer and Urban[8] concluded that bioceramic glass bone grafts can be recommended for especially metaphyseal defects instead of autograft and allografts that are frequently used on patients with the juvenile bone cyst. In our study, as well, results were fruitful on the patient group of bioceramic glass bone graft used on the juvenile age group.

Schepers et al.[9], in their study, evaluated the use of bioactive glass particles as fillers on bone lesions and compared them to two hydroxyapatite (HA) materials (calcitite and interpore 200). The osteoconductive effect was observed to be stronger in the cases of bioactive glass. When bioactive glasses are applied, they form a porous matrix that helps osteogenic cells develop by connecting to collagen, growth factors, and fibrin. They have absorbable and nonabsorbable types. They cannot be used with antibiotics or mixtures of bone-building increaser materials. They are more durable than HA implants[10,11].

It was demonstrated in Day et al.[12] research that bioactive glass-ceramics raise the secretion of angiogenic growth factors *in vitro* and escalate the formation of new vessels.

Lin et al.[13] detected in their study that bioactive glass is gradually biodegraded and absorbed by the living bone. An optic microscope used in histological examination revealed that osteocytes grow into bioactive glass. Microscopic examination was not performed in our study, but it was found to be clinically and radiologically compatible with this study.

Study Limitations

This study has some limitations. The most important limitation is its retrospective design. The other important limitation is that the number of included patients was quite low.

Conclusion

Bioceramic glass bone grafts are bone filler materials that possess radiologically superior and clinically similar findings compared to spongious allografts. The statistically significant radiological consolidation success of bioceramic glass bone grafts on FD, which is a benign aggressive tumor, causes the thought that they can be a good option toward the devastating effects of benign aggressive tumors. Bioceramic glass bone grafts are available to be used for adults and children. They can substitute spongious allografts and other modalities. Early results are promising. More comprehensive and long-term monitoring studies are required for more precise results.

Ethics

Ethics Committee Approval: The study were approved by the İzmir Tepecik Education and Research Hospital Research Ethics Committee (date: 24.11.2015, decision no: 22).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.İ., A.K., M.İ., Design: G.İ., A.K., M.İ., Data Collection or Processing: G.İ., A.K., M.İ., Analysis or Interpretation: G.İ., A.K., M.İ., Literature Search: G.İ., A.K., M.İ., Writing: G.İ., A.K., M.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

A Large Osteoid Osteoma of Trapezium: A Regenerative Approach and a Review of Literature

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Osteoid osteoma is a benign bone tumor that usually grows in the long bones of the body and arises from osteoblasts and some components of osteoclasts. It represents the third most frequent type of benign bone tumors, accounting for 11% to 14% of the tumors. The entity usually involves the proximal femur and tibia. It has also been reported in the hand, especially the scaphoid, capitate, and proximal phalanx. The most common symptom is pain, usually during the night, relieved by the use of salicylates and nonsteroidal anti-inflammatory drugs. To date, only 5 cases involving the trapezium have been reported. This article describes a rare case of a large (1.3 cm) osteoid osteoma of the trapezium in a young male patient treated surgically with resection and curettage of the osteoid and provides a review of the existing literature.

Osteoid osteoma is the third most frequent type of all benign bone tumors, accounting for 11% to 14% of the tumors.[1,2] The most common loci are the femur and tibia.[3] Although the involvement of hand bones is more unusual, the most frequently involved bones are scaphoid and capitate.[4] The most common clinical presentation is pain, usually during the night, relieved by salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs). The diagnosis is generally made with a computed tomography (CT) scan that detects the topical "nidus" surrounded by a sclerotic reaction. A definitive diagnosis is made with histological examination. The natural history reveals that osteoid osteomas should regress spontaneously within 6–15 years or by conservative treatment with NSAIDs for 30–40 months.[5–7] Conservative treatment must thus be considered for tumors where the osteoma is not easily accessible. The surgical management is the excision of the nidus that must be removed completely for the pain to resolve.[4,8,9] When the lesion is big, the excision can be followed by bone grafting or internal fixation.[10] Other described techniques are radiofrequency ablation, cryoablation, and laser thermocoagulation.[11,12] Among these techniques, CT-guided radiofrequency ablation is often the treatment of choice for osteoid osteoma.[13]

There have been several published cases of trapezium osteoid osteoma, and all of them were treated by excision and eventually cancellous bone graft. The first osteoid osteoma of the trapezium was described by Hundley[14] in 1976 in a 16-year-old boy with long-lasting wrist pain without a precise diagnosis. The patient was treated with surgical excision with instant pain relief after surgery. In this case report, we describe the case of a young male patient with a 1.3-cm osteoid osteoma treated surgically with resection of the osteoid nidus and curettage of the sclerotic rib and bone defect filled with bioactive glass. Bioactive glass is a bone substitute used clinically as a space filler or for regenerative purposes. The filler effect improves when granules are moistened with blood or saline implantation into the defect.[15] It has osteoconductive properties, does not increase the risk of infection and avoids the donor morbidity of graft harvest.[15–19] The investigation was performed in compliance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. The patient provided written informed consent for both surgery and follow-up. The follow-up study protocol was approved by the internal ethics committee.

Declaration of interests: No benefits in any form have been received or will be received by the authors related directly or indirectly to the subject of this article.

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Table 1
Clinical Outcomes Before and After Surgery

Clinical Examination Test	Before Surgery	T30 After Surgery	T60 After Surgery
Pinch test score	5 kg	15 kg	20 kg
Kapanji score	5	9	9
Visual analog scale score	7	0	0

Table 2
Michigan Hand Outcomes Questionnaire Scores of the Patient

Brief Michigan Outcomes	Before Surgery	T30 After Surgery	T60 After Surgery
	Function (1 very good to 5 very poor)		
Overall, how well did your hand(s) work during the past week?	5	4	2
How was the sensation (feeling) in your hand(s) during the past week?	4	4	2
	Daily activities (1 not at all difficult to 5 very difficult)		
How difficult was it for you to hold a frying pan during the last week?	4	4	2
How difficult was it for you to button a shirt or blouse during the past week?	4	4	2
	Workly activities (1 always to 5 never)		
In the past 4 weeks, how often were you unable to do your work because of problems with your hand(s)/wrist(s)	3	3	5
In the past 4 weeks, how often did you take longer to do tasks in your work because of problems with your hand(s)/wrist(s)	3	3	5
	Pain (1 very mild to 5 very severe)		
How often did the pain in your hands/wrists interfere with your daily activities?	5	3	2
Describe the pain in your hand(s)/wrist(s) in the past week?	5	4	2
	Aesthetics (1 strongly agree to 5 strongly disagree)		
I am satisfied with the look of my hands	1	1	1
The appearance of my hands interferes with my normal daily activities	1	1	1
	Satisfaction (1 very satisfied to 5 very dissatisfied)		
In the past week, how satisfied were you with the motion of your fingers?	5	3	2
In the past week, how satisfied were you with the motion of your wrist?	5	4	2
Normalization	31.25%	37.5%	70.83%

Case Report

A 19-year-old man was referred to our hospital with a history of intense pain localized at the right thumb basal joint for 1 year. The pain was characterized as dull and persistent and was not relieved with NSAIDs. During the first visit, the patient demonstrated limited thumb opposition with a Kapanji score of 5, a weak pinch test with 5-kg strength (20 kg on the other hand), and difficulty in daily activities.[20] His visual analog scale (VAS) was 7, and the Michigan Hand Outcomes Questionnaire showed a value of 31.25%, with a high compromission of daily activities and pain (Table 1, 2).[21] X-rays were negative for pathology (Fig. 1). Magnetic resonance imaging (MRI) showed an intense signal corresponding to the trapezium and a diffuse edema of the surrounding tissue (Fig. 2). A subsequent CT scan (Fig. 3) showed the typical image of the osteoid osteoma, with the presence of the sclerotic nidus surrounded by a cortical reaction. At this point, the patient was counseled on surgery for enucleation of the tumor and grafting with bioglass.

For the surgical procedure, we accessed the tumor with an S incision made on the radial volar side of the first ray. We deroofed the trapezium, isolating the osteoid nidus and the sclerotic bone through a trail of holes made by K-wires (Fig. 4) and taking care not to interrupt the cortex of the trapezium. After enucleation of the nidus with the help of curettes, we filled the bone defect with bioglass mixed with fresh blood (Fig. 5). We reconstructed the capsule, closed the wound leaving a drain, and applied a short arm cast with the thumb included for 4 weeks. The lesion was sent for definitive histological examination, which gave us the diagnosis of osteoid osteoma (Fig. 6).

We followed up with the patient clinically and radiologically monthly for the first 3 months and at 1 year after surgery to rule out exclude recurrence. In the follow-up, we reported the VAS, pinch test, and Kapanji scores (Table 1). At the latest follow-up. the VAS, Pinch test, and Kapanji scores improved ($P < .05$). For the subjective evaluation of the functional and aesthetic outcomes, the authors administered the brief Michigan Hand Outcomes Questionnaire to the patient (Table 2). The brief Michigan Hand Outcomes Questionnaire global score showed slightly better, but not significant, results at 30 days after surgery (37.5%, $P = .633$), whereas it significantly showed improvement at 60 days after surgery (70.83%, $P = .01$).

Discussion

Osteoid osteoma is a benign osteoblastic lesion accompanied by severe pain relieved by salicylates and NSAIDs. It is frequent in individuals aged 10–20 years and in males.[3,5] The most common locations are the femur and tibia, followed by the small bones of

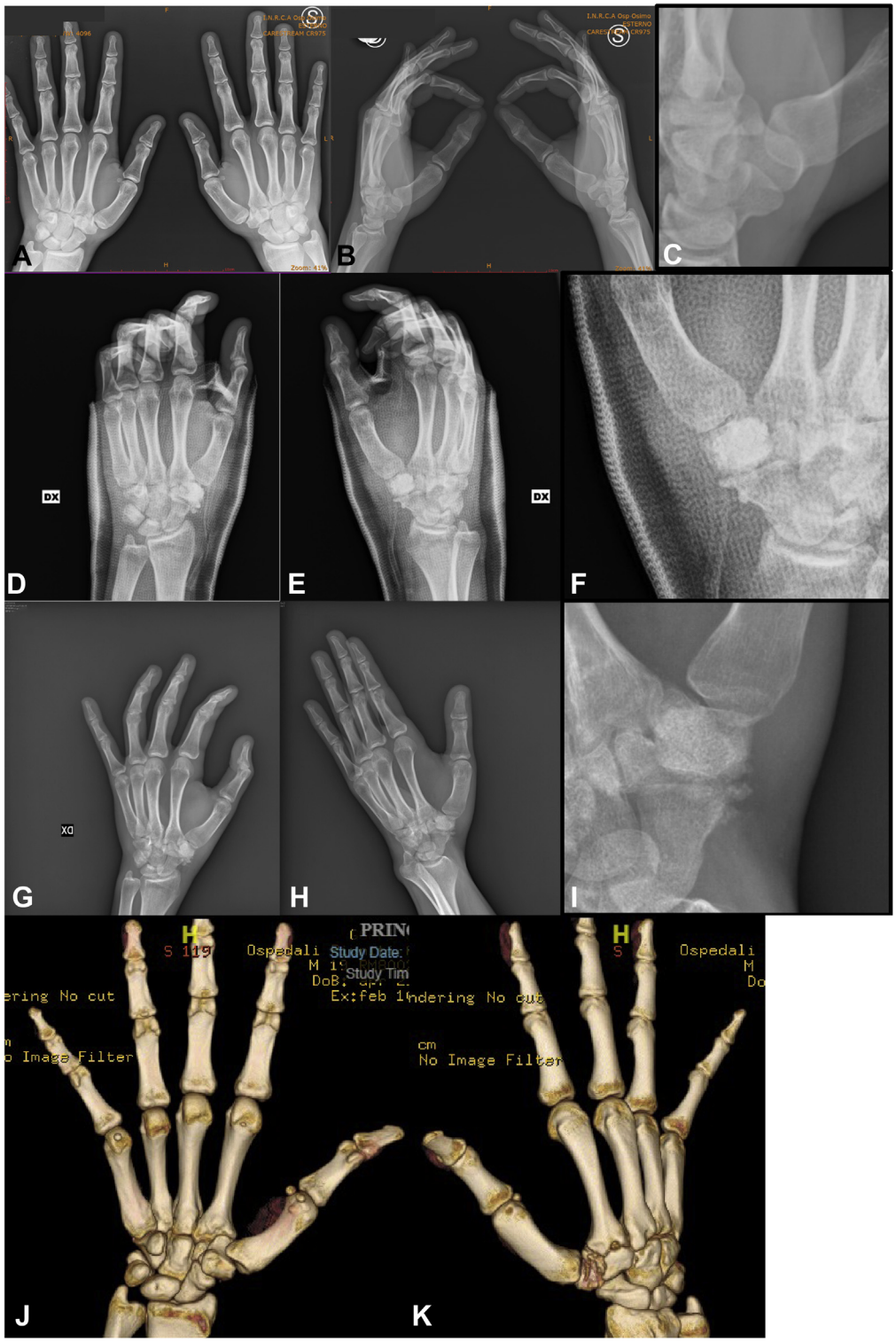

Figure 1. X-ray examinations from months before and after surgery and at 30 days of follow-up. **A**–**C** Radiographs before surgery. The trapezium is quite similar in both hands, both in the anteroposterior and lateral view. **A** Anteroposterior view showing the standard trapezium. **B** Okay sign view showing the normal trapezium. **C** Magnified view of the trapezium. **D**–**F** Radiographs taken in the operating room at the end of the procedure with the cast including metacarpophalangeal joint. A hyperintense image of the trapezium is observed, which is due to the active bioglass applied in the bone cavity. **D** Anteroposterior view showing the trapezium filled with bioglass. The trapezium appears hyperintense. **E** Oblique view showing the trapezium filled with bioglass. **F** Magnified view of the trapezium. **G**–**I** Thirty days after surgery. The trapezium density is similar to that of the normal bone, demonstrating how bioglass is going to integrate. Note that some parts of the active bioglass outside the trapezium will be absorbed in the following months. **G** Anteroposterior view showing the trapezium filled with bioglass. **H** Oblique view showing the trapezium filled with bioglass. **I** Magnified view of the trapezium. **J** One-year follow-up (front view). The appearance of the trapezius is similar to that of a normal trapezius in terms of density and joint relationships with the other carpals. **K** One-year follow-up (lateral view). The appearance of the trapezius is similar to that of a normal trapezius in terms of density and joint relationships with the other carpals.

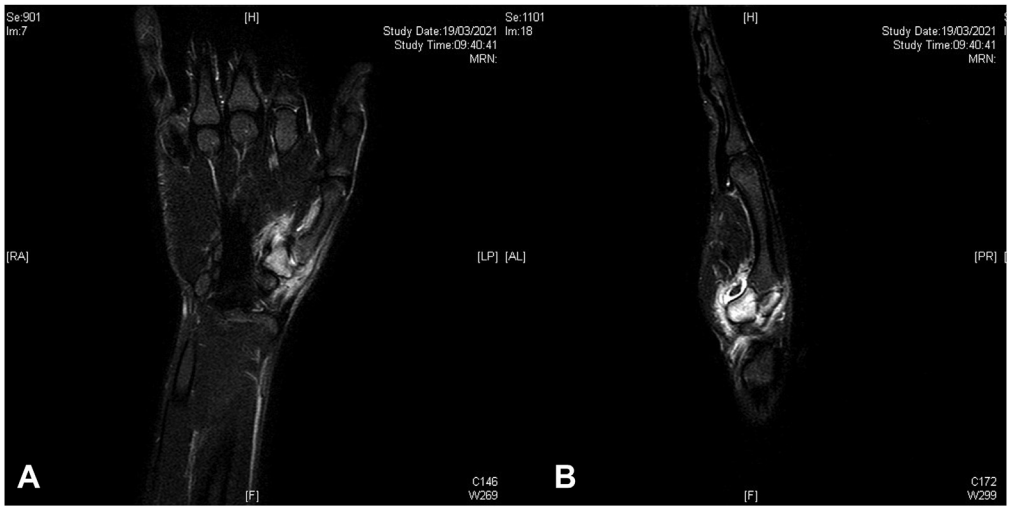

Figure 2. **A** Sagittal and **B** longitudinal views of the MRI examination performed before surgery. The bone aspect is better represented in the CT examination; in fact, the nidus, sclerotic area, and erosion are not visible. The bone edema and flogistic perilesional tissues are visible on the MRI scan.

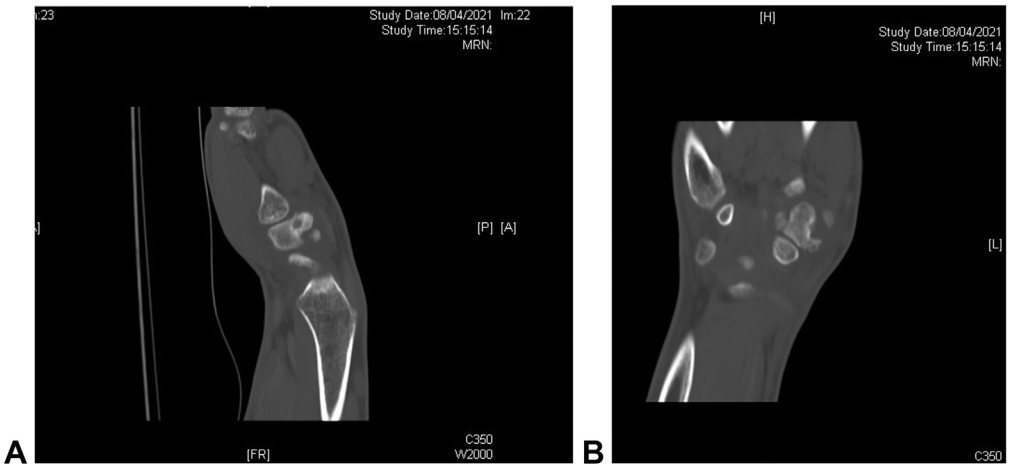

Figure 3. Computed tomography performed before surgery. The erosive aspect of the lesion in **A** longitudinal view and the nidus and sclerotic perilesional area in the **B** sagittal view are shown. The CT examination is the most accurate imaging examination for suspecting osteoid osteoma.

the hand, feet, and spine.[3] It can be found in the bone cortex, subcortical, intracortical, and intraperitoneal, and can rarely occur with more nidi in 1 or more bones.[3,22] The reason for remission after the use of NSAIDs is that nidus osteoblasts display a diffusion of cyclooxygenase-2, an enzyme important for prostaglandin production, in particular prostaglandin E2.[23] This enzyme is the main cause of pain and explains why the tumor is so responsive to cyclooxygenase-2 inhibitors (NSAIDs).[24] This lesion can be confused with osteoblastoma, a similar tumor of bigger size, usually more than 1.5 cm.[9,25] This tumor is characterized by irregular sclerosis, and the nidus is not well-defined.[26] It does not typically regress and does not respond to NSAIDs.[27] Another important condition that can be confused with osteoid osteoma is Brodie's abscess.[22] Plain radiographs are usually the first examinations performed and can show a small radiolucent area, corresponding to the nidus, surrounded by a sclerotic bone area. However, if the tumor is intramedullary, it may not show the surrounding bone sclerosis.[28] The diagnosis of osteoid osteoma is usually suspected when CT scans show the nidus. A highly specific and sensitive finding in diagnosis is the presence of fine, low density, linear, vascular channels surrounding the osteoid osteoma.[29] Furthermore, CT has better accuracy than plain radiography and MRI.[30,31] Magnetic resonance imaging is usually the first examination performed and can show a small radiolucent area, corresponding to the nidus, surrounded by a sclerotic bone area. However, if the tumor is intramedullary located, it may not show that surrounding bone sclerosis.[28] Although not as useful, an MRI examination can clearly show bone marrow edema and periarticular fluid. Care must be taken because the reactive soft tissue mass can be misinterpreted as a malignant tumor of the soft tissue or osteomyelitis.[32,33] Thus, MRI images should not be assessed without CT and x-ray image references.[34] Bone scintigraphy shows a vascular nidus in the arterial phase with a delayed phase within the surrounding reactive bones; the nidus is usually more intense, and the reactive bone is less intense; this is known as the "double density sign," and it is diagnostic of osteoid osteoma.[35,36] In 2010, Bostan et al[37] described a case of osteoid osteoma in a 25-year-old patient with a 12-month history of wrist pain, which occurred particularly at night. The patient was initially treated with orthoses and NSAIDs without success. At the clinical examination, swelling was observed over the dorsoradial aspect of the hand. CT examination showed the sclerotic nidus

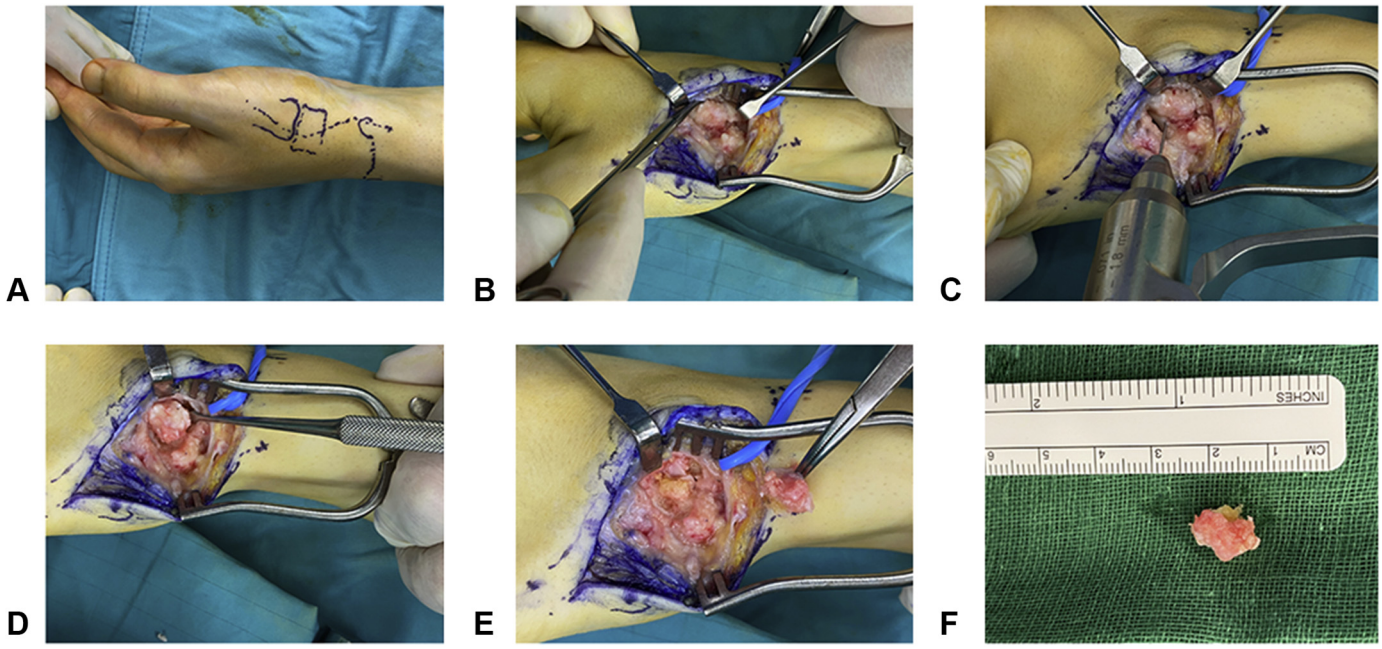

Figure 4. Demolitive part of the surgery. **A** Drawing of surgical access. **B** Exposure of the tumor. **C** Deroofing. A trail was made through several drills performed with 1-mm K-wires. **D** Isolation of the tumor. **E** Trapezium with bone loss. **F** Tumor size of 1.3 cm.

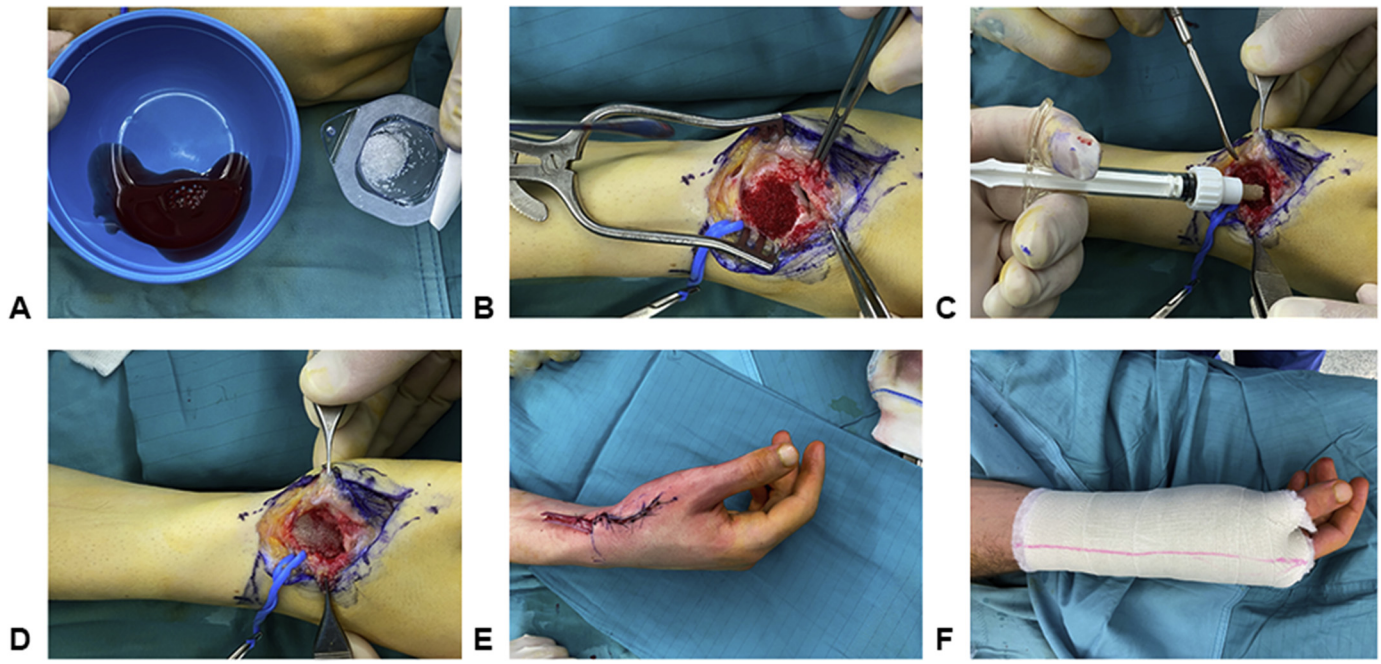

Figure 5. Reconstructive part made with bioactive glass. **A** Bioglass granules are mixed with fresh blood cells. **B** Filler of bone loss with bioglass granules. **C** Coverage of the granules with glass bone putty (45S5 bioglass plus a binder made with polyethylene glycol and glycerol). **D** Complete application of bioglass. **E** Hand after surgery sutured with a drainage in situ. **F** Short arm cast including the thumb.

surrounded by a radiolucent osteoid tissue, and MRI examination showed bone marrow edema associated with a focal lesion of the trapezium hypointense. The patient was treated with excisional biopsy, and after surgery, the patient had immediate pain improvement, and no recurrence was observed in follow-up.[37] In 2017, Park et al[38] described an osteoid osteoma tumor in a 29-year-old patient initially treated for calcification periarthritis with several steroid injections until follow-up, debridement with no effect, until an ulnar deviated x-ray examination showed a sclerotic bone lesion, suspicious for osteoid osteoma and treated with curettage. The patient experienced immediate improvement in clinical pain and no recurrence at a 1-year follow-up. In 2017, Roberts et al[39] described a case of a 34-year-old woman with osteoid osteoma initially confused with carpometacarpal arthritis. In this case, an MRI scan showed a hypointense circular lesion along the dorsal aspect of the trapezium, and a CT study was

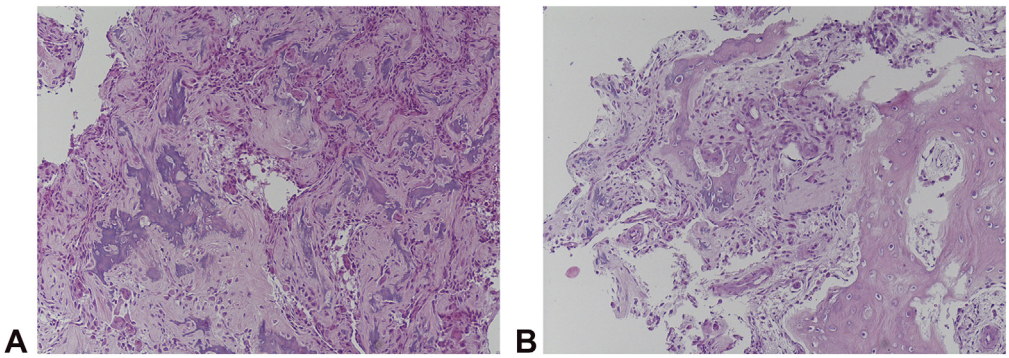

Figure 6. The nidus as the well-defined area made of irregular bone trabeculae of different mineralization **A**, usually surrounded by the osteoblast cells **B**, is shown.

conducted to better characterize the lesion. The lesion was treated with curettage, and the diagnosis was confirmed by histopathology. After excision, the patient experienced complete pain relief and did not have any recurrence.[39] In this study, because of the unusually large tumor size of 1.3 cm, we filled the bone loss with bioactive glass to avoid donor morbidity in such a young patient. There are many kinds of bioactive glasses, and we elected to use GlassBONE (Noraker) in 2 different formulations, “granules” to fill the bone defect and “putty,” a formulation with glycol polyethylene and glycerol, which grants ligand property useful for roofing the filled area.[40] Bioglass is a bone substitute, first used in hand surgery by Hench et al[41] in 1967; it is a bioactive material that can bond to the bone because of a specific chemical reaction. A bioactive material does not cause minimal rejection, is recognized as a biological material, and bonds with the tissue for mechanical interference. It is composed of silicon dioxide, calcium oxide, sodium oxide, and phosphoric anhydride; the equilibrium among these components makes the bioglass active. The gold standard of bioactive glass is the 45S5 (comprising 45% of silicon dioxide, 24.5% of sodium oxide, 24.5% of calcium oxide, and 6% of phosphorus pentoxide).[42] When the bioactive glass is in contact with biological fluids, several chemical reactions cause silicon hydrolysis, creating a silica gel layer similar to the bone hydroxyapatite (carbonated hydroxyapatite). The carbonated hydroxyapatite layer absorbs growth factors; these factors attract the M2 macrophages that promote lesion healing and attract staminal mesenchymal cells, which become the osteoblasts.[43] This process starts generating and depositing proteins of the extracellular bone matrix (collagen I).[40,44] To conclude, bioactive glass causes osteoblasts and osteocytes to spread along the glass surface; this means that the material is mainly osteoconductive.[45,46] In this study, after the tumor excision, the bone loss had to be filled, and we chose a bioglass to avoid donor site morbidity.

Conclusion

Analyzing the reports in the literature, we can conclude that osteoid osteoma should be suspected when a patient presents with long-lasting wrist pain with unclear diagnosis, associated with radial side tenderness surrounding the thumb, night pain responsive to NSAIDs, and negative x-rays. The approach has to start with a clinical examination, including the Kapandji test, which shows a reduction of thumb opposition compared with the contralateral hand. Although x-rays can be negative, a CT scan can provide us with the most accurate image of a nidus, whereas an MRI image can show bone edema and surrounding tissue inflammation and exclude other pathologies. A definitive diagnosis is made by histological examination. In our opinion, the best treatment is the curettage of the osteoid osteoma, avoiding trapeziectomy if the carpometacarpal joint is not involved. If the lesion is larger in size, bone grafting, bone substitutes, or bioglass can be useful. The patient typically shows pain relief after surgery and should be followed monthly for 3 months after surgery, and at 6 months to a year with a CT scan to rule out recurrence, then new clinical and radiological control after 3 months and a final control made with CT examination after other 6 months to exclude recurrence.

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Three-dimensional printed titanium pseudo-prosthesis for the treatment of a tumoral bone defect

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Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocytic cells with a granulomatous appearance that generally affects children. The etiology of LCH is still unknown. However, it has been associated with exposure to certain solvents, smoking, and a family history of cancer, thyroid disease, or LCH.[1] Its estimated annual prevalence is of 1 case per 560,000 adults.[27] Three forms of presentation have been described: located in the skeleton as solitary or multiple eosinophilic granuloma, chronic disseminated disease such as Hand-Schueller-Christian disease, and acute subacute diffuse disease such as Letterer-Siwe disease.[8]

In the adult population, LCH frequently presents as a lytic bone lesion.[13,27] It may appear in short bones, ribs, pelvis, vertebral bodies, clavicle, and scapula. It may also develop in the diaphysis of long bones. However, the location of LCH in the hands and feet is very uncommon, and its presence in the clavicle is extremely rare.[27]

The diagnosis can be confirmed with a core needle biopsy. An extension study should be made to detect any systemic diseases or dissemination. Various therapeutic options have been used in the management of LCH depending on the severity of the disease. These options have ranged from observation to chemotherapy, surgery, radiotherapy, photodynamic therapy, immunotherapy, and stem cell transplant.[1,16]

The use of low doses of radiotherapy has been found to achieve good results.[10] A combination of vinblastine and steroids has also been used for the treatment of LCH; however, no standard chemotherapy has been established for the management of LCH in adults.[25] Nevertheless, a surgical resection with clean margins is usually the recommended treatment.

On the other hand, the use of three-dimensional (3D) printing represents a technological advance that is progressively becoming more popular in orthopedic surgery and traumatology. This technique is increasingly being used in surgical planning and in the reproduction of predesigned templates that serve as osteotomy guides in joint replacement procedures.[6,15,17,20,24]

In this study, we present a novel application for 3D printing in orthopedic surgery, using a 3D printed porous titanium graft for the treatment of a bone defect after an extensive resection of the middle third of the clavicle in a patient with LCH.

Case report

The patient was a previously healthy 37-year-old man who worked as a maintenance laborer, with no known drug allergies, and smoker of 20 cigarettes per day. He previously attended the emergency department of another hospital presenting with a 3-week history of shoulder pain. An x-ray of the clavicle was performed in which a small lytic lesion appears on the middle third of the clavicle (Fig. 1, *A*). However, this lesion was not initially detected, and the patient was treated with oral analgesics and discharged. Two months later, the patient presented in our center with a 3-month history of left clavicular pain and swelling without previous trauma. Clinical examination revealed a tender mass located on the left supraclavicular fossa associated with local edema. The patient was febrile, and the active and passive mobilization of his left shoulder was painful. However, the neurovascular examination of the left upper extremity was

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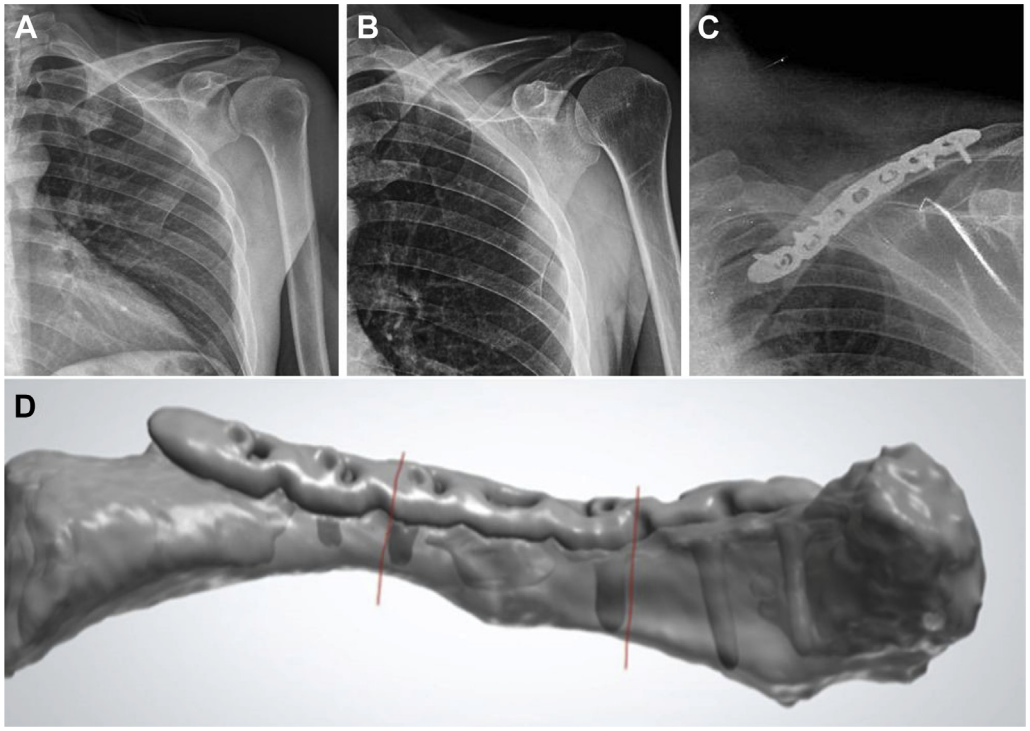

Figure 1 (**A**) A well-defined lytic lesion involving the middle third of the left clavicle. (**B**) This lesion evolved into a pathological fracture. (**C**) Postoperative radiological control after initial intralesional resection, curettage, and osteosynthesis. (**D**) A 3D reconstruction of the clavicle which included the previously synthesized fracture and the tumoral lesion; the red lines mark the planned resection margins. *3D,* three-dimensional.

normal. This patient provided consent for publication of this case report.

Plain x-rays revealed an evolved and displaced pathological fracture involving the middle third of the left clavicle associated with a well-defined 2.5-cm lytic lesion. The tumor appeared to spare bone cortices (Fig. 1, *B*). The blood tests showed a mild white cell count increase (23 × 10 ˆ 9 / L), an unaltered c-reactive protein, and negative tumor markers.

Given the pathological nature of the fracture and the smoking history of the patient, our initial differential diagnosis was of metastasis vs. bone cyst. Accordingly, a chest x-ray was performed showing no evidence of any pulmonary disease.

The patient was then subjected to an intralesional resection and curettage, and samples were collected for pathological analysis. The bone defect was then filled with synthetic and bioactive bone graft substitute (GlassBONE, Noraker, France), and the fracture synthesized with an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). Postoperative x-rays showed a satisfactory reduction of the fracture (Fig. 1, *C*). The pathological analysis confirmed the diagnosis of LCH (ie, eosinophilic granuloma subtype). Then, a positron emission tomography–computer tomography was performed to detect any other possible lesions. The positron emission tomography–computer tomography revealed the presence of pathological trace uptake in the middle third of the left clavicle (SUV max 4.15). No other metabolic abnormalities were detected.

The case was then presented in our institutional musculoskeletal tumor committee to determine the best therapeutic strategy. Several options were considered including observation, wide resection with oncological margins followed by reosteosynthesis using an autologous bone graft, radiotherapy, and wide resection followed by a clavicular reconstruction using a 3D printed porous titanium graft "pseudo-prosthesis". After taking in consideration the patient's age and the tumor's location and after discussing the available options with the patient, we decided to proceed with the clavicular reconstruction using a 3D printed "pseudo-prosthesis".

Description of the surgical technique

Implant design

We contacted the 3D design company 4DiMedical (Ortoplus, Malaga, Spain). A fine-cut computer tomography scan was then performed to make a detailed 3D reconstruction of the clavicle which included the previously synthesized bone and the 2.5-cm tumoral lesion (Fig. 1, *D*). Then, a customized cutting template was printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. The cutting template was adapted to a 1.3-mm saw blade and included holes for its fixation with 1.8-mm Kirschner wires (Fig. 2, *A* and *B*).

We then printed a 3D porous titanium pseudo-prosthesis resembling the size and shape of the resected area. Its trabecular titanium structure was designed to facilitate bone growth through the implant (Fig. 2, *C* and *D*). This pseudo-prosthesis also included a medial and lateral intramedullary fin to provide additional rotational stability.

Surgical intervention

The patient was subjected to a brachial plexus block of the left upper extremity. The patient was then positioned in a "chair bed" position. A longitudinal incision was made over the previous scar. A progressive dissection was made to expose the previously used anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA). The plate was then extracted, and the clavicle was exposed. A 3D printed biocompatible resin (MED610) radio-opaque cutting guide

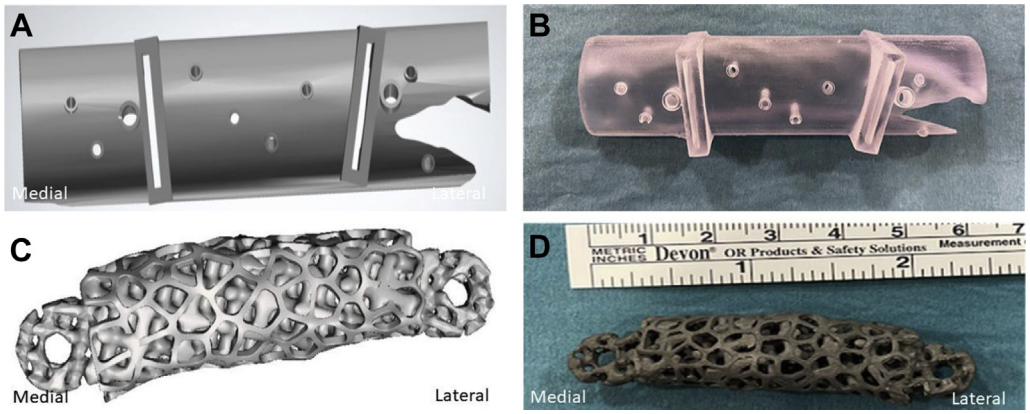

Figure 2 (**A** and **B**) The customized cutting template was designed and printed to perform the clavicular osteotomy with clean 14-mm proximal and distal oncological margins. (**C** and **D**) A 3D porous titanium pseudo-prosthesis with the size and shape of the resected area was designed and printed. It included a medial and lateral intramedullary fin to provide additional rotational stability. *3D,* three-dimensional.

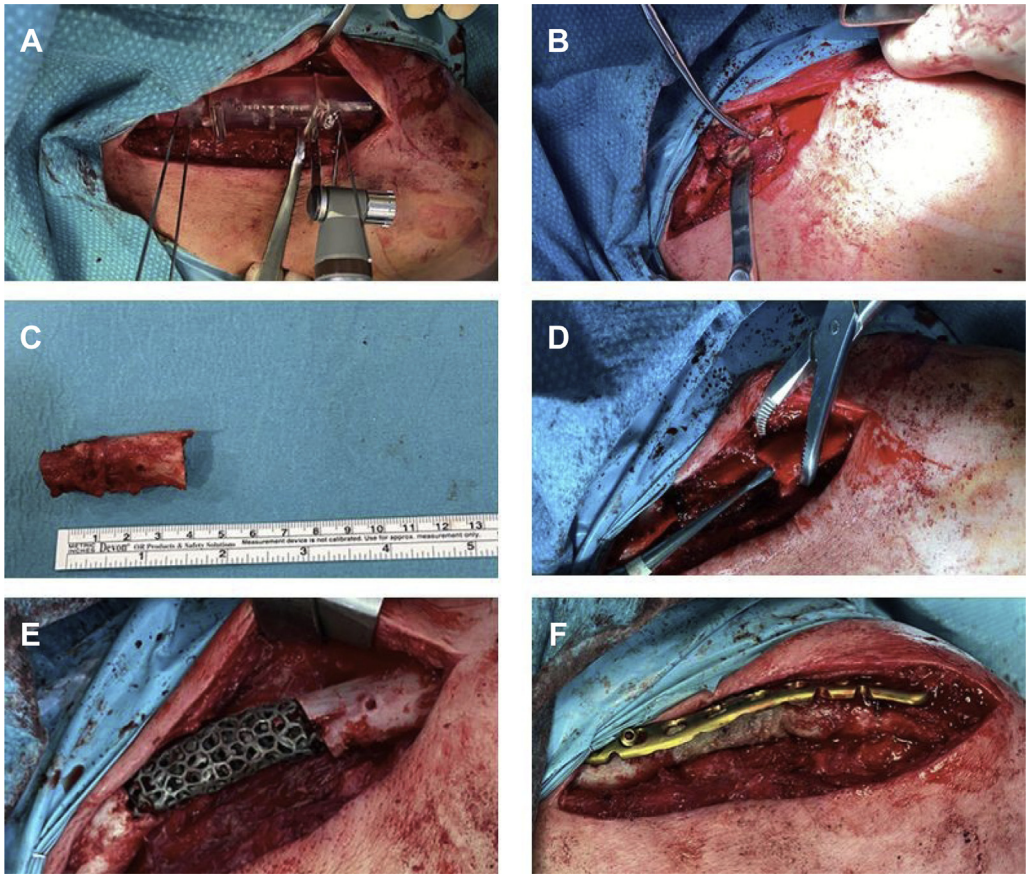

Figure 3 (**A**) The cutting template was fixed on the clavicle with four 1.8-mm Krischner-wires. (**B** and **C**) The selected bone segment was removed and measured. (**D**) The intramedullary canal was drilled proximally and distally using a 2-mm burr. (**E**) The titanium implant was placed in the bone defect. (**F**) The clavicle was fixed using an anatomic clavicular plate; the implant's trabeculas were filled with a bioactive bone graft substitute.

was positioned on the clavicle and fixed with four 1.8-mm Kirshner wires. A 62-mm long osteotomy was performed, achieving a complete excision of the tumor with oncological margins (Fig. 3, *A–C*). Then, the intramedullary canal was drilled proximally and distally using a 2-mm burr. The titanium implant (Ti6AL4V) was positioned following the "press-fit" method. Once the implant was stabilized, the clavicle was fixed using an anatomical clavicular plate (DePuy Synthes, Raynham, MA, USA) and locking screws. The implant's trabeculas were filled with bioactive bone graft substitute (GlassBONE, Noraker, France) (Fig. 3, *D–F*). Finally, the wound was washed with normal saline, and the wound was closed with 2-0 and 3-0 Vicryl.

Evolution

The final histopathology report confirmed the diagnosis of LCH with disease-free margins. The operated extremity was immobilized in a sling until the removal of the sutures 2 weeks after

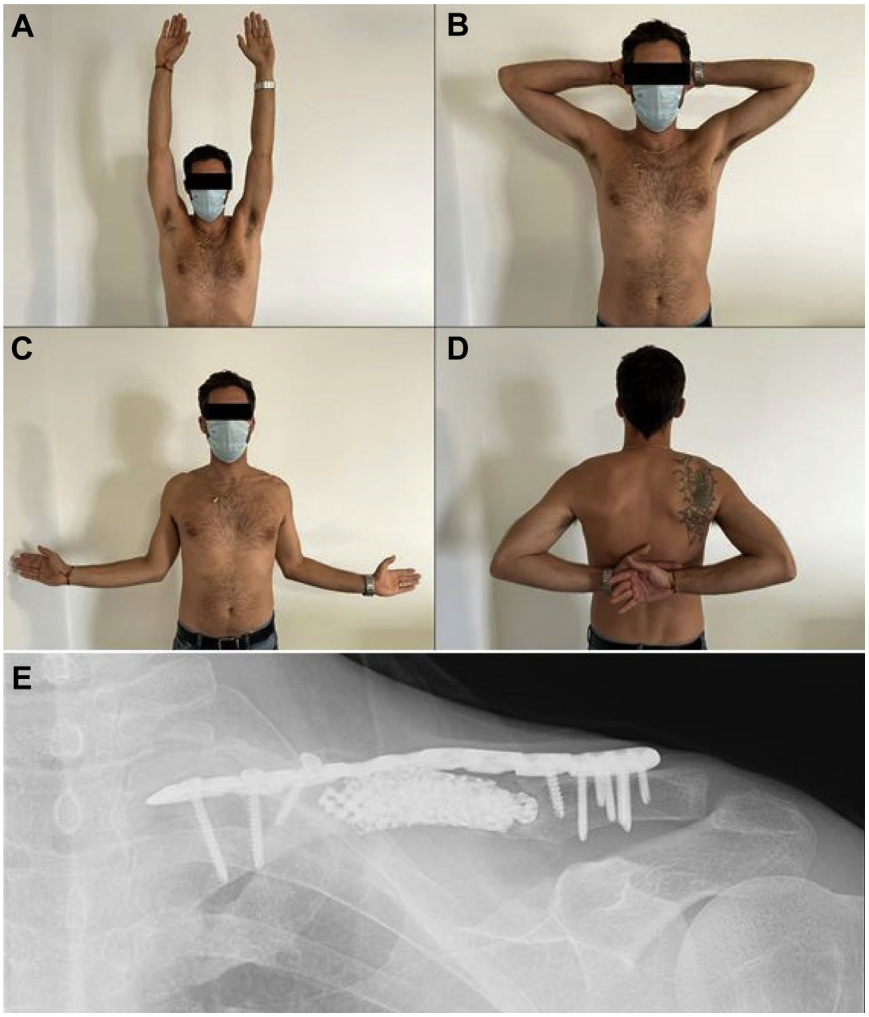

Figure 4 (**A-D**) Two years after surgery, the patient had a complete range of motion of the left shoulder. (**E**) The follow-up x-ray 2 years after surgery.

surgery. Then, pendular exercises of the shoulder and passive physiotherapy were initiated. The operated extremity was kept non–weight-bearing, and efforts were avoided. No postoperative complications were observed, and the evolution of the wound was satisfactory.

At 3 months after surgery, the patient presented with a complete range of motion and no pain on palpation or mobilization. The patient was authorized to initiate progressive loading of the operated extremity and to resume his regular physical activities. On his last follow-up appointment, 2 years after surgery, the patient led a normal life without any type of functional limitation; he had a Constant score of 100 and a disabilities of the arm, shoulder, and hand score of 2.5 (Fig. 4, *A–D*). His follow-up x-ray was also satisfactory (Fig. 4, *E*).

Discussion

Langerhans histiocytosis is a rare disease in adults.[13] It is difficult to determine its incidence in this age group because most of the published reports have been focused on the pediatric population. In children, LCH has been found to be more common in males (male-female ratio of 2:1). However, in the adult population, this ratio may vary depending on the series. According to the Rizzoli Institute,[18] the diagnosis of LHC progressively decreases with age (ie, 55% of the cases with LHC occur between 0 and 9 years, 30% between 10 and 19 years, 8% between 20 and 29 years, and 5% between 30 and 39 years). The treatment of LHC depends on the extent of the disease and may range from curettage and corticosteroid injection, polymethyl methacrylate filler, to local radiotherapy and systemic chemotherapy in certain cases.

The clavicle is a rare site of LHC.[26] Most of LHC reports in the literature involving this bone were treated by curettage of the lesion, steroids, and plate fixation. However, relapses often require adjuvant radiotherapy.[10,27] Some authors have postulated that a combination of surgery with localized radiotherapy would be the best therapeutic if the presence of residual disease is confirmed.[3,4]

In our case, the presence of residual disease would have been an indication for local radiotherapy. However, we believed that the eradication of the tumor was possible without exposing the patient to radiation if the lesion was completely resected. Therefore, we decided to perform a second excision with oncological margins and a subsequent reconstruction of the clavicle with the intercalary titanium pseudo-prosthesis. The location of the lesion required a resection that could have compromised the anatomical function of the left upper limb.[2] However, the titanium pseudo-prosthesis provided adequate mechanical stability and continuity and preserved the functionality of the clavicle.

The use of the titanium pseudo-prosthesis avoided exposure to radiotherapy in our relatively young patient. In a previous study, Kriz et al determined that the possible indications for radiotherapy in LHC would be in case of unresectable lesions, if the resection compromised the anatomical function, recurrent or progressive lesions, adjuvant treatment followed by incomplete or marginal resection, as well as pain or symptoms that compromise the quality of life.[10] However, radiotherapy can induce secondary leukemias, malignant meningiomas, osteosarcomas, and breast, lung, and thyroid malignancies over time.[5,14,21,23] This risk may persist up to 25 years after exposure. In head and neck tumors, the rates of radiation-related tumors have been reported to be of 15% within 5 years. This prevalence is even higher in patients with breast cancer reaching up to 50%, mainly involving the contralateral breast.[5] Moreover, radiation is also associated with numerous side effects such as sore skin, fatigue, hair loss, nausea, vomiting, esophagitis, mucositis, diarrhea, urinary and bladder changes, and headaches.[19] In our opinion, the negative effects of radiation are not unremarkable, and its use should be individualized in each case and reserved for situations in which no other viable options are viable. Nevertheless, in our study, radiotherapy would have been considered if the tumor recurred after the second surgical procedure.

The treatment of bone defects faces significant challenges to preserve the functionality of the affected extremity. In this case, the inadequate management of the bone defect could have hindered the mobility and strength of the operated extremity and altered its cosmetic appearance.[12] Several methods have been traditionally used for the reconstruction of bone defects in orthopedic surgery. These include leaving the bone defect and the use of bone allografts and vascularized bone grafts. However, the risk of bacterial infection has been estimated to be of 11.7% for large allografts and 0.7% for small grafts.[28] The use of bone allografts could also result in nonunion rates in approximately 21% of the cases.[22] Moreover, vascularized bone allografts are technically demanding and are associated with a significant morbidity on the donor site.[7,9,11] Thus, the use of 3D printing in orthopedic surgery and traumatology could become an additional surgical option in the management of complex fracture reconstructions. Moreover, this technique could provide accurate bone cutting guides in oncological surgery that could help perform precise osteotomies with disease-free margins based on preoperative imaging. It could also help produce customized osteosynthesis plates and print replicates of the operated bone.[17] In addition, it could be used to replace bone segments with implants of an equal size, shape, and volume. This could be particularly easier to achieve in cases affecting small bones, exposed to lower mechanical demands. In this case, the implant successfully replaced the bone defect of the clavicle, preserving its continuity and original length. Consequently, the strength and functionality of the affected extremity were preserved. Moreover, the empty spaces within the trabecular structure of the implant could facilitate the formation of woven bone. These spaces may be also filled with bone substitutes to enhance the osteogenesis process.

Finally, the use of 3D printing to reproduce intercalary segments for the replacement of bone defects is a promising field that needs further development. This new technique could provide an additional therapeutic tool that could minimize the morbidity associated with other conventional treatments.

Conclusion

The use of a 3D printed pseudo-prosthesis achieved an excellent clinical and functional outcome in the treatment of a large bone defect, after a resection of an LCH of the clavicle. 3D printed pseudo-prostheses could be useful instruments for the treatment of bone defects after large bone resections in musculoskeletal tumors.

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Comparison of the Results of Glassbone and Tricalcium Phosphate Graft Used in Bone Tumors

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ABSTRACT

INTRODUCTION: Bone defects caused tumors sometimes may not heal with bone tissue. In such cases, bone defects may need to be filled with bone graft materials to facilitate or start healing. The purpose of our study is to compare results of glass graft (GG) (GlassBone NORAKER) and tricalcium phosphate (TCP) grafts that we use in benign bone cysts clinically and radiologically.

METHODS: 41 patients with benign bone tumors (mostly simple bone cysts (SBC) and aneurysmal bone cysts (ABC) had been treated between either glass graft or tricalcium phosphate graft between 2013-2015. Patients were divided into two groups as those treated with GG and TCP grafts. Graft consolidation evaluated radiologically with x-rays monthly.

RESULTS: There were 20 men and 21 women (51.2%) with a mean age of 22.0 years (range 14-32 years). In patients using GG, compared to patients using TCP, radiological consolidation was observed faster between 14.-16. months (p = 0.0001).

DISCUSSION AND CONCLUSION: We conclude that in the treatment of benign bone tumors GlassBone can be used as an alternative to tricalcium phosphate grafts. We also noticed that patients treated with GlassBone showed a faster rate of fusion radiologically.

Keywords: bioactive glass, tricalcium phosphate, bone tumor

INTRODUCTION

Bone defects caused by trauma or pathological events are major clinical and socioeconomic problems. [1] Bone grafts are one of the surgical procedures used in bone regeneration in orthopedic surgery. [2] More than 2 million bone grafting procedures are performed worldwide each year, which is the most common tissue transplantation procedure after blood transfusion. [3]

During the last 40 years, regenerative medicine researchers have focused on producing materials that resemble bone properties and are not resorbable.[4] Autologous bone grafts are used as the gold standard for bone defects. It is preferred because it has a high osteogenic capacity, does not cause immunological reactions, and does not cause virus infections such as HIV and HBV. However, autografts have complications such as graft failure and morbidity (chronic pain, wound problems, blood loss, etc.). Complications such as infectious diseases and immunological rejection are also present in allografts. [5-7] These complications in allografts and autografts highlight biomaterials as grafts.

There are many different types of bone grafts available on the market, and orthopedists can choose from a variety of grafts, including ceramics, bioactive glasses, demineralized bone matrix, allograft, and bone morphogenetic proteins.

Bioceramics have been used as classical bone grafts for the last 40 years. [8] GG (Glass Graft) and TCP (Tricalcium Phosphate) grafts are ceramic-based grafts commonly used in bioengineering. In addition, GGs are grafts with osteoconductive and antibacterial properties. [9,10]

In this study, we aimed to retrospectively analyze the clinical and radiological results of GG and TCP grafts used in the treatment of common benign bone tumors.

MATERIAL AND METHOD

In this study, patients who were treated with GG or TCP grafts between January 2013 and December 2015 and diagnosed with SBC, ABC or other benign bone tumors in histopathological examination were analyzed retrospectively. The Helsinki Declaration Principles were followed in the study. 41 of 47 patients were included in the study, 6 patients were excluded because of a follow-up period of less than one year. All patients' history, clinical

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examination findings and radiological examinations such as direct radiography and MRI were examined. 21 of the patients were female and 20 were male. The patients were divided into 2 groups as those who were grafted with GG or TCP graft after curettage and cauterization. GG was used in 22 patients (53.6%) and TCP was used in 19 patients (Table 1). The size of the tumor was measured by X-ray or MRI. The patients were operated in Ankara Atatürk Training and Research Hospital. Curettage materials taken during the surgery were sent for histopathological examination to confirm the diagnosis in these patients, who were confident that they were clinically and radiologically benign before the operation. Histo-pathologically, it was classified as aneurysmal bone cysts (ABC) (12 patients), simple bone cyst (SBC) (10 patients), and other benign bone tumor (19 patients). In the operation, an oval lid was removed from the cortex with the help of a drill and osteotome. After the tumor was carefully removed with a curette, curettage, burr and cautery were applied to the cavity wall. The cavity was filled with GG or TCP grafts. The filled cavity was closed with a piece of cortex that was opened to reach the tumor. The mean hospital stay was 1.5 days (range 1 to 3 days). Tumor types classified by histopathological examination and location are shown in Table 1. On the 15th day after discharge, the patients were called to the outpatient clinic to have their sutures removed and then for monthly check-ups and evaluated clinically and radiologically.

Statistical Analysis

The conformity of the continuous numerical variables in the study to the normal distribution was examined using the ShapiroWilks test. For the representation of numeric variables, median (interquartile range), mean ± standard deviation, and minimum; maximum descriptive statistics were used. Number (n) and percentage (%) were given in the representation of categorical variables.

Fisherexact test and Yates chi-square tests were used to examine the difference of categorical variables in the study groups, and Mann Whitney U test was used to compare numerical variable values.

The relationship between numerical variables was examined with the Spearmanrocorrelation coefficient. In the case of a significant relationship, if the correlation coefficient is between 0.00 - 0.19, "no relationship or negligible low relationship", "weak (low) relationship" between 0.20 - 0.39, "moderate relationship" between 0.40 - 0.69, 0.70 - 0.89 It was interpreted as "strong (high) relationship" in the range of 0.90 - 1.0 and "very strong relationship" in the range of 0.90 - 1.0.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MSExcel 2007 programs were used for statistical analysis and graphics. Statistical significance level was accepted as $p<0.05$.

RESULTS

In this study, there were 41 patients, 20 male and 21 female (51.2%), with a mean age of 22.0 (14-32 years). The mean follow-up period of the patients was 44 months (range 12 to 86 months).

The mean tumor volume measured by X-ray and MRI was 20.7 cm3 (SD 17.7) in GG patients and 19.5 cm3 (SD 20.2) in TCP grafts.

3 patients were operated for the second time due to growing residual cysts and 1 patient due to infection. Of these patients, 2 were treated with GG and 2 with TCP graft. TCP graft was used in the infected patient. The same grafts were used in the second surgeries.

The union was evaluated clinically by pain relief and radiologically by X-ray. Radiological union was seen in all patients, including patients who were reoperated at 3 months. Compared to the patients who used TCP, in the patients who used GG, 14th-16th days. It was observed that radiological consolidation was faster between months ($p= 0.0001$).

At the end of the 16th month, there was no statistically significant cavity in the X-Ray of the patients who used GG compared to preoperatively. ($p:0.01$) There was a significant difference between

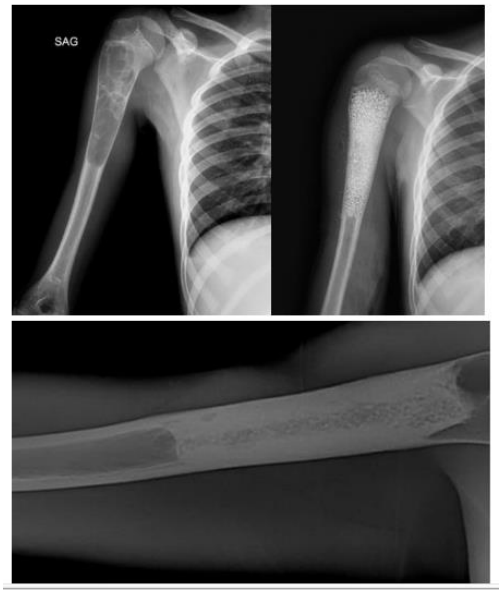

Figure 1: *ABC located proximal to the right humerus in a 14-year-old male patient a) direct radiograph of a lobulated septal cystic lesion extending from the proximal humerus to the diaphysis b) post-operative radiograph after curettage + allograft (glass graft) c) postoperative 10th month radiograph; graft fusion is seen.*

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the patients who used GG and TCP grafts so far. (p:0.01) However, there was no difference between these two groups after 36 months. (p:0.78)

***Table 1**: Demographic Data of Patients*

Data	Total N= 41
Gender, n (%)	
Male	20 (48,8)
Female	21 (51,2)
Age, year	
Mean	22.0
Median (min-max)	24 (14.0-32.0)
Direction, n (%)	
Left	22 (53.6)
Right	19 (46.4)
Graft used, n (%)	
Glass graft, SBC	6 (14.6)
TCP graft, SBC	4 (9.7)
Glass graft, ABC	6 (14.6)
TCP graft, ABC	6 (14.6)
TCP Benign Bone Tumor	9 (21.9)
Glass Graft Benign Bone Tumor	10 (24.3)
Tracking Time, months	
Average	54.0
Median (min-max)	57 (12.0-126.0)

SBC: Simple bone cyst, ABC: Aneurysmal bone cyst
TCP: Tricalcium phosphate

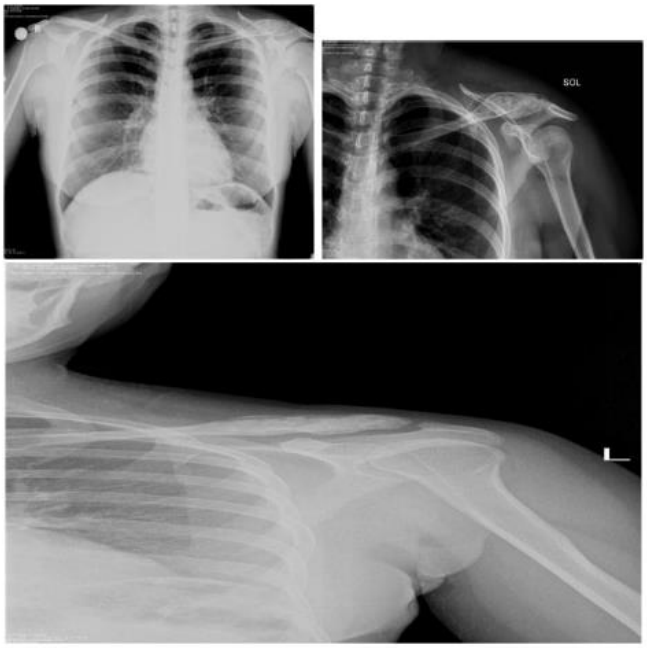

***Figure 2:** ABC located in the left clavicle in a 40-year-old female patient. A) direct radiograph of a septal cystic lesion extending to the diaphysis in the distal clavicle on direct X-ray b) Post-operative direct X-ray after curettage + allograft (tricalcium phosphate) c) Post-operative 4th month X-ray*

DISCUSSION

When the data of our country are examined, simple bone cyst is the third most common benign bone tumor (14%) after osteochondroma and enchondroma, and aneurysmal bone cyst (9%) is one of the most common benign bone tumors [11].

Benign bone tumors are usually treated by curettage and filling of the defect. Bone cement, synthetic bone graft, allograft bone and autograft bone are currently used for defects. Bone cement does not preserve bone stock. In addition, hardened cement does not have the same biomechanical properties as bone [12]. Allografts have risks of infectious disease, deep infection and nonunion. [13] Autologous bone grafts are used as the gold standard for bone defects. It is preferred because it has a high osteogenic capacity, does not cause immunological reactions, and does not cause virus infections such as HIV and HBV. However, autografts have complications such as graft failure and morbidity (such as chronic pain, wound problems, blood loss). Because of these complications, synthetic grafts are preferred.

The risk of infectious disease is eliminated with the use of synthetic grafts, and the use of synthetic grafts does not cause donor site morbidity. Other advantages are that they can be obtained in unlimited quantities and provide sufficient mechanical support to allow early functional rehabilitation. It is also known that synthetic grafts are biocompatible and used for the reconstruction of large bone defects. [14] Ideal bone graft is expected to show osteoconductive and osteoinductive properties, as in autologous bone graft. Also, synthetic grafts are readily available without the risk of viral or bacterial contamination. These grafts should be easy to apply, cost effective and should not be immunogenic. [15]

In addition to their osteoconductive properties, GGs have more osteostimulative properties than TCP grafts.[16] GGs also have antibacterial properties that activate angiogenesis. [17]

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Our aim in this study was to compare the consolidation time of the graft to the bone radiologically in patients in whom we used TCP graft and GG in the defect of benign bone tumors.

Ewaniev et al. retrospectively reviewed 24 patients with benign bone tumors that they operated between 2007 and 2012. Bone defects formed after intralesional curettage were reconstructed with “Pro-Dense (Calcium Sulfate–Calcium Phosphate Synthetic Bone Graft Composite)”. They found that complete radiological resorption and new bone formation with Pro-Dense were typically seen at 5 months postoperatively [18]. Saikia et al, they studied 24 patients who had been reconstructed with a TCP graft or HA (hydroxyapatite). HA was used in 20 of 24 patients and beta TCP was used in 4 patients, and the mean time to union was found to be 9 months (6-18 months) [19].

Linfors et al, they compared the results of 25 patients who used GG and autograft for benign bone tumors. They observed that union started at 12 months in patients who used GG, and there was a significant difference according to the preoperative situation at 24 months. In patients who used autograft, it was observed that there was consolidation in 12 months and there was no bone space. [20]

When the studies in our country are examined, Çelebi et al, in their study comparing cancellous graft and synthetic graft, they achieved an average union time of 149 days for synthetic grafts and 103 days for cancellous grafts. And this difference was statistically significant [7]. In our country, the results of graft use have been reported in many studies [21].

In our study, the consolidation time of the graft was statistically faster in patients who used GG up to 36 months. However, we observed that there was no clinical or radiological difference after 36 months. We think that graft consolidation is earlier because GG activates angiogenesis.

This study had some limitations. The study was a retrospective analysis, and the number of patients was relatively small. However, prospective randomized studies with long-term follow-up are needed to better understand these grafts.

CONCLUSION

As a result, glass grafts can be used as an alternative to tricalcium phosphate grafts in the treatment of benign bone tumors. In addition, radiologically faster fusion is seen in patients treated with glass grafts.

There is no conflict of interest between the authors.

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Chronic Tibial Osteomyelitis; Use of Biactive Glass as an Alternative of Treatment. Report of a Case

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Background:
Chronic osteomyelitis is a disease usually of infectious origin. The main cause is post-traumatic, it affects the bone tissue and surrounding tissue, the most frequent causative agent is Staphylococcus aureus. The most affected bone is the tibia. **Case description:** A 42-year-old male with a diagnosis of chronic tibia osteomyelitis, with sequelae of previous surgical interventions, multiple antibiotic treatments, and type IV B classification by Cierny-Mader. **Methods:** Two-stage surgical management was chosen. Firstly, extensive bone and soft tissue debridement, placement of cement beads medicated with amikacin in the medullary cavity and osteoclast system for irrigation with vancomycin. In the second stage, free fibular bone grafting, fixation and stabilization with screws, bioactive glass placement in areas of interface between stabilized fibula and posterior tibial cortex. **Results:** Before a multitratada chronic osteomyelitis it is necessary to individualize and evaluate treatment alternatives, in this case the surgical management in two time, the use of medication beads, bone graft and the use of bioactive glass, achieved a complete eradication of the infection and favorable clinical evolution with optimal functional recovery of affected limb.

Key words: Chronic osteomyelitis, Tibia, Bioactive glass.

I. Introduction

Osteomyelitis is defined as an inflammation of the bone caused by an infectious agent.[1] The main cause of chronic osteomyelitis is Staphylococcus aureus.[2,3] Lee and Waldvogel classify osteomyelitis as acute, subacute and chronic, hematogenous or contiguous, and with or without vascular deficiency.[4] The Cierny-Mader classification includes pathological and impermeable approaches.[5]
The incidence of osteomyelitis is variable. Hilal et al indicate 21.8 cases per 100,000 person-years.6 It affects men in a greater percentage, mean age is 52 years, the most frequently affected bone is the tibia, the most common cause was post-traumatic.[5,6,7,8]

The diagnosis of osteomyelitis is based on the clinical history, physical examination, result of laboratory and imaging studies.[8,9] Surgical treatment should include radical debridement, removal of dead tissue, soft tissue reconstruction, and restoration of bone stability.[10] Current surgical treatment of chronic osteomyelitis is commonly with surgical implantation of polymethylmethacrylate (PMMA), mixed with antibiotics, in the affected anatomical area, after extensive debridement and pulse lavage. These PMMA beads are removed in a

second surgical procedure.[11,12,13,16] The gold standard for bone defect restoration is still considered autologous bone grafting.

But it is not free of complications.[15] Bone graft substitutes are commonly used to replace and regenerate bone loss due to trauma, infection, disease, or to provide stability around implanted devices.[14,15.] In this context, bone graft biomaterials current generation are an alternative treatment and are designed to stimulate specific cellular responses at the cellular and molecular level.[17,21] Characteristics of biomaterials: Bioactivity any interaction or effect that the materials have on cells. Biocompatibility, absence of cytotoxic, genotoxic effects or immune response. Osteoconductive and osteoinductive involves exchanges of ions with biological fluids that allow the formation of a mineral layer, a direct biological coupling between the biomaterial and the bone.[13,14,20]The release of biomaterials will stimulate the incorporation and proliferation of stem cells, resulting in the differentiation and proliferation of osteoblasts.[15] The release of ions such as sodium, calcium, and silicon increase the local pH and osmotic pressure, guaranteeing antibacterial properties.[14, 15] There are various bioactive glass compositions on the market. In this case, Glass Bone (BG) 45S5 was used. It is a biomaterial with properties that meets the aforementioned characteristics.[18,19,21,22]

II. Clinical Case

42-year-old male patient, peasant occupation. He went to the traumatology and orthopedics outpatient service for presenting fetid secretion and ulcer at the pretibial level of the left leg. Anamnesis: current illness begins at the age of 22 years in an acute and insidious way with increased volume and pain in the metaphyseal region of the left tibia, he was subjected to surgical toilets on three occasions and the application of multiple antibiotics for prolonged periods without improvement. Physical examination: presence of fistulas in the proximal metaphyseal region 1 cm in diameter, both with communication to the spinal canal and with active, purulent and fetid exudate. Paraclinical Hb 13mg/dl, HTC 30%, Cr 2.3mg/dl, Urea 40mg/dl, culture of E. coli wound exudate sensitive to moxifloxacin and amikacin, anteroposterior and lateral X-ray of the left leg showing anterior cortical condensation from proximal metaphyseal region to the distal third of the tibial diaphysis with the presence of a lytic zone of approximately 3 cm in the proximal metaphyseal region. After these findings, it was classified as chronic tibial osteomyelitis type IV B according to the host with added systemic disease chronic renal failure (CRF). Definitive surgical treatment in 2 stages was chosen.(fig. 1)

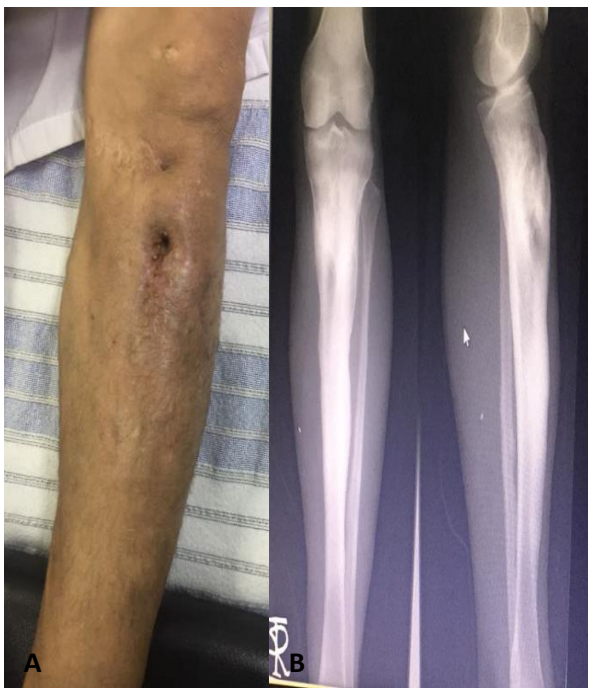

Fig 1.A:Fistulas in the proximal metaphyseal region. B: AP and lateral radiography of the left tibia, lytic area in the tibial metaphyseal region and anterior bone condensation up to the distal diphyseal region.

In the first stage, an anterior linear hemidiaphysectomy is performed up to the proximal region at the metaphyseal level with resection of sequestered bone tissue up to the region of the anterior tibial tuberosis, medullary evacuation of said anatomical region, obtaining abundant fetid yellowish secretion, scarification of the medullary canal until tissue is obtained. bleeding bone, amikacin-medicated cement beads were placed in the medullary cavity and intramedullary osteoclysis system for irrigation with 100ml physiological solution plus 1g of vancomycin every 24 hours for 10 days.[23](fig.2)

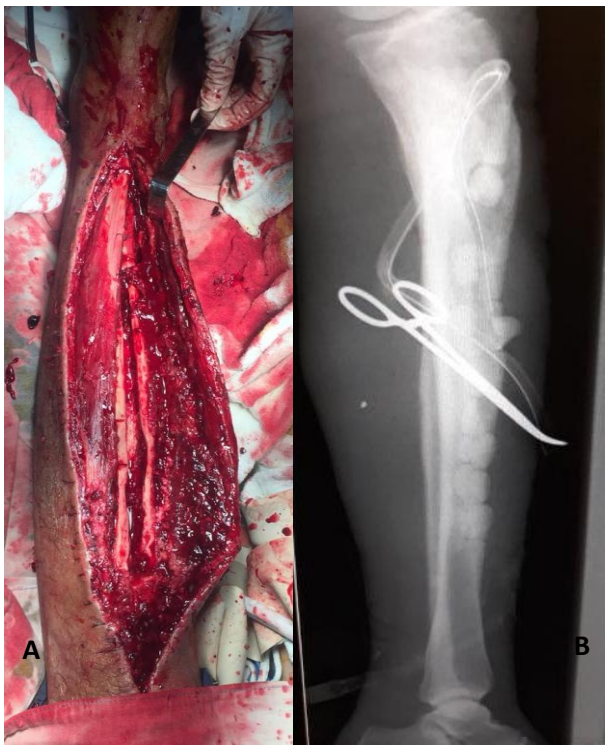

Fig 2. A: Anterior cortical resection. B: Osteoclysis system and PMMA medicated with amikacin.

In the second surgical stage, the non-vascularized free fibula is taken, the fibula is obtained with the desired length and it is presented in the exposed medullary canal, fixation and stabilization is carried out with 4.5 titanium screws with the placement of 4 of a standard 30mm measurement. Subsequently, the bioactive glass is placed in interface areas between the stabilized fibula and the posterior cortical bone of the tibia along its entire length, as well as the total filling of the medullary cavity in the metaphyseal region (16 grams of 1mm bioactive glass were used), the surgical wound is closed, and remains hospitalized, amikacin 250mg every 12 hours and Moxifloxacin 400mg every 24 hours are applied. He was discharged from the hospital 5 days after the second surgical intervention with a wound in the healing phase, fistulas closed without expense, antibiotic moxifloxacin 400mg po every 24 hours, for 6 months, and monthly liver function test controls. One month later, the patient presented clean healed surgical wounds, closed fistulas, no signs of infection, full range of motion, muscle hypotrophy, radiographic control with graft in the integration phase, no signs of instability of the osteosynthesis material, PFH in normal parameters, continued with moxifloxacin 400mg every 24 hours and rehabilitation exercises. Last assessment 3 months later, the patient was already walking without support and laboratory tests within normal parameters. (fig3)

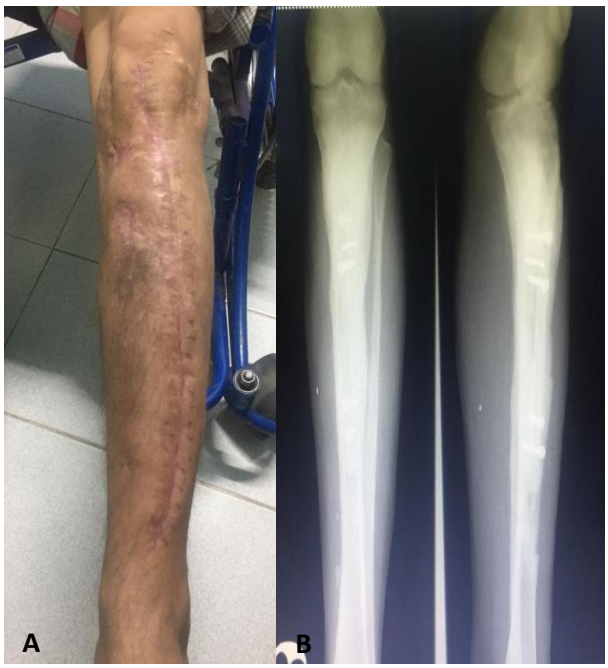

Fig 3. A: Closure of fistulas and surgical wound without evidence of exudates. B: Bone osseointegration of the fibula in the tibia.

III. Conclusion

Chronic osteomyelitis is a complicated infection to treat, most cases management involves a multidisciplinary approach, the primary care provider plays a key role in the initial diagnosis and coordination with other specialists. Surgical treatment is the essential part of treatment, complementation with adequate antibiotic treatment significantly improves the success rate. The treatment must be individualized and assess the available management alternatives, assessing the cost benefit. Treatment strategies depend on several factors: characteristics of the host, the segment involved, the size of the lesion, the location of the lesion, and the substitute or support material to be used. Several studies have shown that management with bone graft material alone is associated with different cure rates ranging between 60 and 90%, however, there are problems with the use of bone autografts such as insufficient amount of graft, post-surgical morbidity in donor area, infections and hemorrhage mainly. The concept of polytherapy gains strength in the orthopedic field and consists of simultaneously implanting two or three fundamental components for healing. Combination therapy is a logical option, especially in elderly individuals with associated comorbidities and a limited capacity for tissue regeneration. For these reasons mentioned before a chronic osteomyelitis of the tibia that did not evolve correctly after previous surgical treatments and before a patient with added systemic disease, a two-stage surgical treatment was decided. The polytherapy concept is also taken into account. An extensive surgical debridement was performed, PMMA impregnated with amikacin was applied, an osteoclysis system with vancomycin irrigation in the second stage, an autologous fibular graft was performed and bioactive glass was applied, with which a complete eradication of infection and recovery of limb function. In the 12-month follow-up, the patient shows no signs of infection with recovery of 90% of the function of the affected limb.

IV. Conflict of interests.

The authors of this article have no conflicts of interest.

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Case Report

Saving the lower limb with GlassBONE™ - Successful surgical revision of pseudarthrosis after infected open proximal tibia fracture type IIIC with bioactive glass grafting - A case report

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ABSTRACT

Background: The management of bone defect due to trauma or surgical debridement is a current problem in orthopedic trauma surgery, often complicated by infection and bone nonunion. The graft is one of the most challenging variables in surgical treatment. Bioactive Glass (BAG) as a biocompatible and osteogenic product is a promising bone substitute showing good results in maxillo-facial-, spine surgery and treatment of osteomyelitis. Surprisingly, there is very little data on BAG use in trauma surgery.

Case presentation: A 51-year-old male patient, involved in a motorcycle accident, suffered an open proximal tibia fracture, type IIIC, of the left leg. Patient was admitted in January of 2013 to a general orthopedic department for surgical treatment. After several surgical revisions due to infection, vascular damage, and bone nonunion, the patient was successfully treated with Masquelet therapy followed by GlassBONE™ grafting (GlassBONE™ 45S5; Norarker). The patient demonstrated excellent results over the course of a two-year follow-up.

Conclusions: In our experience, GlassBONE™ 45S5 has proven to be an effective bone substitute even in difficult grafting conditions, including multiple surgical revisions for bone nonunion and infection. In our case, at the end of 2 years and 3 months of follow-up, the patient reported no pain, and had no signs of infection. Bone union and full weight bearing was achieved.

This case report is oriented by the CARE guidelines for clinical case reports; the patient gave consent for publication.

Background

Bone fractures account for the most widespread trauma in humans [1]. The management of bone defect and bone loss due to fracture or surgical debridement is a current problem in orthopedic trauma surgery. Bone loss usually requires grafting and implantation of stabilizing material, elevating the risk of infection and subsequently the risk of bone nonunion [2]. Bone nonunion leads to diminution of quality of life and even disability posing a vast impact on health systems and economies. A recent review of Schlund et al. found that 10–15% of patients experienced impaired fracture healing or even bone nonunion after bone injury [3]. In open fractures, the risk of nonunion is reported to be more than 30% [4]. In a study on 104 tibial shaft fractures, Karladani showed a relative risk of

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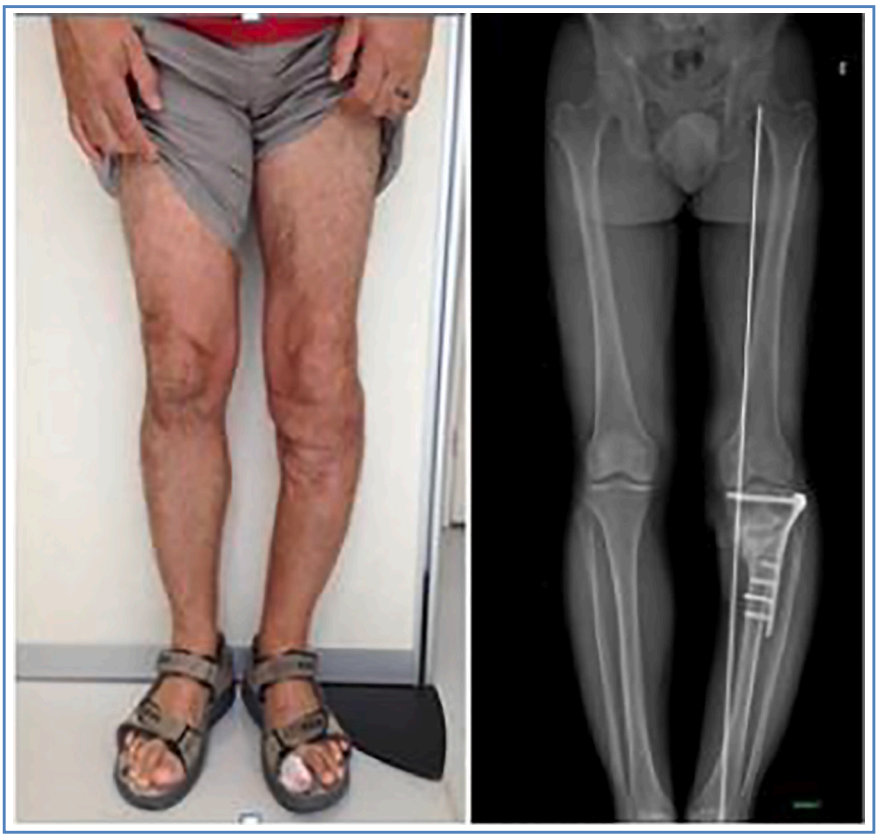

Fig. 1. Clinical aspect and anterior-posterior view (ap view) of leg axis showing varus deformity before Masquelet therapy.

8.2% of open fractures to develop nonunion [5].

The surgical management of bone defect has been addressed in a variety of ways, including bone-transfer, free soft-tissue flaps or antibiotic loaded polymethylmethacrylate (PMMA) [6,7]. Autologous bone grafting is limited by the amount of graft material accessible for harvest and large bone defects may not be able to be sufficiently filled. For example, some patients who have already undergone harvesting from both iliac crests and/or harvesting via reamer-irrigator- aspirator (RIA), may not be candidates for bone grafting due to anatomical reasons. In addition, autologous bone grafting requires a second surgical intervention, posing postoperative risks including infection, pain and serious cosmetic anomalies [8,9]. The main disadvantages of PMMA application include its multiple resistances and the requirement of additional intervention resulting in potential risk of associated complications and morbidities [10,11].

There is a need of a bone substitute that does not require harvesting, which is biocompatible, carries no risk of viral or bacterial disease transmission, has unlimited availability, and provides stable restitution of the bone. BAG, a biomaterial of the ceramic family, seems to meet these requirements in mechanical strength, biodegradability, and its osteoinductive and osteointegrative properties [12,13]. BAG induces the formation of hydroxyapatite by releasing calcium ions, responsible for its osteostimulative effect. In addition, it has an osteoconductive effect allowing bone to grow on its surface [14–16]. In our clinical case, we used the original form of BAG, GlassBONE™ (NORARKER) for grafting. GlassBONE™, belonging to the SiO2-Na2O-CaO-P2O5 system (Bioglass) was invented by Dr. Larry Hench in the late 1960s and is a degradable, bioactive glass (glass that activates specific responses of cells) with the ground-breaking characteristic to bond to bone [17–19]. 45S5 is the base of many variants of bioactive ceramics including S53P4 BAG, which is a promising BAG. This BAG is currently involved in a clinical trial comparing the outcome of two different treatment strategies involving nonunion of the tibia and femur. One group is treated with S53P4 BAG grafting after Masquelet therapy, the other group is treated in the regular way with autologous bone- and tricalcium phosphate grafting [20]. Open fractures with large skin lesions (greater than 5 cm), as we are presenting in our case report, are known to have a 5.7 times greater risk of delayed healing or nonunion than fractures with no skin injury [2]. In trauma surgery, the risk of infection is also elevated by the implantation of foreign material (fixation material) [21]. BAG could be an attractive biomaterial in trauma surgery due to its osteoconductive and osteostimulative effects as well as its antimicrobial properties. Bacterial adhesion and proliferation are inhibited with BAG due to increase of the local pH and elevation of osmotic pressure by release of sodium and calcium ions and phosphorus salts [22]. The great advantage of this local bactericidal action, without the addition of synthetical antibiotic, is that no bacterial resistance will be created, and no adverse reactions should be seen.

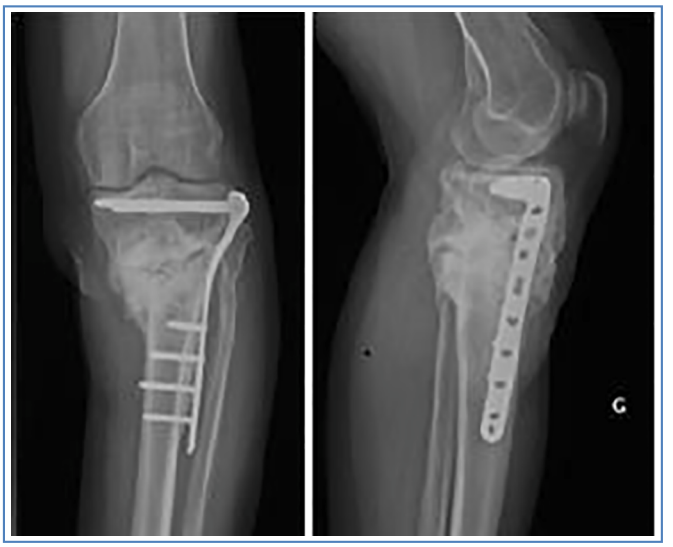

Fig. 2. ap- and lateral view of left leg before Masquelet therapy.

1. step:
Material removal + bacteriological samples
cement spacer
antibiotic therapy

2. step:
*Extensive auto-and allograft (*GlassBONE ™*) + BMP*
plate fixation via medial approach

Fig. 3. Therapy plan.

Case presentation

We report the case of a 51-year-old male who presented with an open proximal tibia fracture type IIIC of the left leg due to a motorcycle accident in January 2013. For three years, (between the initial surgery in January 2013 until March 2016) the patient underwent several surgical revisions to correct and combat vascular damage, bone nonunion and infection. Even after numerous attempts to achieve healing, patient's result was unsatisfying, as once again, nonunion and infection of the fracture site was noted. Successful treatment was finally initiated in September 2016 by Masquelet therapy followed by GlassBONE™ grafting in a second procedure showing excellent results upon 2-year follow-up.

A 51-year-old male was addressed to the orthopedic department (France) to receive medical treatment of an open proximal tibia fracture type IIIC of the left leg. Medical history: smoker, no diseases, no regular medication. The immediate surgery in January 2013 consisted of open reduction and internal plate fixation (lateral LCP, antero-lateral approach) and vascular bypass of popliteal artery. The postoperative phase was complicated by severe wound healing disorder, leading to septic osteitis with skin necrosis and bone exposition in March 2013. Treatment consisted of medial gastrocnemius muscle flap and skin graft at University Hospital. The tissue samples taken during surgery were positive for staphylococcus multi-r, *Enterobacter cloacae* multi-r and enterococcus species multi-r. Antibiotic therapy with Vancomycin and Co-trimoxazole (Trimethoprim/Sulfamethoxazole) was initiated. In December 2013 fracture of fixation material occurred leading to the necessity of several surgical revisions between December 2013 and October 2014, including material changement, decortication and partial resection of the tibia. In the two surgical revisions (January and October 2014) the same initial surgical approach (antero-lateral) was used. Internal fixation was performed as initially with lateral LCP. Allograft (half femoral head, Tissue Bank of France and OSTEOpure™, European Cell and Tissue Bank), and autograft (iliac crest) with Bone Morphogenetic Proteins (BMP) substitution were performed.

One year later, despite repeated surgical revisions and antibiotic treatment, the wound was inflammatory with subcutaneous collection without fistulation. X-ray and CT-scan performed in September 2015 showed that bone union was still not achieved. In addition, severe tibial varus deformation (10°) at the fracture site was noted (Figs. 1, 2). The suspected underlying infectious process was confirmed by bone scintigraphy in December 2015 with fixation at the site of fracture and surrounding soft tissues.

The final treatment we are presenting in this case was preoperatively confirmed by a pluridisciplinary meeting in April 2016. Treatment strategy consisted of a two-step therapy (Masquelet-therapy followed by auto- and GlassBONE™-grafting and plate fixation

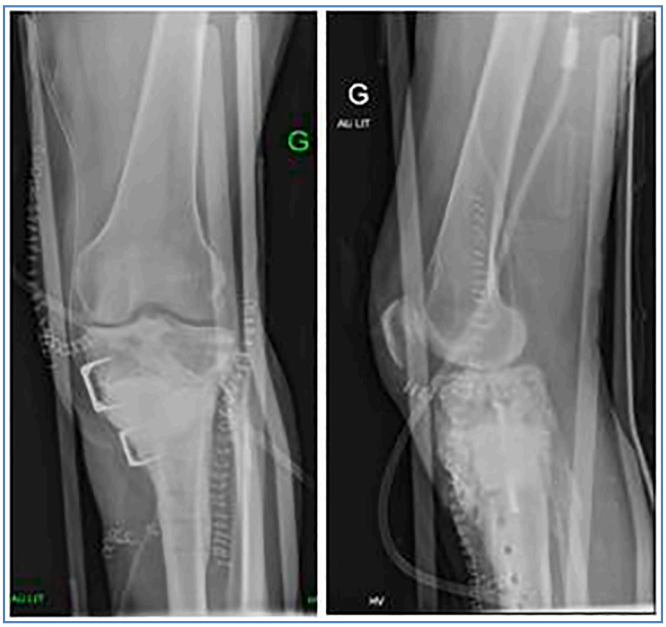

Fig. 4. ap- and lateral view of left knee after cement spacer implantation.

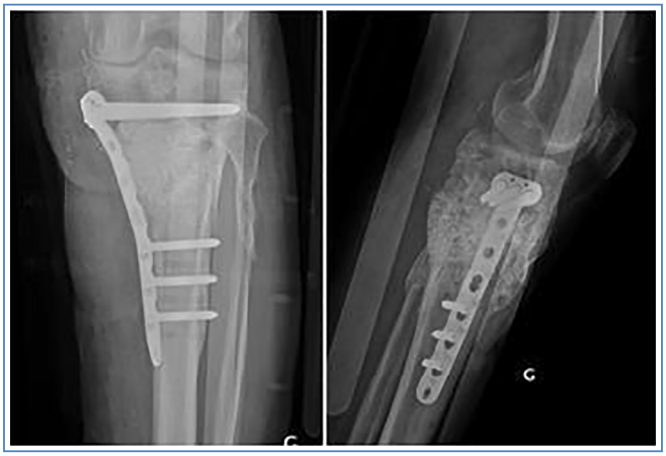

Fig. 5. ap- and lateral view of left knee after GlassBONE grafting and plate fixation.

via different surgical approach (medial approach to proximal tibia)) (Fig. 3).

Preoperative exams were performed: Scintigraphy with polynuclear cells marked with 99mTc- HMPAO confirmed an osteo-infection at the lateral side of left tibia. As an additional complication, (in March 2016) preoperative C.T. angio and vascular Doppler ultrasound revealed a lower limb arteriopathy with stenosis (>70%) of the left inferior popliteal artery. This required pre-operative vascular surgery in order to prime the vascular conditions for Masquelet and grafting surgery. Angioplasty of the left inferior popliteal artery was performed in June 2016 with good results. No complications, no stenosis was found during the follow-up.

Step one: material removal and Masquelet therapy

In September 2016, the first step of treatment was performed (Centre Hospitalier Saint Joseph Saint Luc, Lyon, France). Material associated to partial resection of the tibia was removed and a cement spacer was put in place. Provisory osteosynthesis via clamp was performed (Fig. 4). Multiple bacteriological samples were taken including PCR analysis. During surgery, due to correction of the varus, damage of popliteal artery occurred necessitating a venous bypass by allograft. Intraoperative thrombosis of the venous bypass was successfully managed by thrombectomy in the immediate postoperative suites. Subsequent postoperative evolution was positive (C.T. angio confirming good collateral flow despite repeated thrombosis of the venous bypass. There was no indication for revascularization,

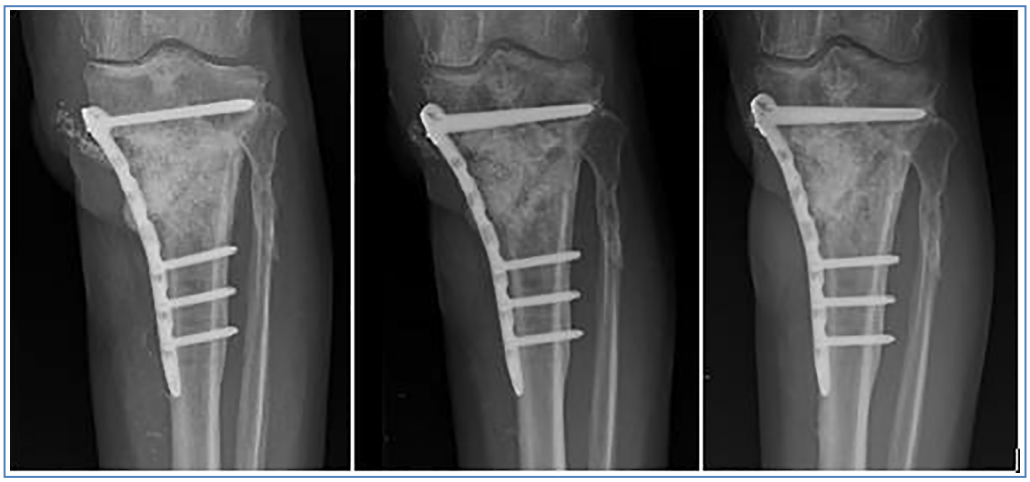

Fig. 6. ap view of left leg at 1 month, 6 months and 24 months postoperatively.

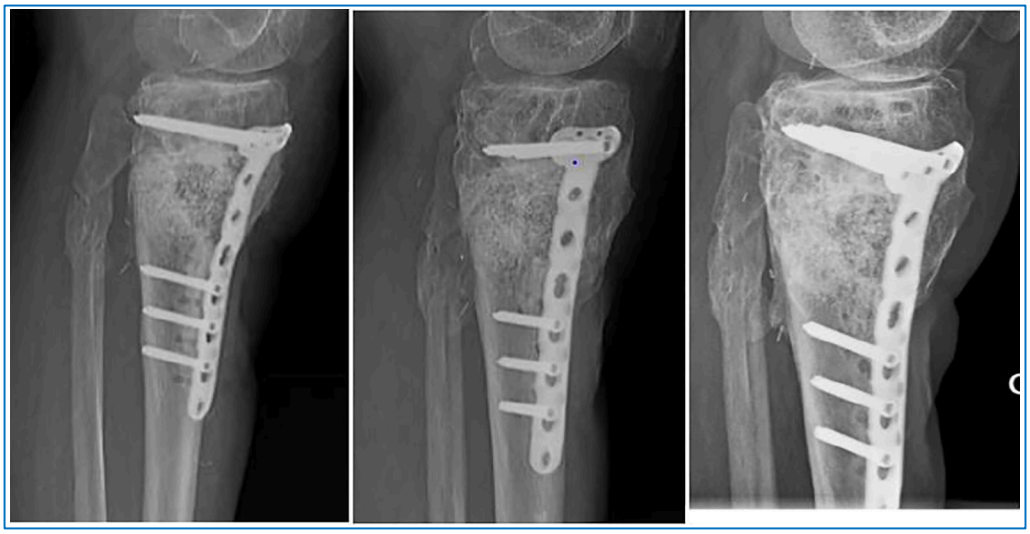

Fig. 7. Lateral view of leg at 1 month, 6 months and 24 months postoperatively.

but medical treatment prescribed with Acide acétylsalicylique 75 mg per day). Antibiotic therapy with Tazocilline + Vancomycin was initiated until reception of negative bacteriological samples. The patient left hospital on day 20 in good physical condition. Bacteriological samples were negative; no weight bearing was allowed.

Step two

Three months later, in January 2017, second surgical procedure (Centre Hospitalier Saint Joseph Saint Luc, Lyon, France) was performed without complications. Via medial approach, the cement spacer was removed, respecting the induced membrane. Again, multiple bacteriological samples were taken including PCR analysis. The bone defect was filled with extensive auto- and allograft (Iliac crest, GlassBONE™) within the borders of induced membrane and fixed via medial LCP (Fig. 5). Postoperatively, the patient received antibiotic therapy for 5 days (Vancomycin) until the reception of the bacteriological analysis, showing negative results in all samples. The patient left hospital on day 7 in good condition without weight bearing. Clinical and radiological follow-up was performed on months 1, 3, 4, 6, 10 and 27 post operatively.

Control 1-month post operatively showed good results. Radiographically there was no secondary displacement of material, consolidation was beginning. Bacteriological samples and PCR were negative. There was no pain or sign of infection. Progressive weight bearing (15 kg) was started, adding 10 kg each week. During the following clinical controls, (3, 4, 6, and 10 months post operatively) the patient showed an excellent clinical evolution. Radiographically progressive homogenization of the graft and bone consolidation was noted with no material loosening. At 6 months postoperatively, the patient was able to regain half-time work

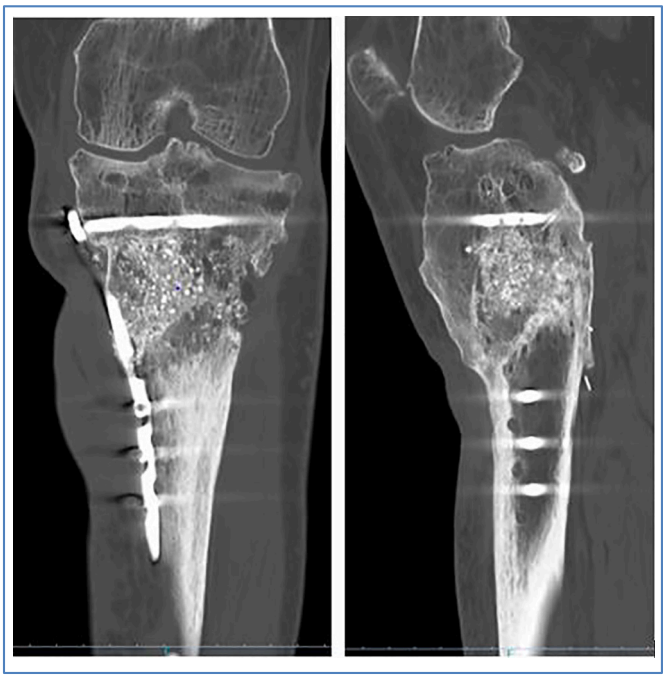

Fig. 8. CT-scan: ap and lateral view of left leg 18 months postoperatively.

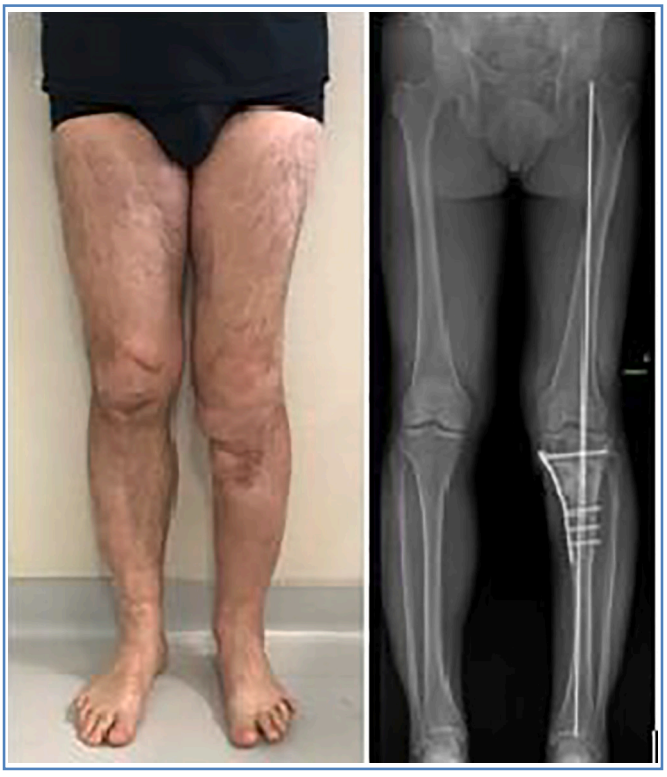

Fig. 9. Clinical aspect and ap view of leg axis 24 months postoperatively.

activity. Pain at the antero-lateral side of the left tibia of ischemic character, due to the poor vascular status, was reported only after extensive walking or standing (>2 h). At 10-month postoperative evaluation, clinical status was still very satisfying. The pain symptomatology did not restrict the patient's daily life activities. Radiographically, bone consolidation was found and there was no deformity of axe nor signs of material loosening. 2 years postoperatively, radiographs and CT-scan showed transformation of the GlassBONE™ into bone and perfect bone consolidation with no material loosening (Figs. 6, 7, 8, 9). Clinical exam was very satisfying: no limping and walking was possible without crutches. The walking distance however was limited (pausing each 300 m) due to vascular claudication on peripheral obliterative arteriopathy.

Discussion and conclusions

In our case, a patient presenting with multiple complications after initial surgery of an open fracture of the proximal tibia was finally successfully treated with BAG grafting. This in a terrain of high risk as open fractures with large skin lesions are known to have a 5.7 times greater risk of delayed healing or result in nonunion than fractures with no skin injury [2]. There is little long-term data on BAG in long bones. Good results were shown in a case report of remodeling of the tibia after grafting a large cavity of the proximal tibia in treatment of fibrous dysplasia with BAG-hydroxyapatite (70% and 30% iliac crest). In the 13-year follow-up, the Swedish study group showed excellent clinical and radiographical results and histological degradation of BAG (no more BAG material in bone biopsy 13 years after grafting) [6]. BAG also shows good results in repairing bone defects of benign neoplasm. In a 2-year follow-up, 34 patients with larger bone defects (ranging from $3 \times 2 \times 1$ cm to $11 \times 3.5 \times 3$ cm) were grafted with a mixture of BAG and autogenous red bone marrow with rare complications. Bone remodeling was achieved 6 to 10 months postoperatively, and radiographically the majority of the implanted BAG was absorbed [23].

Another interesting point to take into consideration concerning our case is the area of fracture. Bone defects in metaphyseal area differ from the diaphyseal area concerning the mechanical environment and challenges. In contrast to a metaphyseal bone defect, where filling of greater cavities, reestablishing a support for the joint surface, and regaining bone stock are the primary objectives, in diaphyseal bone defect, repairing the cortical continuity is the main goal. There is clinical evidence that the filled defects in metaphysis heal faster when filled than when left open [24,25].

GlassBONE™ provides the quality of giving initial support and filling. It is available in granules and is therefore suitable for any size and form of cavities. Furthermore, it is subsequently resorbed and provides osteoconduction for new, in-growing bone [26]. In addition to variations concerning the mechanical environment and its challenges, there are several studies indicating a difference in the process of fracture healing in metaphyseal bone compared to the diaphysis. Inoue et Al. compared the bone repair mechanism of the metaphysis and the diaphysis of the mouse tibia. This study showed that in the metaphysis, the fracture was filled with newly formed bone produced from the bone marrow without detection of a cartilage formation on the periosteal side. This was contrary to the diaphysis, where cartilage was formed at the fracture site and then subsequently replaced by bone on the periosteal side. Furthermore, the study indicated that after injury, osteogenic markers in the bone marrow and medullary callus appeared earlier in metaphysis than in the diaphysis [27]. In addition, the metaphyseal region is rich in cancellous bone and contains more mesenchymal stem cells with high osteogenic potential [28]. This fact might suggest that the metaphyseal region is more efficient in providing mesenchymal stem cells to the injured bone marrow than the diaphyseal region. This condition might also have played a beneficial role for the successful bone-union in our case since the site of pseudarthrosis was mainly situated in the metaphyseal region. The Glassbone-autograft mixture was consequently placed in a favorable area regarding mesenchymal stem cell availability. In addition, based on the well-studied experiences with Masquelet-therapy in long bone defects, we suppose that the graft effectively consolidated since it was surrounded by the induced pseudo membrane, known to express osteoinductive growth factor molecules, comprised of osteoprogenitor cells, which stimulate osteogenesis [29–31].

A critical point of our case report is that we mostly utilized x-ray for measurement of union and bone healing while SPECT could be a more precise but also noninvasive method for showing an increase in the rate of mineral metabolism and remodeling of the cortex.

In our case, we grafted with a mixture of BAG and autograft relying on established trauma surgery experience. However, there should be more investigation regarding whether the use of BAG alone or in combination with autograft is superior (being interesting in many cases where autograft harvesting is complicated). A promising clinical trial that started in 2018 compares the treatment of nonunion of the tibia and femur with S53P4 BAG grafting alone in Masquelet therapy to regular combined grafting of autologous bone and tricalcium phosphate [20].

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Case Report

A case report of upper limb loss of substance: Use of functional gracilis free flap, brachioradialis transposition and bioglass for bone regeneration

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ABSTRACT

Complex trauma of the upper limb is a common consequence of involvement in serious accidents. Loss of substance including nerve, bone, tendons and vascular defects are challenging surgical issues. A 27- year-old male presented with complex upper limb trauma and loss of a proximal third of the posterior forearm structure as well as loss of active finger extension, ulnar and radial nerve territory anesthesia and ulnar fracture. A composite nerve-tendon-muscle-skin gracilis free flap was retrieved from the contralateral leg, related to tendon transfer of BR to ELP, to supply active hand extension. The patient was required to adhere to intensive post-surgical rehabilitation and monitored for a 3-year follow-up period. Our assessment revealed adequate skin trophism and sufficient muscle strength recovery against resistance (M5). The functional flap associated with tendon transfer was considered an efficient procedure for the management of a complex trauma with loss of posterior interosseous nerve and bone exposition. The free re-innervated gracilis flap may be used to repair complex soft tissue defects with exposed bone and to restore finger extension following severe forearm injuries.

Introduction

Upper limb injuries are common occurrences of complex trauma following road, industrial or ballistic accidents. A complex injury affects the bone and the associated soft tissues such as nerves, vessels, tendons and skin. Reconstruction of these defects is a challenging enterprise in regenerative and hand surgery owing to the peculiar anatomy and biomechanics of this region. In reconstruction, the availability of local and regional flaps, able to repair the relevant structures is scarce with the gracilis free flap remaining the sole

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option for this kind of trauma. The extensor mechanism of the hand is sub-served by the radial nerve and the posterior interosseous nerve (PIN), the terminal branch of the radial nerve. In the case of injury distal to the PIN, wrist extension may be spared, due to the presence of lateral extensor muscles, the brachioradialis (BR), the extensor carpi radialis longus and brevis (ECRL and ECRB) in addition to the extensor carpi ulnaris (ECU). Extension of the long fingers and thumb is invalidated as the innervation of the relative muscles (extensor common digits and extensor pollicis longus) is pertaining to the PIN. Extension of the hand and wrist is fundamental to enable prehension which is described as "all the functions that are put into play when an object is grasped by the hands—intent, permanent sensory control, and a mechanism of grip." [1]. The prehension phase involves approach, grip and release of grip [2]. If the patient is not able to stabilize the wrist, the grip strength is consequently attenuated from 25% to 50% [3]. To release the grasp, thumb and finger extensions are required with the engagement of the extensor digitorum communis (EDC) and the extensor pollicis longus (EPL) muscles intrinsic to proximal interphalangeal (IP) extension. We present a patient that reported complex trauma with loss of cutaneous proximal third of the dorsal forearm and extrinsic hand muscle tendons as well as interosseus posterior nerve and ulnar defects. We aimed to restore hand extension and to cover the cutaneous loss of substance with a gracilis re-innervated free flap [4]. The aforementioned flap is considered an optimal muscle to reconstruct the extensor digitorum communis muscle of the forearm (EDC) supplied with relevant pedicle and single motor nerve (obturator nerve) to regenerate motor skills and secure skin coverage regarding cutaneous loss of substance. In addition, we proposed the use of the Brachioradialis pro Estensor pollicis longus as a tendon transfer [5,6].

Case report

A 27-year-old male from Italy presented as victim of car and motorcycle collision with injury to the distal third of the right forearm [Fig. 1A, D]. The intervention procedure was conducted according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The patient submitted written informed consent for surgery and follow-up with related protocol confirmed by the local Ethics Committee. A physical examination revealed abundant loss of substance of the third distal of forearm in bone and soft tissues. The patient reported anesthesia in the ulnar nerve distribution (IV e V fingers) and paralysis to the intrinsic muscle determining inability to flex the metacarpal (MCP) joints and to extend the interphalangeal (IP) joint. Intrinsic impairment had caused a reduction in pinch and grip strength along with paralysis of the adductor pollicis, flexor pollicis brevis and the first dorsal interosseus muscles. Consequently, the patient was affected by diminution of pinch strength and finger abduction due to dysfunction of the palmar interosseus muscle. Moreover, the patient displayed deficit in extension of the long fingers and the opponens pollicis. The patient had received emergency orthopedic and plastic surgery treatment in our hospital before the procedures herein described. The initial assessment and intervention envisaged fixation of the ulnar bone by external fixator [Fig. 1B, C, E], tissue damage was estimated as a lesion of the posterior interosseus nerve (PIN), loss of the vascular and nervous pedicle at the distal third of forearm, the ulnar nerve was damaged and sutured with 8/0 Nylon, the ulnar artery was cauterized (the previous doppler revealed vascularization from radial artery), and a first debridement of the wound was performed. The injury site showed signs of contamination and was dressed as an open wound [Fig. 1B, C] with iodate bandage. After 6 days the patient was submitted to a new debridement, fasciotomy of dorsal hand was performed, and Negative Pressure Therapy was applied on the wound at the distal third of forearm. After 45 days from the initial surgery, no wound or bone infection was detected therefore reconstruction process was initiated [Fig. 1F]. A composite gracilis free flap was selected. The patient was prepped and draped as per standard procedure with exposure of the pubic symphysis and the medial condyle of the femur [Fig. 2A]. General anesthesia was administered to transpose the tendon of BR pro EPL [Fig. 3] using the Pulvertaft suture technique as in previous surgical interventions [5,6] and the flap was harvested [Fig. 2B]. The contralateral gracilis muscle is appropriate for harvesting due to its accessibility towards the site of the donor vessels. We performed a longitudinal incision of 20 cm in length at 3–4 cm beneath the pubic symphysis, precisely between the adductor tubercle and the medial condyle of the femur [Fig. 2B]. We continued the incision to the muscular fascia until identification of the gracilis muscle. The adductor longus was also identified and retracted superiorly. The neurovascular anatomy is discernible by posteriorly retracting the gracilis muscle from the underbelly of the adjacent portion of the adductor longus muscle. The obturator nerve is located at 1–2 cm above the vascular pedicle. The dissection along the neurovascular pedicle was then extended to the appropriate length. The dimension of the forearm gap was matched to the approximate muscle template length. The inferior edges of the muscle were transected to determine a neo-tendon [Fig. 2B]. The neurovascular bundle is not to be separated from the underbelly of the muscle during harvesting under any circumstances. The obturator nerve and vessels were dissected to reach the maximal length [Fig. 2D]. The vessels were lowered only after complete dissection of the forearm and identification of the vessels. The leg incision was subsequently sutured using the standard procedure and drainage tubes were inserted. The recurrent artery of the radial artery was identified and isolated on the lateral side of the forearm including two comitans veins and the interrupted PIN. The free flap was inset into the forearm, the obturator nerve was sutured to the PIN [Fig. 2G], the gracilis tendon was sutured to the EDC using Pulvertaft techniques, the vascular pedicle was sutured to the forearm vessels (recurrent radial artery and two comitans). Arterial and venous anastomoses were performed via 9-0 nylon sutures under the operating microscope [Fig. 2F]. Drain tubes were inserted and layered closure was adopted for the incision [Fig. 2I]. Following surgery, the patient was monitored for several months initiating a rehabilitation program with a specialized physiotherapist. The BR pro EDP extension was assessed using the Geldemacher evaluation scheme [7]; the function of the gracilis flap was evaluated in compliance with the Medical Research Council Muscle Strength Grading System (MRC) [8] and general hand function was verified via the Michigan Hand Score [9]. The results are displayed in Table 1. Six months after surgery the ulnar fracture was affected by pseudoarthrosis [Fig. 4A], therefore new surgery for bone defect was managed using Bioglass to avoid iliac crest draft considering the patient's medical history of surgical interventions. The area of ulnar pseudoarthrosis was meticulously debrided and irrigated. All non-viable bone tissues were removed [Fig. 5A, B]. After identification of 2 cm bone defect [Fig. 5C], we implanted an activated Bioglass spacer in the site of the bone defect

previously prepared with a biologic camera. The ulna was then stabilized using an internal ORIF [Fig. 5D-G]. The Bioglass was activated according to the following procedure: 40 cc of venous blood was taken from the patient's contralateral arm and placed in two 20 ml vials and centrifuged for 9 min at 3200 rpm, the blood was then divided into three parts, the upper fraction containing monocytes, the central fraction containing platelet rich plasma and the bottom fraction containing the corpuscular elements. The first upper fraction was collected using two syringes of 5 cm^3 [Fig. 5E] to activate the Bioglass granules [Fig. 5F]. On termination, a radiography was performed [Fig. 4B]. Three months later [Fig. 4C] and five months later [Fig. 4D], the patient was monitored, and we observed satisfactory outcomes in the injury site. Currently, post-radiographic follow-up is limited by a short follow-up. Clinical results are displayed in Fig. 6 and Videos 1 and 2 on completion of follow-up.

Discussion

Subsequent to free-tissue transfer, the gracilis muscle has been acknowledged as a favorable tissue source to reconstruct minor traumatic or iatrogenic impairments, due to its accessibility in leg adduction and adequacy owing to anatomical consistency and easy harvesting potential. The gracilis muscle is suitable for functional segmental harvest and transfer due to the architecture of parallel muscle fiber and longitudinal neurovascular organization. The gracilis flap is similar in width and length to the flexor and extensor muscles of the forearm. The tendinous distal third is adequate for flexor and extensor tendon attachment of the digits, allowing for remarkable finger function recovery. Pickrell and colleagues [10] used the muscle to reconstruct the rectal sphincter and were the first investigators to define the transplantation of the gracilis muscle in 1952. The gracilis muscle accommodates identification due to its palpability and predisposition of tendinous insertion. To date, studies have reported few cases of posterior interosseus nerve injury during hospitalization in relation to median, ulnar and radial nerve injuries. Besides, the functional outcome following primary repair or grafting is relatively poor when compared to events concerning other nerves. A limited number of studies have indicated traumatic PIN palsy as a complication in Monteggia fractures or in lacerated forearm injuries [11]. Management of impaired nerves in closed injuries has been the subject of controversy. Some authors recommend conservative treatment using braces and watchful waiting.

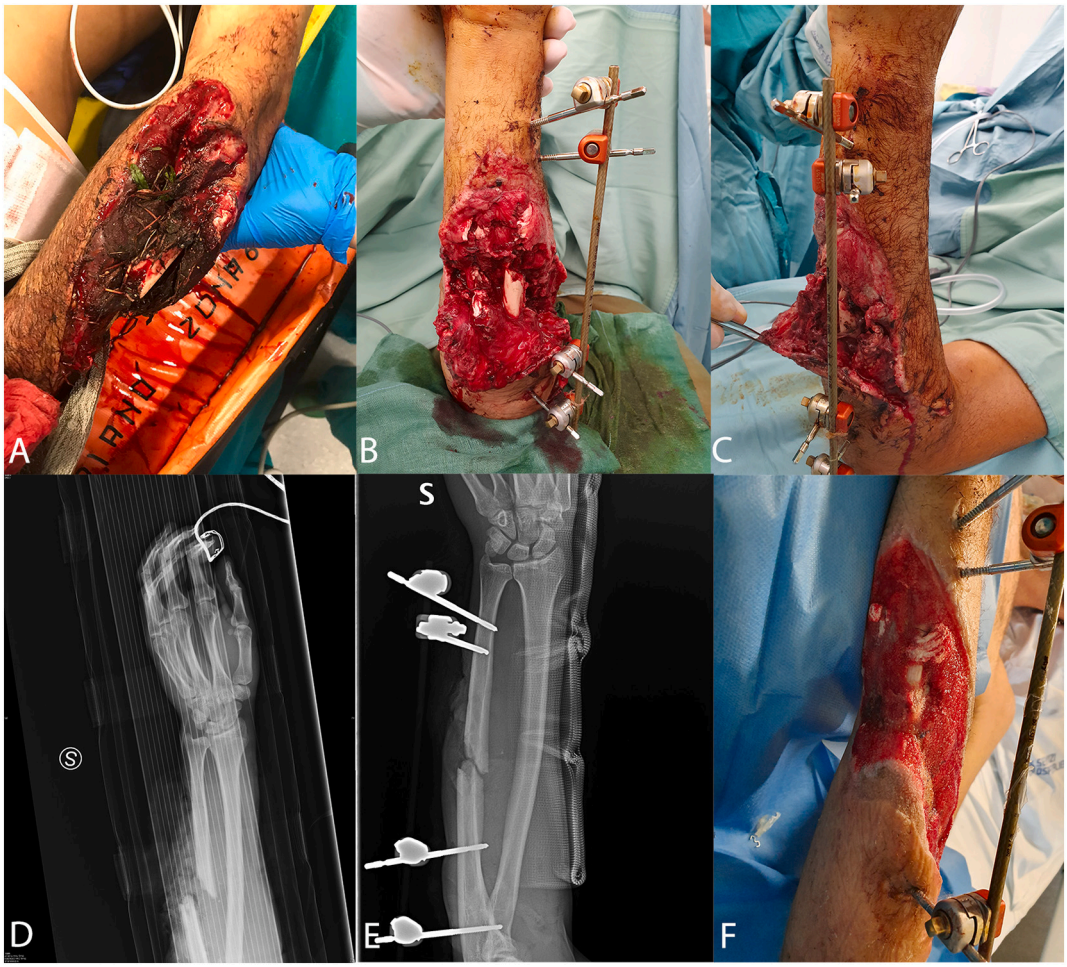

Fig. 1. Clinical presentation of 27-year-old trauma of forearm and emergency room treatment of the ulnar bone and tissue damage.

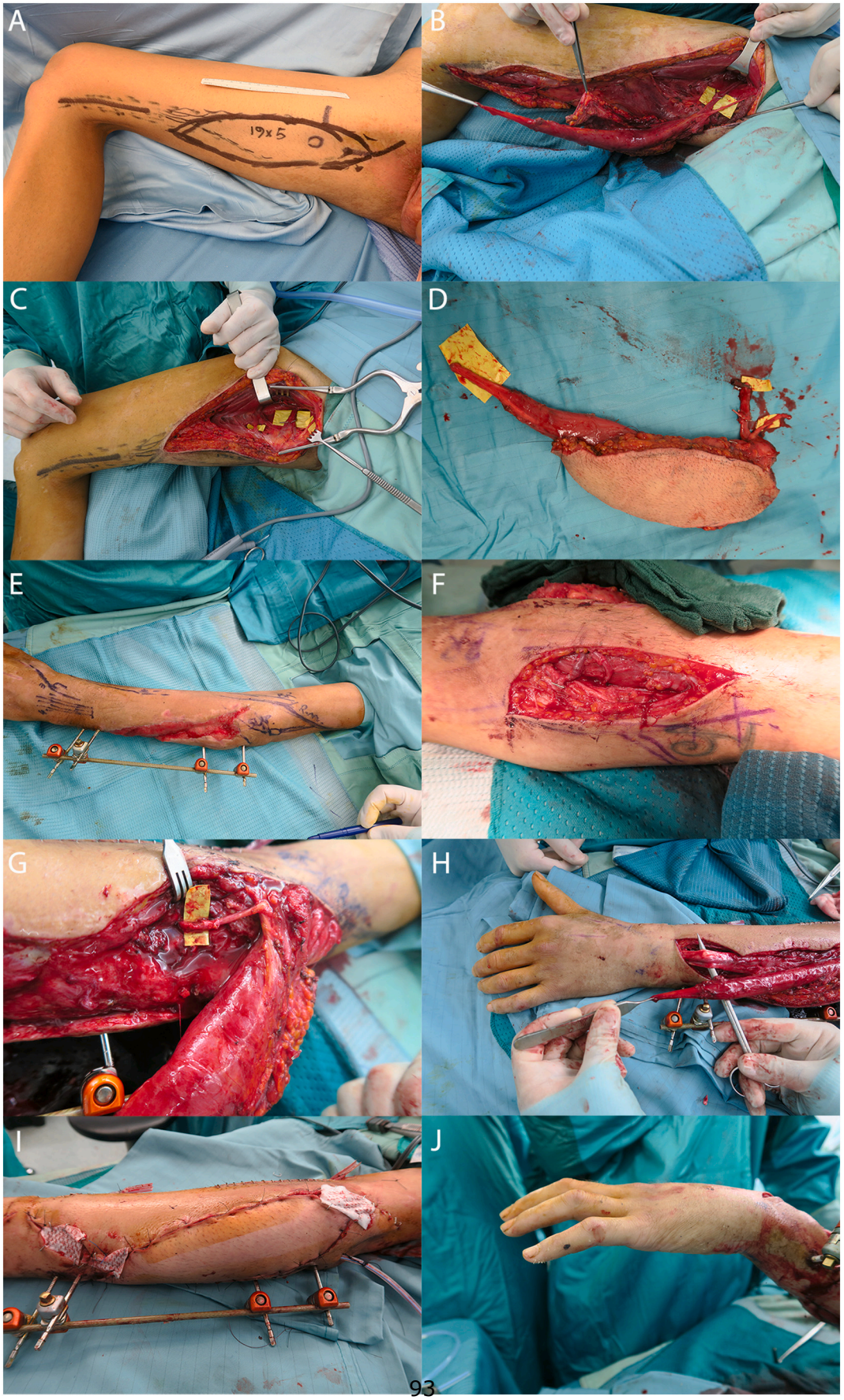

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Fig. 2. Gracilis Flap for reconstruction of tissue defect and finger extension.

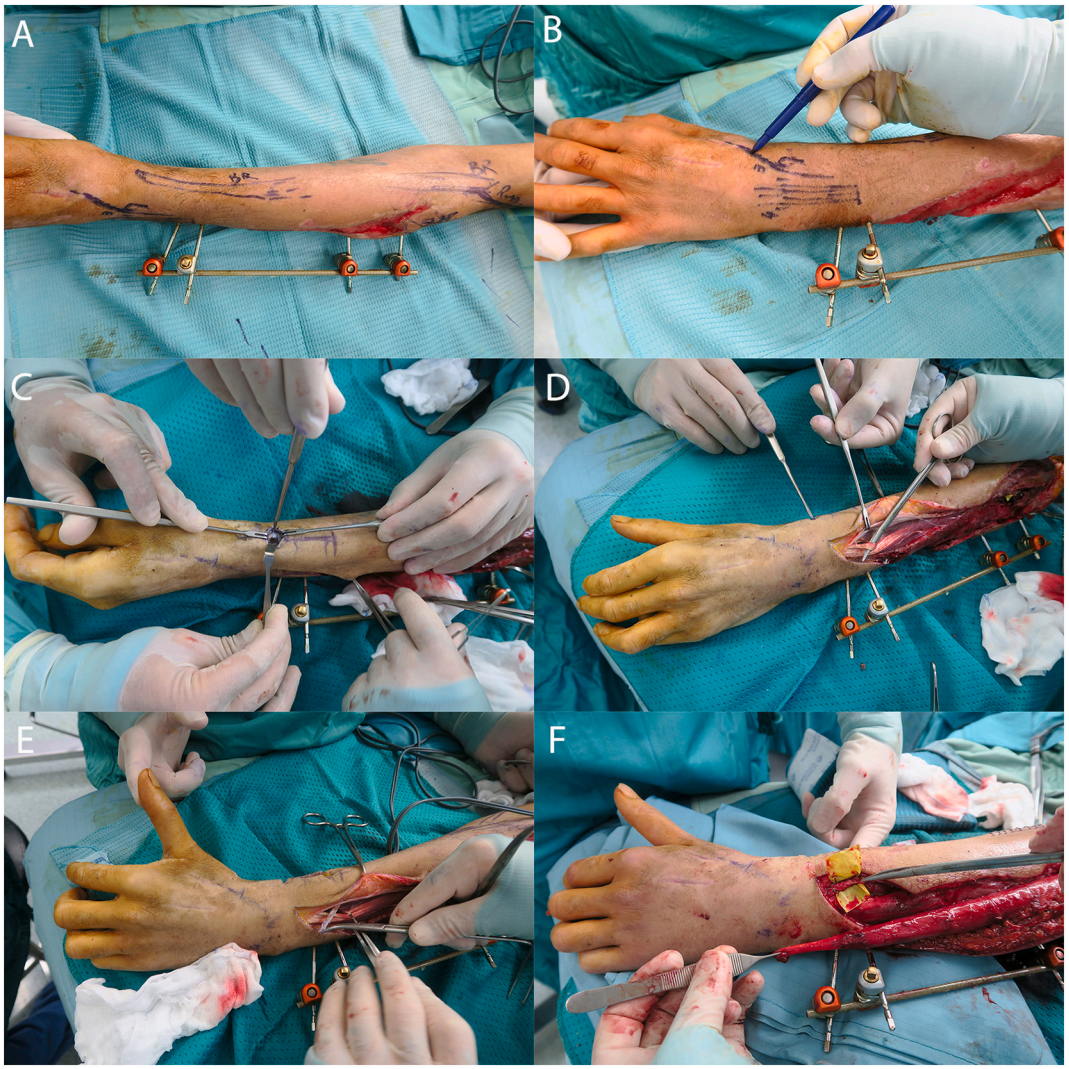

Fig. 3. Brachioradialis to Extensor Pollicis Longus for reconstruction of Thumb extension.

Surgical exploration is recommended in absence of motor re-innervation after 8 months. In open traumas, on the other hand, surgical exploration is mandatory and strongly recommended whereby direct neurorrhaphy is performed. A nerve graft is recommended in the case of nerve laceration presenting a gap greater than 3 cm. Peripheral nerve regenerative potential following severe trauma is specifically unsatisfactory in extremely complex cases [12]. In our patient, the strategy to restore extension of the finger and thumb considers the use of the posterior interosseous nerve stump as a donor. A fundamental condition is the presence of full active wrist extension, which indicates the importance of radial nerve intactness. When we had to face the problem of one stage reconstruction for bone coverage and hand extensor mechanism reconstruction, we searched on literature about gracilis free flap, and we found no article talking about gracilis free flap for upper limb functional reconstruction, we found instead many different cases of gracilis free flap used for facial reanimation [13–15], lower limb reconstruction [16,17], breast reconstruction [18].

We stress the importance of free gracilis flap for these cases because of the good result it brings. We took the patient in operating room for gracilis free flap functional transfer, and we followed him up for 18 months. Wound healing occurred following 18 months of surgery and hand movement was partially retrieved with ability to undergo normal daily activities. After that we got a good functional result for the patient, who come back in daily activity without heavy limitation, we had to menage the ulnar fracture, which underwent to pseudoarthrosis. To avoid ulterior donor site damage for the patient who already undergone to multiple operations, we choose the Bioglass reconstruction [18–21]. The Bioglass technique follows the Masquelet procedure which enables and enhances formation and consolidation of the bone attributable to the regenerative process (without bone allograft). The removal of non-vital bone tissue and

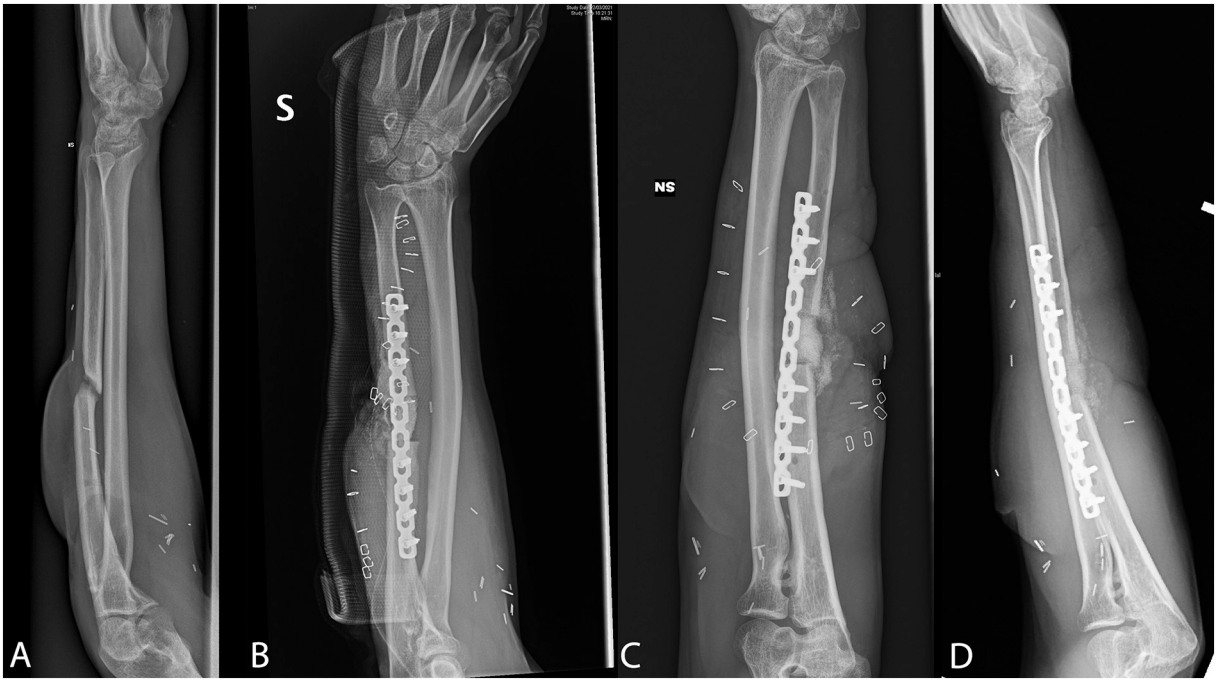

Fig. 4. Pseudoarthrosis of ulnar fracture after six months and radiographic follow -up after bioglass treatment.

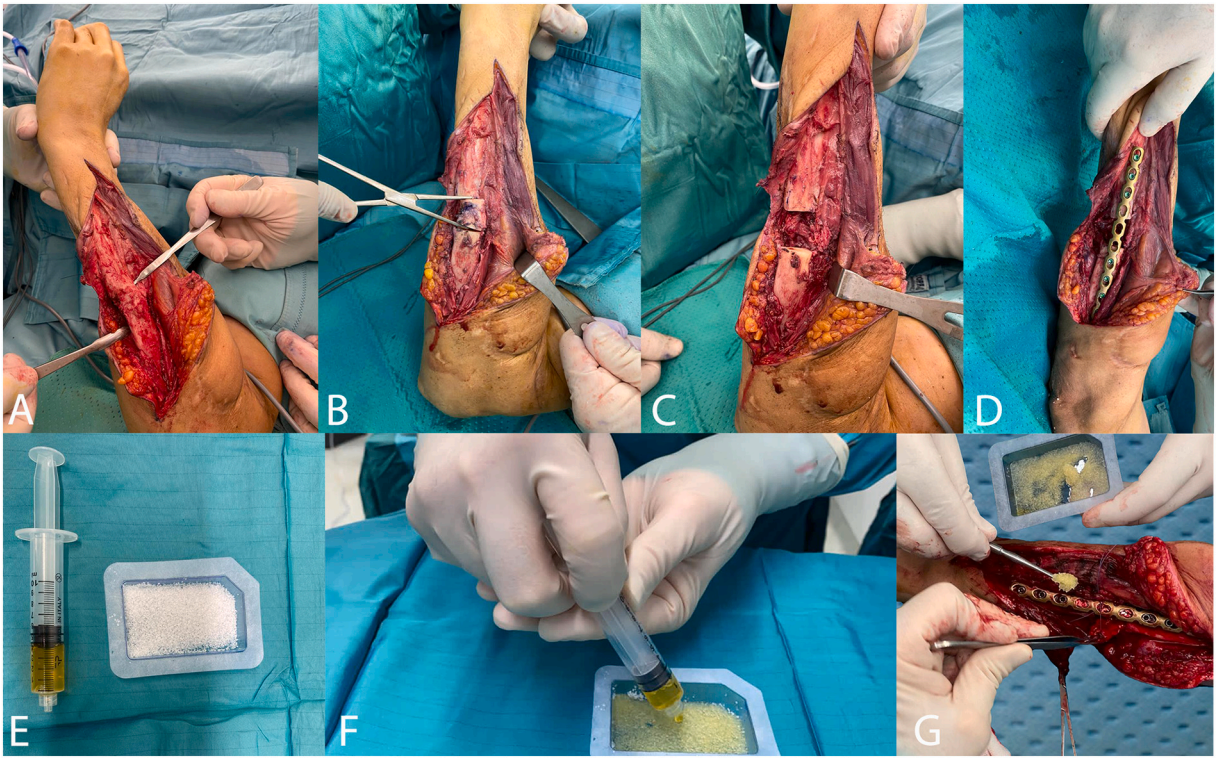

Fig. 5. Bioglass procedure for treatment of ulnar pseudoarthrosis.

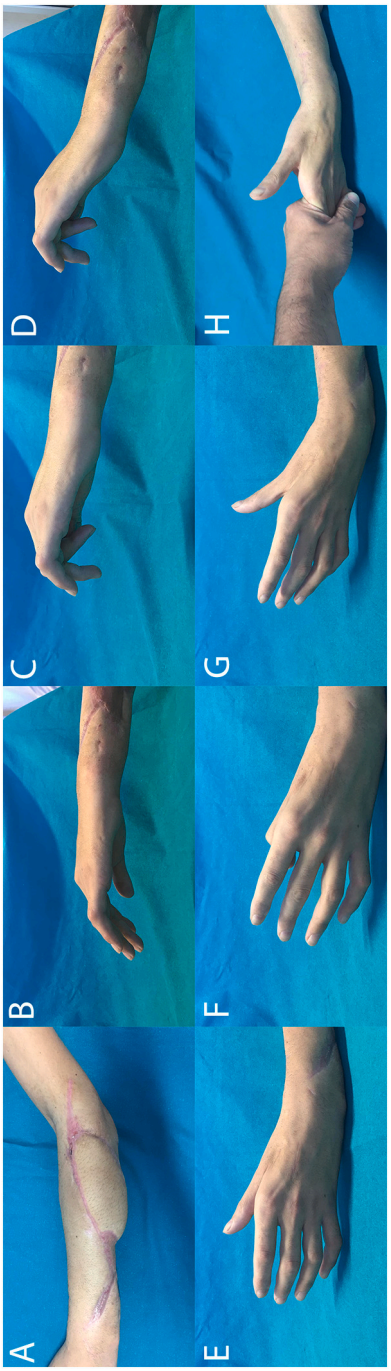

Fig. 6. Clinical outcomes after one-year followup, with optimal outcomes in finger, thumb and wrist flexion.

Table 1
Evaluation score.

	T30	T180	T360	T720
Geldmacher score				
Radial abduction range	2	2	2	2
Elevation deficit	2	4	4	4
Opposition distance	2	2	2	2
Flexion extension deficit	2	4	4	4
Total score	8	12	12	12
Michigan hand outcome				
Overall hand function	6	6	6	6
Activities of day living	10	8	4	2
Work	2	2	2	2
Pain	2	6	8	8
Aesthetics	6	6	6	6
Satisfaction	8	6	2	2
MRC				
	M0	M3	M3	M5

the use of osteoprogenitor cells or osteoinductive growth factors are imperative for the Bioglass technique to enable defect filling and the closure of chamber with a collagen membrane. Furthermore, sufficient mechanical stability is to be ensured with plate fixation to avoid minimal movement of the graft. The aim of our study is not talking about bone pseudoarthrosis treatment, which has widely been discussed in literature, both with bone graft [22], or regenerative solution such as bioglass [18–21], bone marrow aspirate concentrate [23], platelet rich plasma [24]. Our objective is to let surgeon consider that the gracilis free flap may be considered as an ideal therapeutic option for reconstruction of upper limb lesions involving multiple tissue damage with loss of hand extension in view of its composite characteristics aforementioned as well as its ability to be innervated by a single motor nerve and tendon. Furthermore, bone grafts may be avoided by using Bioglass, a valuable material for small extra-articular bone gaps.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tcr.2022.100609.

Statement of informed consent

Informed consent was obtained from the patient included in the study.

Ethics statement

The study respects all ethical requirements in its objectives and methodologies. We strictly comply with widely recognized international codes of practice such as the Nuremberg code, the Helsinki agreement, the conventions of the Council of Europe on human rights and biomedicine, with particularly attention to EU legislation: 2001/83/EC, 86/609/EEC and FP7 Decision nr 1982/2006EC. Human biological samples are necessary because we need to test human cells, which have unique biological characteristics, distinct from those of animals. The overall intention in the project is to reduce the number of animal experiments. Only adult patients who are able to give consent will be included. All the patients, that are the subjects of our study, donated their consensus to scientific treatment and publication of their clinic situation and images. We have obtained written informed consent from all patients. This study was approved by our Internal Ethical Committee without any registration in public registry because this study is not a clinical trial.

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Declaration of competing interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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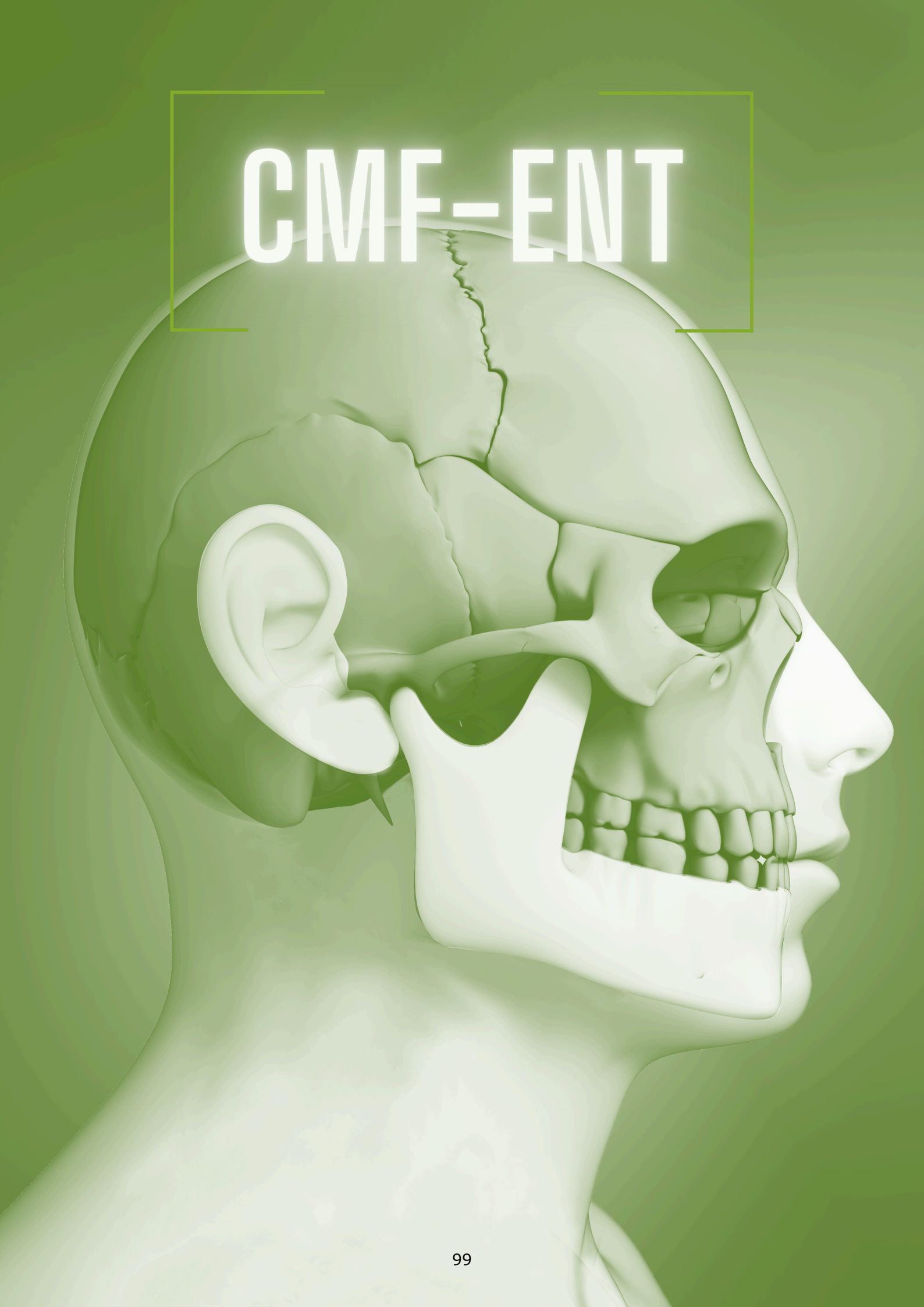

Cranio-maxillofacial surgery includes orthognathic surgery (jaw size or positioning anomalies), stomatology (tumors and cysts, implantology, etc.), cranial and facial malformations and facial traumatology in both children and adults, although tumor types, biological behavior and oncological management vary between the two populations (Wasserzug et al., 2018). It aims to treat trauma to the skull and face, often involving soft or hard tissue lesions with distinct developmental origins, cellular properties and healing outcomes.

Craniofacial reconstruction aims to restore facial function, form and aesthetics, taking into account craniofacial growth (Teven et al., 2015). Cranial bone grafts are used to treat a variety of post-traumatic defects such as orbital fractures, post-resection defects due to bone tumors, congenital anomalies and aesthetic reasons. For small mandibular defects and alveolar clefts, different graft materials are used, such as iliac bone splinters, cranial bone splinters or synthetic materials. Large mandibular defects often require vascularized bone flaps containing free flaps for reconstruction. Despite rigid internal fixation, three-dimensional stability can be compromised, especially if the defect between bone segments is large, leading to proliferation of fibrous rather than bony tissue along the osteotomy (Çelik. 2018).

An acute otitis media is an infection of the middle ear. Cholesteatoma is the most serious form chronic otitis media characterized by the production of skin that will invade the middle ear or mastoid (Yew et al., 2012). It is classified as a benign tumor due to its variable clinical expression, frequent superinfection, tendency to recurrence, and high risk of potentially serious complications such as erosion of adjacent structures, hearing loss, and others. Sometimes, antibiotics are enough to clear the infection (Mendlovic et al., 2021; Minovi & Dazert, 2014). But to completely remove the cholesteatoma or when conservative treatments have failed, otologic surgery is the treatment of choice to create a dry and safe cavity without recurrence (Hamed et al., 2016).

The surgical management can be classified into two main techniques canal wall down mastoidectomy (CWDM) and canal wall up mastoidectomy (CWUM) (Alves et al., 2016; Mendlovic et al., 2021).

Mosher, in 1911, started the idea of mastoid obliteration to promote healing of a mastoidectomy defect. He described an obliteration technique using a superiorly based postauricular soft tissue flap, which was failed. These findings encouraged surgeons to associate other filler materials inside the bowl (Mosher, 1911).

Palva (Palva & Mäkinen, 1979) modified and popularized the technique, further adding to it the use of bone chips and bone pate in combination with an anteriorly based musculoperiosteal flap.

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Allograft bone vs. bioactive glass in rehabilitation of canal wall-down surgery

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Canal wall-down (CWD) mastoidectomy creates a radical cavity that modifies the anatomy and physiology of the middle ear, thus preventing it from being self-cleaning and causing epidermal stagnation in the posterior cavities. Canal wall-down tympanomastoidectomy with reconstruction (CWDTwR) can obliterate such radical cavities. The main objective of this study was to compare postoperative results after CWDTwR by using either bone allografts or 45S5 bioactive glass as a filling tissue with an 18-month follow-up. This was a single-center observational trial including all patients undergoing CWDTwR. Patients were divided into two groups according to the filling material used: allograft bone (AB group) or 45S5 bioactive glass (BG group). Clinical monitoring was performed regularly, with control imaging performed at 18 months (CT scan and DW MRI). The two groups were compared with the t test for quantitative variables and the chi square test for qualitative variables (no revision surgery, audiometric results, complications, mastoid obliteration volume). Thirty-two patients underwent CWDTwR between October 2015 and 2018. The mean age was 48 years, and 71.9% (23/32) were men. A total of 46.9% (15/32) of the patients had undergone at least 3 middle-ear surgeries prior to CWDTwR. The most frequent preoperative symptom was otorrhea (100.0%, 32/32), and only 12.5% (4/32) experienced dizziness. Fifteen and 17 patients underwent surgery with bone allografts and 45S5 bioactive glass, respectively. At 18 months post-operation, 53.3% of the patients (8/15) in the AB group presented with recurrent otorrhea versus 5.9% (1/17) of patients in the BG group (p = 0.005). Seventy-eight percent (7/9) of symptomatic patients had undergone revision surgery at 18 months postoperation: 40.0% (6/15) in the AB group and 5.9% (1/17) in the BG group (p = 0.033). One patient's surgery was cancelled due to the COVID-19 pandemic, and one patient refused surgery. The effects of CWDTwR with bone allografts are disappointing in early follow-up, with significant resorption leading to a 40.0% revision surgery rate. 45S5 BG is a simple solution, with preliminary results that are superior to those of AB. However, prospective controlled studies with longer follow-up times are needed to evaluate the value of BG versus other synthetic materials (such as hydroxyapatite) in surgical management of CWDTwR.

Trial registration: retrospectively registered.

Abbreviations

AC	Air conduction
ABG	Air–bone gap
AB	Allograft bone
BC	Bone conduction
BG	Bioactive glass
CT	Computed tomography
CWD	Canal wall down
CWDTWR	Canal wall-down tympanomastoidectomy with reconstruction
CWU	Canal wall up

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DW	Diffusion weighted
ENT	Ear nose and throat
HRCT	High-resolution computed tomography
HU	Hounsfield units
MR	Magnetic resonance
MRI	Magnetic resonance imaging
OR	Odds ratio
PTA	Pure-tone audiometry
T1-w	T1-weighted
T2-w	T2-weighted

Cholesteatoma is an aggressive disease that can lead to serious complications. It is well known that only surgical treatment can eradicate cholesteatoma and prevent its recurrence. To ensure complete removal of all of the epidermis that is present in the middle ear, resection of pathological tissue is typically accompanied by removal of healthy structures. Canal wall-down (CWD) mastoidectomy, which consists of removal of the external auditory canal posterior wall, allows for good visualization of the cavities, particularly the epitympanic region. In cases of major lysis of the bony framework, multiple recurrences requiring iterative surgery, or unfavorable anatomical conditions (such as a highly sclerotic mastoid, dural herniation, or a narrow corridor between the facial nerve and sigmoid sinus), a technique known as "canal wall-down tympanoplasty" enables obtaining low levels of residual cholesteatoma ranging from 0 to 13%[1]. Creation of such radical cavities modifies the anatomy and physiology of the middle ear, thus preventing it from being self-cleaning and causing epidermal stagnation in the posterior cavities. Additionally, the patient may be hindered during aquatic activities by direct thermal stimulation of the directly exposed lateral semicircular canal, which causes dizziness. Finally, conventional air hearing aids can be affected if the cavity is of a large size or in cases of recurrent otorrheic episodes[2]. To overcome these disadvantages, various surgical techniques have been developed to restore the primary anatomy of the external auditory canal by using the overlapping sliced cartilage autograft technique or mastoid and epitympanic filling techniques. Mosher introduced the concept of mastoid obliteration in 1911 when proposing creation of a flap from the back of the auricle[3]. Subsequently, many techniques have been proposed to reconstruct the posterior canal wall and to obliterate the mastoid and epitympanic cavities involving several materials, including biological tissue (muscle flaps, autografts with a mixture of bone dust and biological glue, or "bone pâté")[4,5], as well as bone allografts; more recently, use of synthetic tissues, such as bioactive glasses, has been suggested[6–9]. Regarding use of bioactive glasses in middle ear surgery, several updates are important to consider for otologists: (i) several studies have been published on safety, anatomical and functional characteristics, and improvement of quality of life[10,11]; (ii) for some authors, bioactive glass appears to be the most reliable synthetic material in middle ear surgery[6]; (iii) performance in mastoid obliteration has now been established in the literature (with results showing that CWD revision surgery with mastoid obliteration and posterior canal wall reconstruction is superior to CWD revision surgery without mastoid obliteration in treatment of the troublesome mastoid cavity in both children and adults[12]); (iv) secondary mastoid obliteration is a safe and useful technique for treating the troublesome mastoid cavity in both children and adults (it is associated with a low cholesteatoma recidivism rate and a high rate of a trouble-free ear in the long term[13]); and (v) rates of recurrent and residual disease after CWU or CWD tympanoplasty with mastoid obliteration are shown to be qualitatively similar to, or better than, rates that have been previously reported for techniques without filling[14]. Canal wall-down tympanomastoidectomy with reconstruction (CWDTwR) enables reconstruction of the bony framework and filling of the cavities without the postoperative drawbacks of the CWD technique, as the framework is restored and supported by filling at end of procedure. This technique, which can be performed during the first operation for cholesteatoma, is useful regardless of the method employed to eradicate cholesteatoma[15] and can safely be performed on an outpatient basis[16].

The main objective of this study was to compare the efficacy of two materials used for mastoid filling in rehabilitation of radical cavities, bioactive glass 45S5 (BG, GlassBone® Injectable Putty; Noraker, Lyon, France) and cancellous bone dust, referred to as allograft bone (AG) herein (AG, Phoenix® chips 5–7 cc bone graft; TBF, Moins, France). The primary endpoint was the absence of new surgery at 18 months from all causes (persistent otorrhea or the presence of a residual cholesteatoma on MRI at 18 months). The secondary objectives included comparison of the postoperative course of hearing outcomes and the proportion of mastoids filled at 18 months. The last objective was based on the primary endpoint; our goal was to identify predictive factors of surgical success among selected preoperative variables.

Methods

Study design

The present study was conducted in a tertiary center. A retrospective chart review was performed for all patients who underwent reconstructive tympanoplasty after CWD mastoidectomy for cholesteatoma from July 2010 until January 2019. Although some patients had undergone reconstructive tympanoplasty on both sides, each patient was viewed as a single entity. This study complies with the ethical and legal requirements of French law (April 15, 2019) and the Declaration of Helsinki. This study was approved by an institutional review board (Agreement: 19–61), and oral informed consent from all participants was obtained.

Characteristics of participants

Patient demographics, radiological evaluations, diagnoses, surgical details, complications, and clinical and audiological outcomes were collected. Inclusion criteria included all patients scheduled for CWDTwR after CWD mastoidectomy for cholesteatoma. Details regarding how to perform the surgical technique have already been

published[17]. Exclusion criteria included patients who had undergone CWD mastoidectomy for any reason other than cholesteatoma, subjects with other middle ear diseases, and patients with less than 18 months of follow-up. All patients received standard preoperative assessment, including history, physical examination, and pure-tone audiometry (PTA), consisting of both air conduction (AC) and bone conduction (BC) threshold measurements inside a standard soundproof room before the intervention. Following the recommendations of the committee for Hearing and Equilibrium of the American Academy of Otolaryngology—Head and Neck Surgery, audiological data were collected to reduce hearing measurement variability between studies[9]. All patients underwent PTA tests from 250 Hz to 4 kHz as well as at 8 kHz to measure high-frequency hearing preservation. The means of the thresholds for bone and air conduction at 0.5, 1, 2, and 4 kHz were used to form a four-tone pure-tone average; as the 3 kHz frequency is not evaluated in our center, the mean of the 2 and 4 kHz frequencies was considered for the 3 kHz frequency. The functional results were evaluated by comparing the preoperative and 1-year postoperative bone conduction threshold level averages.

Interventions and comparisons

All patients were evaluated radiologically at 18 months postoperatively using a high-resolution computed tomography (HRCT) scan of the temporal bone and MRI to measure the volume and location of the mastoid and epitympanic obliteration and any possible signs of complications or residual cholesteatoma in the middle ear. Temporal bone HRCT acquisition was performed using a Discovery 750HD CT scanner (GE Healthcare, Chicago, USA) with the following parameters: a collimator of 0.625, with reconstruction with 0.6 mm slice thickness at 0.4 mm intervals. MRI studies were performed with a 3-T MR device (HDxT, GE Healthcare) with an eight-channel head coil. MRI acquisition was centered around the temporal bone and consisted of axial T1-weighted (T1-w) spin echo imaging (slice thickness 1.5 mm), high-resolution 3D T2-weighted (T2-w) imaging (slice thickness 0.4 mm), axial and coronal nonecho planar (EP) diffusion-weighted (DW) imaging (slice thickness 3 mm), and a 3D spoiled gradient-recalled T1-w fat-saturated sequence acquired after gadolinium injection (0.2 mL/kg, Dotarem). HRCT images were reconstructed for each ear in the plane of the lateral semicircular canal. IntelliSpace Portal software (Medisys, Philips Research, Suresnes, France) was used for 3D semiautomated quantitative assessment of mastoid obliteration at baseline (18 months postoperatively). First, an experienced otolaryngologist segmented the mastoid volume in 3D using an interactive mouse "click and drag" function within the lesion on HRCT axial slices. With non-Euclidean radial basis functions, a 3D segmentation mask was generated and edited in the same way for all slices. With the 3D segmentation mask and the image matrix dimensions and slice thickness, the software calculates the volume (in cm^3)[18–20]. All quantitative and qualitative image analyses were then performed by two experienced radiologists, and a consensus between the raters was used in cases of conflicting evaluations.

Surgeries were performed by one senior surgeon who was an expert in this surgery to ensure as much similarity in the surgical approaches as possible and to reduce the impacts of the learning curve and operator skill differences. All of the patients for whom other surgeons performed this procedure were excluded from the study (5 interventions). All surgeries were performed with the patients under general anesthesia and included the NIM-Response 3.0 facial nerve monitoring system (Medtronic, Jacksonville, FL, USA). A retroauricular skin incision was made, and a musculoperiosteal flap was created. Perichondrium and cartilage grafts were harvested from the cymba and cavum conchae to compensate for the posterior canal wall defect of the external acoustic meatus and to cover the entire filled zone. After complete removal of the cholesteatoma, reconstruction was started in the middle ear, including ossiculoplasty and tympanic membrane grafting. CWDTwR was conducted using a large cartilage graft with perichondrium to reconstruct the posterior canal wall. The last step before suturing involved epitympanic and mastoid cavity obliteration by using either BG or AG (AG was used before BG, which was available 12 to 20 months later). It was important that the BG was perfectly isolated from the external acoustic meatus by carefully covering all of the cartilage with perichondrium (details regarding the procedure have been previously published[17]). Careful suturing of the musculo-periosteal flap and the retroauricular incision with absorbable sutures was necessary to prevent dissemination of the implanted BG. All patients received perioperative antibiotic prophylaxis with amoxicillin/clavulanic acid, which was continued for 7 days postoperatively (pristinamycin in the case of allergy to amoxicillin). Except for patients with heavy medical comorbidities or for social reasons, most procedures were conducted as a one-day surgery in the ambulatory setting.

Statistical analysis

The need for revision surgery was the primary criterion for defining BG obliteration efficacy. Surgical revision was necessary for two main reasons: (i) recurrent otorrhea or difficulty in fitting the hearing aid and (ii) enclosure of the cholesteatoma within the obliterated cavities or residual disease on 18-month postoperative MRI. Residual cholesteatoma was evaluated on 18-month postoperative MRI. A positive functional impact on hearing was defined as a postoperative ABG of strictly less than 20 dB. Categorical variables are summarized as frequencies and percentages, and continuous variables are described as means and standard errors. At diagnosis, characteristic comparisons between groups were assessed with the chi square test for categorical variables and the independent two-sample t test for continuous variables. An odds ratio coefficient with its 95% confidence interval (CI) was calculated for each characteristic included in a multivariate logistic regression model to identify predictive factors of surgical success. Surgical success was defined as the absence of surgical revision. Variables were included if they were known to have a strong influence on postoperative healing or if their p values were > 0.20 after univariate logistic regression analysis. Results were considered statistically significant at p value ≤ 0.05. Statistical analyses were performed with R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics approval and consent to participate

This study complies with the ethical and legal requirements of French law (April 15, 2019) and the Declaration of Helsinki. This study was approved by the institutional review board "Comité d'Ethique du CHU de Lyon" (Agreement: 19-61). Oral informed consent to participate was obtained from all of the participants.

Results

Preoperative demographic data

Thirty-two patients were included according to the inclusion criteria. The mean age was 47 ± 15 years; there were 23 males and 9 females, 18 right ears and 14 left ears. A total of 46.9% (15/32) of the patients had undergone at least 2 tympanoplasties before CWD mastoidectomy for creation of a radical cavity and to ascertain definitive eradication of cholesteatoma (3rd operation). All patients had otorrhea at management, but only 12.5% (4/32) had vertigo. Conventional hearing aid fitting was considered difficult for 11 of the 68.8% (22/32) of patients who needed one. There were 10 patients whose residual hearing after one or more tympanoplasties was sufficiently good and thus did not need any hearing aids. A total of 62.5% (20/32) of the cohort had undergone CWD mastoidectomy before 2010, and the remaining 37.5% (12/32) of patients underwent the procedure between 2010 and 2019. The average overall patient follow-up time was 15 ± 9 years. The patients were divided into two groups to compare the efficacy of the filling materials: BG was used for 51.5% (17/32) of the patients, comprising the BG group, whereas cancellous bone meal was used for 46.9% (15/32), comprising the AB group. The demographic, audiometric and clinical characteristics of the patients by group are detailed in Table 1. The mean postoperative follow-up time differed significantly between the BG group (33 ± 8 months) and the AB group (44 ± 13 months) because their use was sequential (AB was first used; BG was used later, when available). No other significant differences were found preoperatively between the two groups; in other words, the patients were considered to be comparable with regard to age, sex, otologic and medical history, initial clinical presentation, and audiometric status for the remainder of the statistical analyses.

N (%)	BG Group n = 17 (51.5%)	AB Group n = 15 (46.9%)	p value
Age (years)	51 ± 19	44 ± 10	0.142
Sex			
Male	11 (64.7%)	12 (80.0%)	0.444
Female	6 (35.3%)	3 (20.0%)	
Operated side			
Right	9 (52.9%)	9 (60.0%)	0.964
Left	8 (47.1%)	6 (40.0%)	
Otologic history (years)	15 ± 9	14 ± 9	0.97
Number of interventions			
1 or 2	9 (52.9%)	6 (40.0%)	0.383
≥ 3	8 (47.1%)	9 (60.0%)	
Date of CWD surgery			
< 2010	11 (64.7%)	9 (60.0%)	1
≥ 2010	6 (35.3%)	6 (40.0%)	
Medical history			
None	14 (82.4%)	13 (86.7%)	0.486
Facial palsy	0 (0.0%)	1 (6.7%)	
TBF failure	3 (17.6%)	0 (0.0%)	
T21	0 (0.0%)	1 (6.7%)	
Preoperative clinical symptoms			
Otorrhea	15 (88.2%)	13 (86.7%)	1
Vertigo	2 (11.8%)	2 (13.3%)	
PTA air conduction threshold (dB)	52 ± 13	57 ± 27	0.94
PTA bone conduction threshold (dB)	25 ± 10	31 ± 35	0.416
PTA-ABG (dB)	26 ± 11	26 ± 14	0.985
Postoperative follow-up (months)	32 ± 8	44 ± 13	< 0.006*

Table 1. Patient demographic data, preoperative presentations and operated side. Quantitative variables are shown as the mean (standard error), and qualitative variables are shown as the total population (percentage). Surgery corresponds to the date of canal wall reconstruction tympanoplasty. *Corresponds to statistical significance (p value < 0.05). Pure-tone average (PTA) air and bone conduction thresholds were computed as the average thresholds at 0.5, 1, 2, and 3 kHz. PTA air bone gap (PTA-ABG) closure was computed as the difference between PTA air and bone conduction. CWD surgery: canal wall-down surgery.

Postoperative clinical outcomes at 18 months

Eighteen months after reconstructive surgery, 40.0% (6/15) of the patients in the AB group and 1 patient in the BG group had undergone revision surgery (p = 0.033). Of the 6 patients who needed revision surgery in the AB group, 4 presented with persistent otorrhea and material extrusion and 2 with residual cholesteatoma. The patient in the BG group needed revision surgery for residual cholesteatoma. Another patient presented with material extrusion from the retroauricular scar, but local care was sufficient to heal the wound; therefore, no surgery was performed. In the AB group, 26.7% (4/15) of the patients presented with otorrhea but did not need revision surgery. A total of 88.2% (15/17) and 33.3% (5/15) of patients in the BG and AB groups, respectively, were satisfied with the radical cavity reconstruction (no otorrhea, no residual cholesteatoma or revision surgery needed and good aquatic tolerance) (p = 0.005). The detailed results are shown in Table 2.

Hearing results

Before CWDTwR, 25% of the patients had slight hearing loss (PTA air conduction threshold < 40 dB), 50% had mild to moderate hearing loss (PTA air conduction threshold between 40 and 70 dB), and 25% had severe to profound hearing loss (PTA air conduction threshold > 70 dB). The mean preoperative PTA air conduction threshold was 53 ± 21 dB, and there was no significant difference between the BG (52 ± 13 dB) and AB (57 ± 27) groups (p = 0.940). The same results were found regarding the PTA bone conduction threshold and the PTA-ABG between the two groups, as detailed in Table 1. The mean PTA bone conduction thresholds were 31 dB and 25 dB preoperatively and 32 dB and 28 dB postoperatively in the AB and BG groups, respectively. The mean PTA air conduction thresholds were 57 dB and 52 dB preoperatively and 46 dB and 44 dB postoperatively in the AB and BG groups, respectively. Differences between the pre- and postoperative values were not significant for either bone or air conduction audiometry, with p values of 0.454 and 0.663, respectively. Air–bone gap closures were 12 dB and 11 dB in the AB and BG groups, respectively, with no significant difference between the two groups, as detailed in Table 2.

Radiological obliteration

Bone attenuation measurements in Hounsfield units (HU) in the region of interest of the obliteration material were significantly different between the two groups (p < 0.001). Indeed, the mean bone attenuation in the AB group was 555.05 ± 138, versus 870.15 ± 45 in the BG group. Mastoid volume measurements were similar in both groups: 2.10 cm^3 and 2.09 cm^3 in the AB and BG groups, respectively (p = 0.850). On the other hand, there was a significant difference in the proportion of mastoid cavity obliteration between the AB and BG groups (34% ± 30 vs. 76% ± 25, p = 0.001). Details of the volume measurements are shown in Fig. 1. Regarding the precise localization of the obliteration, successful epitympanic obliteration was achieved in 88.2% (15/17) of the patients in the BG group and 13.3% (2/15) in the AB group (p < 0.001). No middle ear opacity was found on HRCT images in either group. MR images were analyzed to identify residual cholesteatoma; 2 were identified in the AB group and 1 in the BG group, but the difference was nonsignificant. Details are shown in Table 2.

Predictive factors of surgical success

The primary criterion for surgical success was lack of a need for revision surgery at 18 months regardless of the motivation (residual cholesteatoma or persistent otorrhea). Multivariate logistic regression was performed after

	BG Group	AB Group	
	n = 17 (51.5%)	n = 15 (46.9%)	p value
Otoscopy			0.005*
Healing complete	15 (88.2%)	5 (33.3%)	
Otorrhea	1 (5.9%)	4 (26.7%)	
Extrusion rate	1 (5.9%)	6 (40.0%)	
ABG closure (< 20 dB)	12 (70.6%)	10 (66.7%)	1
Conventional hearing aid			0.001*
Not necessary	7 (41.2%)	3 (20.0%)	
Good fitting	9 (52.9%)	2 (13.3%)	
Failed fitting	1 (5.9%)	10 (66.7%)	
Time before CT scan	20 ± 3	21 ± 5	0.806
CT scan assessment at 18 months			
Bone attenuation measurements (HU)	870.15 ± 45	555.05 ± 138	< 0.001*
Total mastoid volume (cm^3)	2.09 ± 0.6	2.10 ± 0.8	0.850
Obliteration volume of the mastoid (cm^3)	1.62 ± 0.83	0.63 ± 0.30	0.002*
Mastoid cavity obliteration (%)	76.40 ± 25	34.44 ± 30	0.001*
Successful epitympanic obliteration	15 (88.2%)	2 (13.3%)	< 0.001*

Table 2. Postoperative clinical and radiological results. Quantitative variables are shown as the mean (standard error). * corresponds to statistical significance (p value < 0.05).

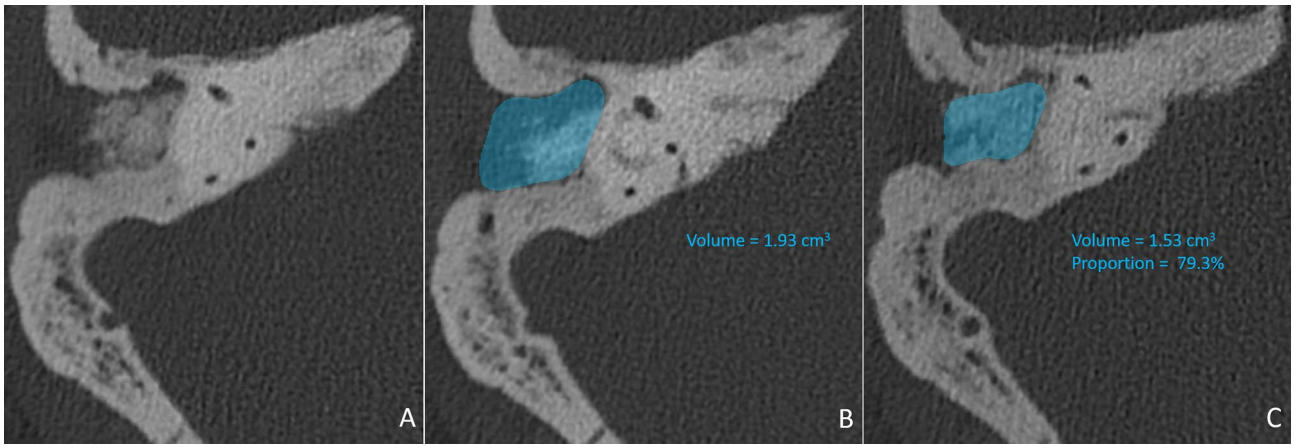

Figure 1. (**A**) Postoperative right ear high-resolution computed tomography (HRCT) scan of the temporal bone at 18 months postoperation to show how volumetric measurements were performed. HRCT images were reconstructed for each ear in the plane of the lateral semicircular canal. (**B**) Mastoid volume assessment at baseline (18 months postoperation, blue). IntelliSpace Portal software (Medisys, Philips Research, Suresnes, France) was used for the 3D semiautomated quantitative assessment of volume. It was segmented in 3D by using an interactive mouse "click and drag" function within the lesion on HRCT axial slices, after which a 3D segmentation mask was generated and edited in the same way for all slices. With the 3D segmentation mask and the image matrix dimensions and slice thickness, the software calculated the volume (in cm^3). (**C**) Mastoid obliteration volume assessment at 18 months postoperation (blue). The same software (Intellispace portal) was used for 3D semiautomated quantitative assessment of mastoid obliteration volume.

adjusting for age, sex, number of previous surgeries, year of CWD mastoidectomy, and the type of obliteration material used. The only relevant factor significantly predictive of the absence of revision surgery at 18 months was use of BG as the obliteration material (OR = 20.25, 95% CI [2.481–50.547]; p = 0.016). For the number of surgeries, two or fewer was taken as a reference. Usually, the need for 3 or more surgeries for cholesteatoma eradication is associated with highly aggressive disease. The reference categories chosen for the year of CWD mastoidectomy and for sex were between 2000 and 2010 and female, respectively. None of these variables had any impact on the estimated OR, indicating a stable model. The multivariate logistic regression results are shown in Table 3. The odds ratios and 95% confidence intervals for selected variables are also shown in a forest plot in Fig. 2.

	Coef	95% CI LL	95% CI UL	p value
Age	1.085	0.997	1.218	0.096
Sex				
Female	Reference			
Male	1.505	0.089	42.318	0.778
Number of surgeries				
1 or 2	Reference			
3 or more	0.361	0.037	2.697	0.334
Year of CWD mastoidectomy				
Before 2010	Reference			
2010–2018	0.395	0.037	3.249	0.4
Obliteration material	Reference			
Cancellous bone meal	20.245			
45S5 bioactive glass		2.481	50.547	0.016*

Table 3. Multivariable logistic regression model for predictive factors of postoperative success. Postoperative success (no surgery at 18 months) was estimated through a multivariable logistic analysis to identify explanatory variables. Estimated coefficients are adjusted for confounding factors. Results are shown with 95% confidence intervals (95% CIs). If the 95% CI excludes 0, the results are statistically significant, represented by * (p value < 0.05). Coef: estimated coefficient; 95% CI: 95% confidence interval; LL: lower limit; UL: upper limit.

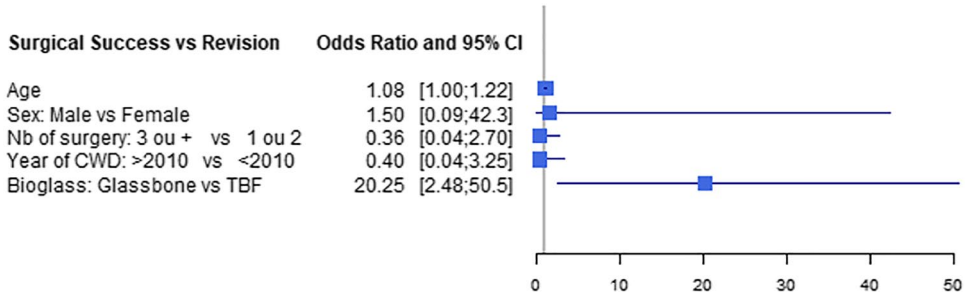

Figure 2. Forest plot of estimated coefficients from multivariate logistic regression. Results are reported as odds ratios with their 95% confidence intervals.

Discussion

Forty percent (6/15) of patients in the AB group and one patient in the BG group presented with persistent otorrhea or residual cholesteatoma that needed revision surgery. There was no statistical significance found between the pre- and postoperative bone or air conduction audiometry thresholds or for ABG closure between the two groups. A total of 88.2% (15/17) and 33.3% (5/15) of the patients were satisfied with the radical cavity reconstruction in the BG and AB groups, respectively. The only significant predictive factor of surgical success was use of 45S5 bioactive glass relative to bone allografts after adjusting for age, sex, year of CWD mastoidectomy and number of previous surgeries.

The interest and reliability of the rehabilitation technique evaluated in this study has resulted in development of various obliteration techniques immediately in the first step of the management of cholesteatoma. The "remove and rest" technique with mastoid obliteration, as described by Gantz[8], allows for obliteration of the mastoid cavity on the first-stage surgery for cholesteatoma. It offers wide exposure for cholesteatoma resection (when the bony framework of the external auditory meatus is removed), without the discomfort of a radical cavity after a classic CWD procedure (because the framework supported by the obliteration material is restored). Another study[21] showed no significant difference in quality of life between CWD and CWU surgery, which was confirmed by an even more recent study[22].

Currently, the advantages and disadvantages of the obliteration materials chosen (biological versus synthetic) remain controversial. Biological materials (muscle, fascia, or fat) from the patient are sometimes lacking because of previous surgery[6,23]. Advantages of biological materials focus on financial cost; however, one disadvantage is that the material tends to retract over time[6]. Bone parenchyma[24] is similar to human bone and induces local osteogenesis. However, its use remains controversial due to the high rate of postoperative infection and its high resorption rate. This resorption leads to recurrence of tympanic membrane atelectasis due to bony defects in the posterior wall of the external acoustic meatus. The long-term failure rate is reported to be greater than 50%[6,24]. Nevertheless, some authors have shown that the rate of postoperative infection can be significantly reduced with peri- and postoperative administration of antibiotics[25]. In this study, there was a discrepancy in the follow-up of patients (44 months versus 32 months for the AB and BG groups, respectively) because AB was the first obliteration material that was available, 12 months prior to BG. Symptoms (mainly otorrhea) recurred after the first month in favor of very rapid resorption of the material, which was the reason for the modification of our choice of material and not of surgical technique.

To solve these problems, many synthetic materials, such as hydroxyapatite, two-phase calcium phosphate, bioactive glass, titanium, and silicone, are now available[6,26]. These materials are easy to use and immediately available in great quantities without the need for an additional patient sampling site (for example, the contralateral ear), which would extend the operating time[26]. However, use of new synthetic obliteration devices still requires close clinical and radiological monitoring. For example, SerenoCem has been reported to cause secondary resorption of bone adjacent to the implantation site, thus leading to its withdrawal from the market[27].

The efficacy of mastoid obliteration is based on the depiction of a new external auditory meatus in the correct position on postoperative otoscopy, which can also identify complications such as infection or extrusion of the material. Nevertheless, several studies have shown good results with use of BG, with an overall extrusion rate of less than 0.5%[6]. In 96% of cases, the ear is dried out[6,9,28]. Although hydroxyapatite remains the second most commonly used synthetic material for mastoid obliteration, its use does not seem to produce stable results in the long term. Indeed, unlike BG, the overall incidence of extrusion is reported to be greater than 15%[6], but these results are not consistent[6]. According to the author's experience, BG might have a better outcome than hydroxyapatite because of better osteointegration and antibacterial properties leading to less infection and extrusion, therefore enabling restoration of a self-cleaning ear once healed. Among the weaknesses of this study, one limitation includes the number of patients. Indeed, the sample size was small because of the highly focused nature of the surgical procedure and the patient population of a single surgical center. However, a single surgical center was needed to homogenize the surgical procedure. Additionally, this study was retrospective. Obviously, a retrospective review is less satisfactory than a prospective randomized study, but surgeries were initially performed with AB and then with the BG technique due to the disappointing results of recurrent otorrhea in the first group and the availability of the materials. Furthermore, there was a relatively short follow-up time, which may explain the very low residual cholesteatoma rate (2/15 for the AB group and 1/17 for the BG group), even though the follow-up time was sufficient to estimate recurrence or residual cholesteatoma. There was a recent

review of the literature that aimed to compare data between single-stage tympanoplasty and mastoid obliteration for acquired cholesteatoma. Although it is difficult to compare different studies, it was shown that the rate of recurrent and residual disease after use of single-stage mastoid obliteration with either CWU or CWD tympanoplasty is qualitatively similar to, if not better than, rates that have been reported for nonobliterative techniques. However, it should be noted that although surgeon preference and patient factors remain determinants in the choice of surgical technique, CWU tympanoplasty with obliteration may be preferred to CWD tympanoplasty with obliteration because recurrence of infection is lower[14]. Canal wall reconstruction techniques have several drawbacks (risk of residual cholesteatoma and of recurrence of cholesteatoma if canal-tympanic continuity is not perfectly restored). On the other hand, quality of life after CWD surgery is known to be poorer than after CWU surgery due to creation of a large recess cavity, as previously described. Indeed, it requires more instrumental procedures due to cerumen accumulation in the posterior cavities; precautions must be taken when swimming, as contact with cold water can induce dizziness, making use of air-conduction hearing aids more difficult. Rehabilitation techniques after CWD surgery (CWDTwR), such as that described in this study or immediately during the first procedure [canal wall reconstruction (CWR) tympanoplasty or canal wall up-down[17]], enhance quality of life (less dizziness and otorrhea)[21,22]. All this limits resorting to ENT consultation[24] and facilitates use of air-conduction hearing aids[22].

Conclusion

Canal wall-down mastoidectomy rehabilitation with BG mastoid obliteration can significantly improve the quality of life of patients who undergo multiple operations without increasing risk of recurrent or residual cholesteatoma, provided that the surgical technique is perfectly mastered. Furthermore, BG appears to be more valuable than cancellous bone meal. However, prospective controlled studies with longer follow-up are needed to evaluate the value of BG versus other synthetic materials (such as hydroxyapatite) in surgical management of CWDTwR.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. All of the methods were conducted in accordance with relevant guidelines and regulations.

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Author contributions

M.F. and S.T. contributed to the conception and design of the study and to the first draft of the article. The statistical analyses were performed by M.F. All of the authors (M.F., R.T., R.H., and S.T.) discussed the results and contributed to the final version of the manuscript. This manuscript is original, and it, or any part of it, has not been previously published; additionally, it is not under consideration for publication elsewhere. The manuscript does not contain any individual person's data in any form (including any individual details, images, or videos), and oral informed consent to participate was obtained from all of the participants.

Competing interests

The authors declare no competing interests.

Additional information

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Technical note

Bioactive glass in canal wall reconstruction tympanoplasty

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ABSTRACT

The purpose of this Technical Note is to describe the surgical technique to transform canal wall down tympanoplasty into canal wall up tympanoplasty, that is, to rehabilitate a recess cavity by filling the mastoid and epitympanic cavities with synthetic tissue (bioactive glass) and recreating a normal-caliber external auditory canal. Mastoid cavity obliteration leads to a clinically significant improvement in health-related quality of life without increasing risk of recurrent or residual cholesteatoma, conditional upon technically impeccable surgery.

1. Introduction

Cholesteatoma is an aggressive pathology that can lead to serious complications. Only surgery enables eradication and prevents recurrence. It associates resection of all middle ear epidermis, and anatomic reconstruction of the external auditory canal (EAC), also known as "canal wall up (CWU) tympanoplasty" to achieve a watertight and dry ear. Ossiculoplasty to restore columellar effect is performed in the same or a second step. In case of major lysis of the bony framework, multiple recurrence requiring iterative surgery or unfavorable anatomic conditions such as completely eburnated mastoid or severe prolapse of the temporal meninges or sigmoid sinus, EAC reaming, known as "canal wall down (CWD) tympanoplasty", enables good visualization of the cavities, notably in the epitympanic region. This classical technique gives low rates of residual cholesteatoma, at 0-13% [1]. Creating such a recess cavity changes middle ear anatomy and physiology. The ear is no longer self-cleaning, leading to epidermal stagnation within the posterior cavities. The patient may also be hindered in aquatic activities by direct thermal stimulation of the lateral semicircular canal, which is directly exposed, causing dizziness. And finally, air-conduction hearing aids can be problematic if canal diameter is too great or in case of recurrent otorrhea [2].

To overcome these problems, various surgical techniques were developed to restore primary EAC anatomy by mastoid and epitympanic obliteration (see Table 1). Several filling materials have been used: initially, biological tissue (muscle flap, or autograft with mixed bone powder and biologic glue ("bone pâté")) [3], then bone-bank allograft, and, more recently, synthetic tissue [4,5]. The aim of this technical note is to describe a surgical technique, "canal wall reconstruction (CWR) tympanoplasty", transforming CWD tympanoplasty into CWU tympanoplasty: i.e., rehabilitating a recess cavity by associating EAC bone framework reconstruction to posterior cavity filling with synthetic tissue to restore the original EAC.

2. Surgical technique

With the patient in theater under general anesthesia, in supine position with the head turned 45° contralaterally, facial nerve monitoring is performed (NIM 3.0. Medtronic). After painstaking povidone-iodine disinfection, a second asepsis step is performed to minimize infection risk. The drapes are then placed by the surgeon according to the department's protocol, the pierced drape covering all of the patient, with a retroauricular collection pocket. Installation is checked by the anesthetist and the surgeon before going through the checklist.

The first stage consists in retroauricular injection of local anesthetic and a vasoconstrictor (xylocaine 1% with adrenalin). Otoscopy by microscope uses a speculum corresponding to EAC caliber for precise anatomic assessment. In case of otorrhea, bacteriological samples are systematically taken. The canal is then injected with the xylocaine with adrenalin.

The approach is retroauricular, using the previous arciform incision a few millimeters back of the retroauricular groove. Cartilage is harvested from the concha, wide enough to fill the posterior canal defect and cover the whole filled area: ideally, 1 × 2 cm. A large perichondral or temporal fascia fragment is also harvested. The contralateral cartilage and perichondrium may sometimes be used.

The anterior hinged muscle-periosteal flap uncovers the mastoid region (Fig. 1a). All the epidermis covering the posterior cavities is carefully detached, leaving no epidermal debris, and the tympanomeatal flap is thus inclined toward the EAC (Fig. 1b). The excess

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1879-7296/

Table 1
Pros and cons of the various cholesteatoma eradication techniques.

Technique	Pros	Cons
Canal wall down	Optimized cholesteatoma resection	Modification of ear anatomy and physiology
	Low rate of residual cholesteatoma	Ear no longer self-cleaning
	Simple postoperative clinical monitoring	Risk of intracavity epidermal stagnation
		Risk of poor water tolerance: pain, dizziness bathing
		Risk of difficult heating-aid fitting: frequent otorrhea, wide EAC
Canal wall up	Respect of ear physiology	More difficult resection in confined space
	Self-cleaning ear	Higher rate of residual cholesteatoma
	Good clinical tolerance	MRI monitoring need to screen for residual cholesteatoma
	Easy hearing-aid fitting	
	Good quality of life	
Mastoid obliteration	Lower risk of recurrent cholesteatoma	Risk of filling material extrusion
	Stabilizes EAC reconstruction	Variable risk of absorption depending on material.
	Anti-inflammatory and antibacterial action	More frequent scar superinfection
		MRI monitoring needed to screen for residual cholesteatoma
		CT monitoring needed to assess filling ratio
Canal wall down-up with bioactive glass	Optimized cholesteatoma resection	Risk of filling material extrusion
	Low rate of residual cholesteatoma	More frequent scar superinfection
	Respect of ear physiology	MRI monitoring needed to screen for residual cholesteatoma
	Self-cleaning ear	CT monitoring needed to assess filling ratio
	Good clinical tolerance	
	Easy hearing-aid fitting	
	Good quality of life	

CT: computed tomography; EAC: external auditory canal; MRI: magnetic resonance imaging.

flap is resected. All mastoid cells must be explored, possibly reamed and painstakingly cleaned down to the epitympanum, and the pathological mucosa is carefully removed along with any epidermal debris. The tympanic part of the facial nerve, whether protected by its bony shell or bare, is located and the "small drum" is explored to assess ossicle status for possible ossiculoplasty depending on findings. The cavity is systematically washed with abundant povidone-iodine serum.

The perichondral graft and cartilage fragment are then positioned so as to create a neo-canal. A trick is to create a bone tutor during reaming, to keep the cartilage perfectly positioned (Fig. 1c, white arrows). A bone groove can also be made by the reamer to maintain the cartilage, and this is sometimes simpler. The distal end of the cartilage graft should ideally lie on the tympanic portion of the facial nerve so as to allow access to the whole epitympanic region. Filling with bioactive glass begins from the attic with the epitympanum and ends by complete filling of the mastoid. It is important that the glass should be perfectly insulated from the EAC by carefully covering all the cartilage with perichondrium; filling then proceeds from below (Fig. 1d) to the surface (Fig. 1e). An important tip is to leave no dead space when filling; the bioactive glass can be compressed using a non-woven compress to ensure maximal filling and correct neo-canal caliber.

The muscle-periosteal flap is then brought back and sutured. It is important to perform otoscopy by microscope at end of procedure to check the position of the tympanomeatal flap, which should cover the proximal end of the perichondrium and the positioned cartilage. An expandible POP® intra-auricular dressing is placed in the canal and impregnated with povidone-iodine serum. The wound is closed in 2 planes by separate absorbable sutures on the skin. Strict povidone-iodine asepsis of the whole scar is performed before dressing.

Postoperative care involves daily antibiotic and anti-inflammatory drops in the operated ear, starting the day after surgery. The patient is followed up at day 8 to remove the expandible intra-auricular dressing. Oral prophylactic antibiotherapy is systematically implemented during the first 8 days, with amoxicillin then clavulanic acid at 3 g/day. The patient is seen again at day 45 for an otoscopic check-up of retroauricular healing and a hearing test. Otoscopy finds an aspect the same as for CWU tympanoplasty (Fig. 1f), sometimes with bulging in the posterior wall during the first 3 months. Follow-up is then adapted individually, but nuclear MR diffusion sequence imaging is systematic at 18 months and 5 years. Temporal CT scan may be proposed at 1 year to check mastoid obliteration quality.

3. Discussion

The present technique associates mastoid obliteration to EAC reconstruction to stabilize the reinforcement cartilage, avoid healing defect and thus prevent recurrence by secondary cartilage shift. Even if this happens, it will be limited to the eardrum if the cavity has been properly filled. The cartilage also prevents biomaterial extrusion. The technique optimizes resection and reconstruction in 1 step (or 2 steps), avoiding any functional impact of an enlarged cavity that would never be rehabilitated.

Yet, EAC reconstruction on a CWD technique has several drawbacks. There is a risk of residual cholesteatoma on releasing the cavity epithelium and of recurrence of cholesteatoma if canal-tympanic continuity is not perfectly restored. On the other hand, quality of life after the open technique (CWD surgery) is known to be poorer than after the closed technique (CWU surgery), due to the creation of a large recess cavity. Indeed, it requires more instrumental procedures, due to cerumen accumulation in the posterior cavities; precautions must be taken in swimming as contact with cold water can induce dizziness; and it makes use of air-conduction hearing aids more difficult. The rehabilitation technique (CWR tympanoplasty) described here significantly enhances quality of life [6,7]. It isolates the posterior labyrinth, thus reducing symptoms such as dizziness induced by heat stimulation and prevents avoids otorrhea, which often persists in a non-self-cleaning cavity. All this limits resort to ENT consultation [8] and facilitates use of air-conduction hearing aids [7].

Mastoid obliteration aims to fill the residual cavity so as to limit gas exchange in inflammatory respiratory mucosa. Since the first description by Mosher over a century ago [9], various techniques were developed, initially using autologous material such as muscle flaps, bone pâté or cartilage [10], then, more recently, synthetic materials [4,11,12]. Bioactive glass was claimed to inhibit residual cholesteatoma growth, but with low levels of evidence. At present, discussion focuses on the pros and cons of biological versus synthetic filling materials; The drawback of natural biological material such as

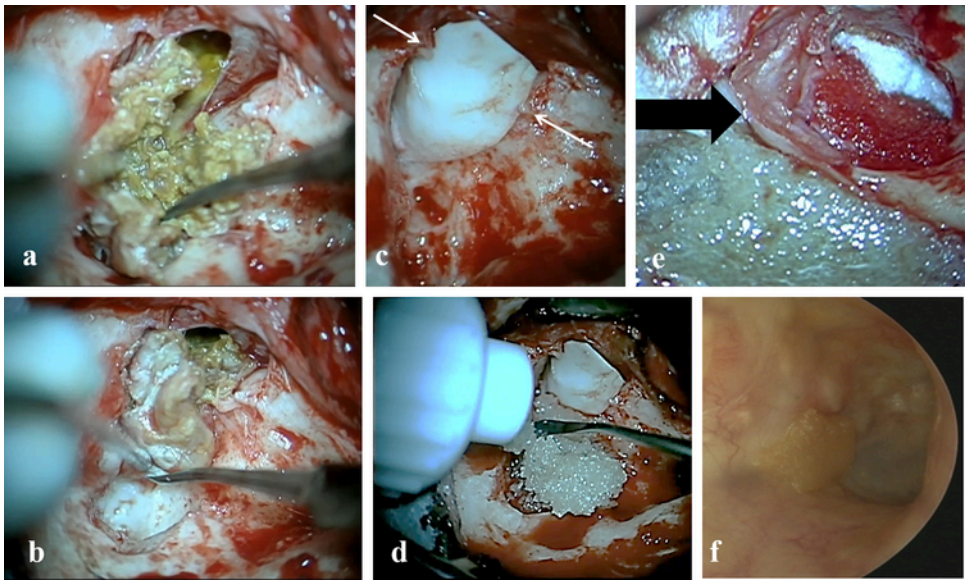

Fig. 1. a: intraoperative view of right ear wall-down procedure. Tympanomeatal flap exposed and all posterior cavities explored; b: all the skin and epidermal remnants covering the posterior cavities are inclined by stripper and fine aspiration toward the neo-canal, taking care to leave no epidermal debris; c: the perichondral graft and cartilage fragment are positioned so as to create a neo-EAC. A bone tutor can be formed to maintain the cartilage (arrows); d: filling begins with the epitympanic region, then the mastoid, from down to up taking care to leave no dead zones; e: all of the posterior cavities are filled. Positioning is checked for the neo-EAC created by the cartilage, which should cover all the perichondrium (black arrow); f: wall-up aspect at 3 months.

muscle, fascia or adipose tissue is that previous surgeries may not have left sufficient quantities [4,10]. The advantage lies in cost-saving, but there is a risk of retraction and fibrosis over time [4]. Bone pâté [8] behaves like physiological bone and induces local osteogenesis. It is, however, controversial, due to high rates of superinfection and of re-absorption, leading to recurrence of retraction pockets due to bone defects in the posterior EAC wall; long-term failure rates are greater than 50% [4,8], although some authors showed that intra- and post-operative antibiotic therapy could significantly limit postoperative infection [11]. To resolve these problems, numerous synthetic materials have been introduced: hydroxyapatite, biphasic calcium phosphate, bioactive glass, titanium, and silicone [4,12]. They have the advantage of being easy to use and immediately available in large quantities without the delay caused by harvesting from sites such as the contralateral ear or earlobe [11]. The efficacy of the mastoid obliteration is assessed otoscopically on the position of the neo-canal. Complications occur: infection or material extrusion in the EAC. Several studies reported good results with bioactive glass, with extrusion rates less than 0.5% [4], and dry ear in 96% of cases [4,13,14]. Hydroxyapatite is still the second most frequently used synthetic material in mastoid obliteration, but long-term results seem not to be stable; unlike with bioactive glass, extrusion rates exceed 15%, although this needs confirming in the longer term [3].

The interest and reliability of this technique associating reconstruction to filling led to the development of a 1-step technique for primary treatment of cholesteatoma: CWR after CWD surgery and posterior cavity obliteration as first described by Gantz [15]. Reconstructing the bony framework and filling the cavities in the first stage of cholesteatoma surgery has the advantage of wide exposure for cholesteatoma resection (removing the bony framework) but without the drawbacks of the CWD technique, as the framework is restored and supported by filling at end of procedure. The technique works whatever method is used to eradicate the cholesteatoma [16], and can safely be performed on an outpatient basis [17]. Another study [6] found no significant difference in quality of life between 50 patients with CWU tympanoplasty and 50 with CWD tympanoplasty and mastoid obliteration; this was confirmed again in a more recent study [7].

4. Conclusion

This canal wall reconstruction technique (or canal wall up-down) with bioactive glass mastoid obliteration significantly improves quality of life without increasing the risk of recurrent or residual cholesteatoma if the surgical technique is perfectly mastered.

Disclosure of interest

The authors declare that they have no competing interest.

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The Laryngoscope

Transcanal Endoscopic Ear Surgery for Epitympanic Cholesteatoma With Obliteration Using Bioglass

Stephane Ayache, MD

Key Words: Cholesteatoma, endoscopy, microscopy, obliteration, bioglass, glassbone.

***Laryngoscope*, 00:1–3, 2021**

INTRODUCTION

The goal of cholesteatoma surgery is to completely remove the disease, to restore hearing when possible, and to prevent residuals and recurrence. The prevention of recurrence is dependent on the quality of the tympanic membrane (TM) reinforcement and the reconstruction of the external auditory canal (EAC) in order to oppose a new TM retraction pocket. The prevention of residuals requires complete removal of the cholesteatoma, relying on optimal visualization of the anatomical spaces harboring the disease. The epitympanum is a prime area for the development of cholesteatoma. Access can be limited with a transcanal microscopic approach, requiring an antromastoidectomy. The transcanal endoscopic approach offers a magnified view of this space and 0° to 45° angled endoscopes. Extensive removal of the scutum posteriorly opens a wide access to the posterior epitympanum and aditus ad antrum. Cartilaginous reconstruction of the scutum should allow excellent stability of the cartilaginous grafts and seal with the tympanal bone to prevent further pars flaccida retraction. This extensive reconstruction procedure, however, remains difficult in a one-handed endoscopic technique. Obliteration of the mastoid, sometimes associated with the epitympanum in microscopic cholesteatoma surgery is thought to bring about a reduction in the rate of recidivism (residuals and recurrences). Their application to endoscopic surgery has so far never been reported. This case presents a transcanal endoscopic procedure for cholesteatoma with epitympanic obliteration using bioglass.

MATERIALS AND METHODS

A transcanal endoscopic approach was performed with the aim of removing an epitympanic cholesteatoma (Fig. 1) without the transmastoid approach, and to reconstruct the scutum after obliteration of the epitympanum at the same time. The preoperative temporal bone CT scan revealed an anterior and posterior epitympanic cholesteatoma without extension into the antrum, a sclerotic mastoid, an overhang of the sigmoid sinus, and a bone erosion of the anterior tegmen tympani (Fig. 2). Rigid 0° and 45° angled, 14 mm long, 3 mm diameter endoscopes were used and coupled with a high-definition 3CCD camera and video system. Bone removal from the scutum was adapted to the extension of the cholesteatoma and performed by an underwater endoscopic drilling. Total obliteration of the epitympanum was achieved using 45S5 Bioactive Glass (Glassbone Injectable Putty, Noraker, Villeurbane, France). Perichondrium was placed to seal off the aditus ad antrum and to prevent possible migration of the Glassbone inside the mastoid, which could secondarily lead to a reduction in the volume of the epitympanic obliteration and a retraction of the cartilages. Moreover, this material must be carefully packed to avoid any cavities within the obliteration. The Glassbone was positioned from the anterior epitympanum to the aditus ad antrum, without bulging in the EAC to prevent any postoperative stenosis. Reconstruction of the scutum was performed using cartilaginous and perichondrium grafts harvested from the tragus and covering the entire surface of the obliteration. The grafts were placed paying particular attention

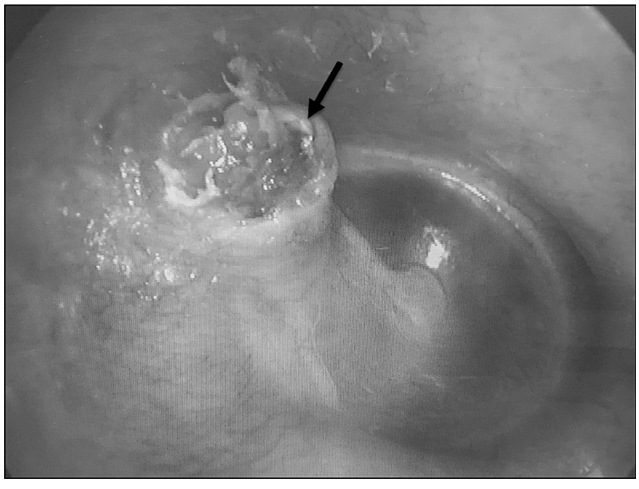

Fig. 1. Preoperative otoscopic examination (black arrow: pars flaccida cholesteatoma).

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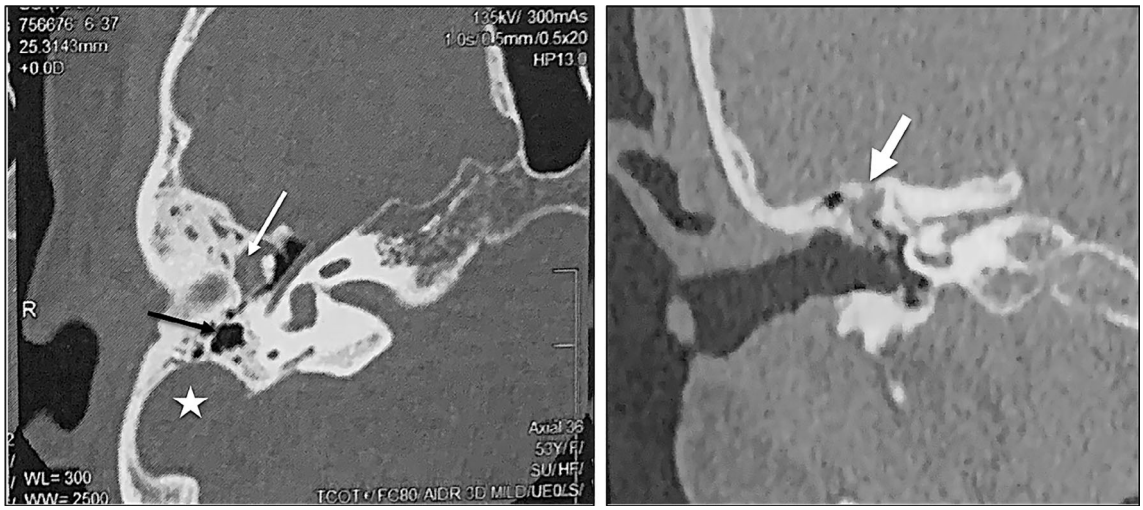

Fig. 2. Preoperative temporal bone CT scan (Left side. White arrow: epitympanic cholesteatoma, black arrow: antrum, white star: overhang of the sigmoid sinus - Right side. white arrow: erosion of the tegmen tympani).

to the sealing between them to avoid any leakage of the Glassbone in the ear canal and to prevent any secondary retraction of the grafts. An ossiculoplasty was performed using a cartilaginous piece between the stapes and the TM. No intraoperative intravenous antibiotic therapy was given. The patient was sent home the day of surgery with a prescription of local antibiotics (ofloxacin drops) for 10 days. The study has been performed according to the Declaration of Helsinki (Video S1).

RESULTS

No pre- or postoperative complication occurred. The texture of the 45S5 Bioactive Glass was well-suited for the epitympanic obliteration using a one-handed endoscopic technique. The healing of the EAC was complete without leakage of the Glassbone. After 1 postoperative year, the patient had a self-cleaning intact ear canal, without stenosis (Fig. 3). The first diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) performed at 1 post-operative year was negative.

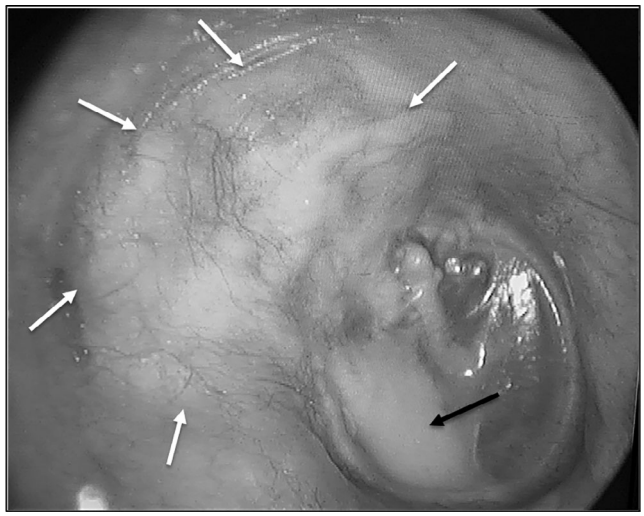

Fig. 3. Postoperative otoscopic examination after 1 year (white arrows: margins of the epitympanic obliteration, black arrow: ossiculoplasty using cartilage).

DISCUSSION

Closed technique cholesteatoma surgery is thought to improve the postoperative quality of life of patients. More respectful of the ear anatomy, this approach could nevertheless increase the risk of residual cholesteatoma.

Mastoid and epitympanic obliteration during microscopic procedures could reduce the rate of recidivism (residual and recurrence) of cholesteatoma. The procedure described in this video combines the value of transcanal endoscopy with that of epitympanic obliteration in cholesteatoma surgery.

Prevention of Residuals

Complete visualization of the cholesteatoma is crucial for preventing residuals. The transcanal microscopic approach, even with large atticotomy,[1] may be limited in the case of posterior extension to the aditus ad antrum. The antromastoidectomy provides access to the posterior epitympanum. This closed technique approach could nevertheless be difficult or even dangerous for neighboring anatomical structures in the event of a sclerotic mastoid and/or a prominent sigmoid sinus. It also requires removal of healthy bone and healthy mucosa of the mastoid. Transcanal endoscopic ear surgery (TEES) uses the magnified vision of 0° endoscopes. Removal of the scutum allows a wide visualization of the epitympanum, becoming a cul-de-sac of the EAC.[2] Visualization of the posterior epitympanum is further improved by the use of 45° endoscopes. Difficulties in reconstructing the scutum after an enlarged transcanal endoscopic atticotomy may be a limiting factor in the removal of cholesteatoma in favor of a transmastoid microscopic approach.

The epitympanic obliteration procedure reported in this video offers immediate benefits by facilitating the scutum reconstruction procedure. The material used constitutes a solid support for the cartilaginous grafts, without the risk of grafts tipping intraoperatively in an empty epitympanum. This is especially true as the atticotomy is large. The posterior limit of the TEES usually described at the level of the dome of the lateral semicircular canal can thus be pushed back and adapted to the extension of the cholesteatoma. A technique by endoscopic transcanal modified canal wall-down mastoidectomy has already been reported.[3] This widened access allows better quality of excision of the cholesteatoma. It could thus help reduce the risk of residuals.

Prevention of Recurrence

Usually, without epitympanic obliteration, reinforcement of the pars flaccida and reconstruction of the EAC should prevent the pars flaccida retraction into the epitympanum under the effect of the negative pressure generated by the blockage of the ventilation pathways of the middle ear. The use of materials resistant to this negative pressure should prevent a new retraction pocket.[1] Various techniques have been reported[1]: reconstruction of the scutum using cartilaginous grafts harvested from the tragus or the concha arranged in a palisade or use of cortical bone graft, use of a periosteal flap in the epitympanum to avoid medialization of the cartilages, and obliteration of the epitympanum.

Our technique could help reduce the risk of cholesteatoma recurrence by preventing pars flaccida retraction.

The arrangement of the grafts, in close contact with the tympanal bone is improved, reducing spaces for a new a new retraction of the pars flaccida. Obliteration also helps to prevent retraction, by mechanically occupying the volume of the epitympanic cavity without the risk of negative pressure.

The limitation of this paper is that this is the report of a single case with only 1 year of follow-up. This is not possible to confirm now that this technique does prevent recurrence of cholesteatoma.

Materials for Obliteration

These materials require criteria of biocompatibility, volume stability over time, resistance to infections, and ease of excision in the event of surgical revision.[4] Autologous materials are the most commonly used.[4] Muscle flaps present a risk of loss of volume and retraction of the flaps. Bone (chips or bone paté) presents a risk of loss of volume but also of secondary ossification requiring drilling in the case of surgical revision. Cartilaginous grafts arranged in a palisade are more stable in volume but limited in quantity.

Synthetic materials (hydroxyapatite granules and bioactive glasses) are used in mastoid obliteration procedures.

Among bioactive glasses, 45S5 Bioactive Glass (Glassbone Injectable Putty, Noraker, Villeurbane, France) is used in spine, orthopedic, and stomatological surgery due to its osteoconduction and osteostimulation properties, bacteriostatic properties, rapid availability, and ease of handling and more recently its good tolerance and safety in mastoid and epitympanic obliteration.[5]

The 45S5 Bioactive Glass is a material available on demand. Its consistency in the form of a paste facilitates its handling, particularly in a one-handed endoscopic technique. Short-term postoperative follow-up focuses on the quality of healing and the caliber of the EAC. In the longer term, follow-up by diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) is similar to that existing for cholesteatomas.

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Tolerance and safety of 45S5 bioactive glass used in obliteration procedures during middle ear surgery: Preliminary results

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ABSTRACT

Objective: Otologists face many disadvantages after extensive mastoid drilling and canal wall down technique in cholesteatoma surgery. Mastoid and epitympanic cavity obliterations or reconstructions after canal wall down procedure using bioactive glass seem to be an interesting solution to overcome some of these disadvantages. Bioactive glass offers many benefits including the availability when there are no sufficient autologous materials for obliteration, its antibacterial activity in chronic infected ear and decreasing the recidivism of cholesteatoma. The objective of this study is to evaluate the tolerance and safety of 45S5 bioactive glass as a filing bone-synthetic material by clinical, audiological and radiological examinations.

Methodology: A retrospective study of 42 patients who had undergone obliteration of mastoid or/and epitympanic cavity with 45S5 bioactive glass between, November 2017 to January 2019. Data from clinical follow-ups, audiological assessment, CT-scan and MRI were analyzed.

Result: The patients' mean age was 49.8 years old. Microscopic examinations showed dry well-healed tympanic membranes and external auditory canals for 95.2% of the patients after 1 year. Inner ear injuries after obliteration were not observed by comparing pre and post-operative bone conduction audiometry (p value 0.457). No facial palsy was reported post-operatively. One-year postoperative radiological assessments did not reveal any silent implantation of cholesteatoma or residual disease.

Conclusion: Mastoid and epitympanic obliterations with 45S5 bioactive glass seem to be a tolerable and safe option in cholesteatoma surgery with favorable outcomes similar to other member of bioactive glass especially the S53P4.

1. Introduction

The primary aim in treating chronic otitis media with cholesteatoma is the complete eradication of the squamosal disease [1]. Surgeons frequently conduct extensive drilling leading to large mastoid and epitympanic cavities. In addition, multiple recurrence of cholesteatoma require a canal wall down technique (CWD) to ensure the complete eradication of the disease by giving access to hard-to-reach areas located in the middle ear, otherwise impossible [2]. However, this technique creates larger cavities without sufficient “on-site” autologous material for reconstruction. In addition, the CWD technique has long-term disadvantages such as recurrent otorrhea that are related to water intolerance, vertigo, difficulty when wearing traditional hearing aids, and the accumulation of keratin debris requiring frequent aural toileting [3].

Mastoid cavity obliteration seems to be an interesting solution to overcome the post-operative disadvantages related to large cavities by improving the middle ear hygiene by constructing a well-aerated middle ear, in addition to hearing preservation as well as decreasing the chance of recurrence of the cholesteatoma [4]. Hellingman et al. demonstrated recently that the obliteration of the epitympanum and mastoid resulted in low residual and recurrence rates [5]. In addition, Csakanyi et al. studied the regulation of middle ear gas pressure in case of mastoid obliteration and demonstrated that mastoid obliteration will result in a reduction of a mucosal surface with better gas exchange which can improve the middle ear gas pressure balance, resulting in less retraction pocket, hence a better long-term outcome [6].

Mosher introduced the concept of mastoid obliteration in 1911 when he proposed the creation of a flap from the back of the auricle [7]. Subsequently, many techniques have been proposed to reconstruct the

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posterior canal wall and to obliterate the mastoid and epitympanic cavities. For example, the use of bone paste, bone chips, cortical bone, muscle flaps, cartilage, hydroxyapatite, silicon blocks, and more recently bioactive glasses as filling materials including S53P4, which has been studied many times in the literature [8,9]. The bioactive glass being a synthetic bone graft, it presents the advantage of being readily available for bone reconstruct when autologous material is not sufficient. It has also been demonstrated that bioactive glasses can act against many aerobic, anaerobic and multi-resistant bacteria [10,11]. One variant of bioactive glass is the 45S5 composition, composed of a mixture of oxides (45% SiO2, 24.5% CaO, 25.5%, Na2O, and 6% P2O5, in weight %). 45S5 bioactive glass (BG) have been used by orthopedic surgeons for filling in cavities caused by radio-necrosis, and by neurosurgeons in cases of CSF leak [12]. To our knowledge, no study has been published to evaluate the tolerance and safety of 45S5 BG in the context of middle ear surgery and mastoid obliteration. The objectives of the present study are to evaluate the tolerance of both the external and middle ear along with the safety of the inner ear after using 45S5 BG as a synthetic bone graft filing material in ear surgeries through clinical, audiological and radiological examinations.

2. Materials and methods

This retrospective study was approved by the institutional ethics committee (Ethics Committee of Lyon; N19-61). All patients gave their written consent for the use of their personal clinical data. The bioactive glass used in all patients included in the present study is 45S5 bioactive glass (GlassBone™ Injectable Putty; Noraker., Villeurbanne, France). The composition of this product given in weight (wt) percentages is 45 wt% silicon dioxide (SiO2), 24.5 wt% calcium oxide (CaO), 25.5 wt % sodium oxide (Na2O) and 6 wt% phosphorus pentoxide (P2O5).

This retrospective study includes all patients operated on by a single senior surgeon at the Department of Otolaryngology - Head and Neck Surgery - in Lyon Sud Hospital, a tertiary center between November 2017 and January 2019. This includes all patients operated on for primary cholesteatoma, revision surgery or rehabilitation of the canal wall down technique and 45S5 BG was used for filling epitympanic and mastoid obliteration cavities. All patients missing audiological and radiological follow-ups, within 1-year post-operation, were excluded from this study.

Cutaneous and middle ear tolerance were evaluated post-operatively after 1 week, 3 months and 1 year. Cutaneous tolerance was evaluated throughout the physical examination of the post-auricular region (wound healing, erythema, swelling, draining and wound infection) and the skin of the external auditory canal (erythema, swelling, stenosis of the external auditory canal). Middle ear tolerance was evaluated by otoscopy under the microscope to see the tympanic membrane, and radiological examination. In the presence of an otorrhea or a skin infection, bacteriological analysis was conducted. All patients were evaluated radiologically 1 year post-operatively using a high-resolution computed tomography (CT) scan of the temporal bone and a magnetic resonance imaging (MRI) in order to observe the stability of the mastoid and epitympanic obliteration, the inflammatory response to the implanted material, and any possible sign of complication or a residual cholesteatoma in the middle ear. As a diffuse inflammation of the middle ear after surgery is very common without obliteration, we considered that the bioactive glass is responsible for the inflammatory reaction when the radiologist described an isolated inflammation, granuloma or marked inflammation around the implanted material comparing to the rest of the middle ear. For all patients, pre-operative PTA (Pure Tone Audiometry) and post-operative PTA (1 year or more after surgery) were collected. All audiometric examinations were performed by certified university clinical audiologists from the same department. Speech discrimination data was not available for all patients, and thus were excluded for the analysis. Data were collected and analyzed according to the recommendations of the committee for Hearing and Equilibrium of the American Academy of Otolaryngology - Head and Neck Surgery [13]. The means of the thresholds for bone conduction at 0.5, 1, 2, and 3 kHz were used to form a four-tone pure-tone average. The functional results were evaluated by comparing the pre-operative and 1-year post-operative bone conduction threshold level averages.

3. Surgery

All patients were operated on under general anesthesia with the inclusion of facial nerve monitoring system NIM-Response 3.0 (Medtronic, Jacksonville, FL, USA). A retroauricular skin incision and the creation of a musculoperiosteal flap were performed. Perichondrium and cartilage grafts were harvested from the cymba and cavum conchae. Primary or revision surgery was then carried-out depending on the case, involving a canal wall up or canal wall down mastoidectomy according to the anatomy and the aggressiveness of the disease with reconstruction performed to eradicate the cholesteatoma. After the complete removal of the cholesteatoma, the reconstruction was started in the middle ear including ossiculoplasty and tympanic membrane grafting (Fig. 2, A). Canal wall down mastoidectomy reconstruction was conducted using a large cartilage graft with perichondrium to reconstruct the posterior canal wall (Fig. 2, B). In a canal wall up and partial canal wall down revision surgery (depending on the anatomy of the middle ear), the position of the neotympanic membrane will still in its anatomical position without important medialization in relation to the facial ridge (Fig. 2, A), where the reconstructed tympanic membrane will be medialized in revision surgery involving a complete canal wall down mastoidectomy (Fig. 1, C). The last step before suturing whether it is a canal wall up or down was the epitympanic and mastoid cavities obliteration using 45S5 BG (GlassBone™ Injectable Putty; Noraker., Villeurbanne, France) (Fig. 2, C, D and E). Absorbable Gelatin Sponge (Gelfoam) was used to separate the attic from the atrium (tympanic cavity) to prevent any particles of BG migration after obliteration (Fig. 2, A). Carful suturing of the muscolo-periosteal flap and retro-auricular incision with absorbable sutures was necessary to prevent the dissemination of the implanted bioactive glass. A pope ear wick (Pope OTO Wick Merocel, Medtronic Xomed, Jacksonville, FL, USA) was inserted into the external auditory canal. The pope ear wick was removed post-operatively on either the 7th or 8th day, after that Ciprofloxacin ear drops was installed on the operated ear twice a daily for 7 days. All patients received peri-operative antibioprophylaxis with amoxicillin/clavulanic acid which was continued for 7 days post-operatively (pristinamycine in the case of an allergy to amoxicillin).

Data and parameters from the patients' medical records were analyzed using SPSS software® (version 21). Paired *t*-tests were used to assess any significance between variables and a value of $P < 0.05$ was taken as statistically significant with a confidence level of 95%.

4. Results

Forty-two patients, who met the inclusion criteria as described in the materials and methods, were included in this study. There were 19 female and 23 male patients with an average age of 49.8 ± 20.80 years (range 12–82 years) at the time of surgery. Fifteen patients were operated on for the first time whereas revision surgeries were conducted for the rest of the group. Among the revision surgery group, 10 patients were operated on for a recurrence of a cholesteatoma with the rehabilitation of the canal wall down technique that had been performed previously by reconstructing the posterior wall of the external auditory canal. The rest were operated on due to a recurrence of the cholesteatoma and obliteration using the canal wall-up technique. Type II tympanoplasty was the most frequent type of reconstruction used in this study and it was performed in 45.2% of cases. The patient demographic data, the type of surgery and the surgical technique are shown in Table I.

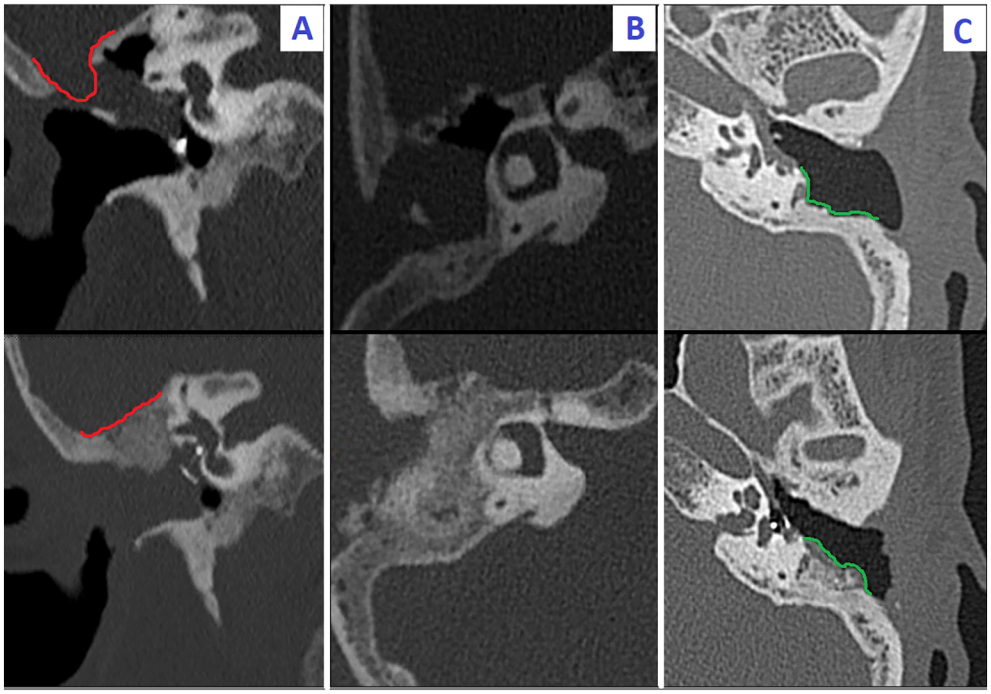

Fig. 1. CT-scan appearance of middle ear before (above) and after (below) obliteration with 45S5 in 3 different cases.
A: (above) Coronal view of CT-scan of a cholesteatoma recurrence complicated with meningocele, (below) 5th day postoperative CT scan, note the position of meninges after obliteration.
B: Axial view of pre and postoperative CT scan demonstrating obliteration of epitympanic cavity.
C: Axial view of CT scan for rehabilitation of canal wall down technique, (below) note the reconstructed posterior wall of external auditory canal.

The microscopic examination at the 7th day post-operative showed normal healing of the external auditory canal and tympanic membrane for 39 patients with, while 3 patients had an inflammatory EAC and otorrhea. Five patients presented with a non-obstructive bulging of the posterior external auditory canal. There was no extrusion of bioactive glass material in the immediate post-operative examination. Thirty-seven patients had normal healing of the retro-auricular wound without associated pain 7 days after the surgery, while 2 patients had a normal healing with pain over the mastoid region, 1 patient had an infected wound with associated pain, and 2 patients had a mild wound dehiscence without pain or extrusion of the implanted material. Bacteriological analysis was conducted on the 4 patients with wound discharge or otorrhea. Different pathological germs were observed in each case, which were Staphylococcus lugdunensis, *Candida albicans*, Citrobacter koser and Haemophiluspara influenzae. All 4 patients with post-operative infection were successfully treated medically with an appropriate antibiotic or antifungal agent along with simple wound care. No major complications were reported in this study such as facial nerf palsy, skull base osteitis or fistulae with a CSF leak.

The patients' 3-month post-operative otoscopic and clinical examinations showed a well-healed ear and retro-auricular wound for all subjects except for 1 patient who showed a persistent wound dehiscence, regardless of the medical management used and needed a surgical closure under local anesthesia. The clinical assessment after 1 year revealed complete healing of the EACs and retro-auricular wounds for all patients (Fig. 3). Two patients showed recurrent otorrhea. Repair of tegmen tympani bony defect with 45S5 BG was done for 2 patients with a meningocele (Fig. 1), no complication was noted on the clinical or

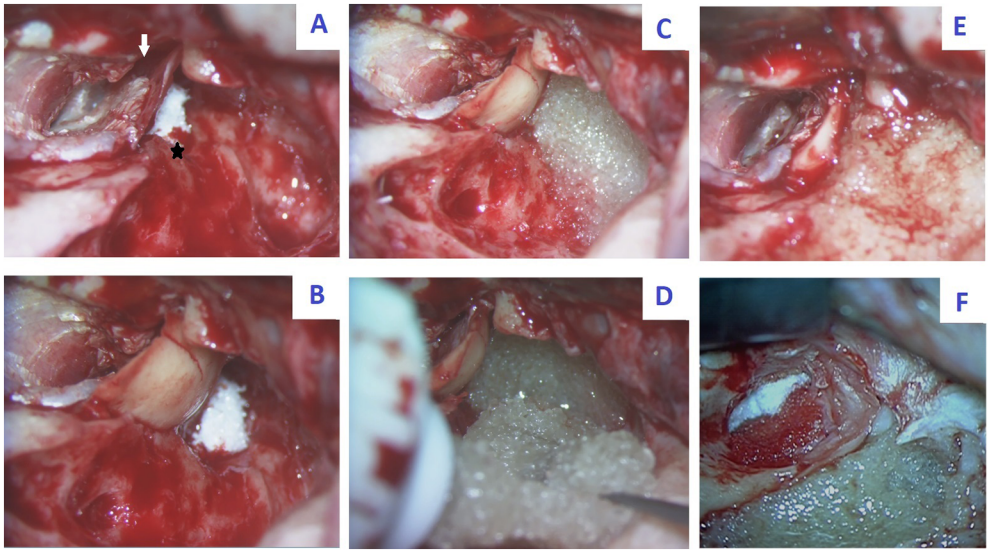

Fig. 2. Intraoperative surgical steps for middle ear reconstruction, mastoid and epitympanic cavity obliterations using 45S5 Bioactive Glass after aggressive primary cholesteatoma surgery with complete posterior was erosion in a left ear.
A: Attic reconstruction with a cartilage (white arrow) and Gelfoam (black star) was used to support the tympanic membrane graft and to separate the attic from the tympanic cavity to prevent any particles of Bioactive Glass migration after obliteration. Note that the position of the neotympanic membrane in relation to the facial ridge, which still in its anatomical position without medialization.
B: A large cartilage graft with a perichondrium were positioned to reconstruct the posterior canal wall.
C: Epitympanic cavity obliteration using 45S5 Bioactive Glass, it is essential to carefully obliterate the supratubal recess.
D: Mastoid cavity obliteration, regular compression of the material with a sterile gauze is important to avoid dead space.
E: Final aspect of the reconstructed ear canal and the obliterated mastoid cavity.
F: After clearing the surgical site and a pope ear wick was inserted before suturing.

Table I
Patients characteristics, type of surgery and post operatory MRI results.

	45S5 obliteration
Patients	42
Mean age at surgery (± SD)	49.8 (± 20.8)
Gender, female (%)	19 (45.2%)
Operated side, left side (%)	23 (54.8%)
Primary surgery (%)	15 (35.7%)
Revision surgery (%)	27 (64.3%)
CWU mastoidectomy (%)	32 (76.2%)
CWD mastoidectomy with reconstruction (%)	10 (23.8%)
CT, particles migration	0/35
MRI, residual	0/42
MRI, inflammatory reaction	2/42

45S5; Bioactive Glass, SD; Standard Deviation, CWU; Canal Wall-Up, CWD; Canal Wall-Down, MRI; Magnetic Resonance Imaging, CT; computerized tomography.

radiological follow-up.

The PTA means of the preoperative thresholds for bone and air conductions were 29.48 dB and 48,16 dB, while being 28,41 dB and 45,11 dB post-operation, respectively. There was no statistical significance found between the pre- and post-operative bone conduction audiometry with a P value of 0.457. Regarding the post-operative imaging, all patients had a MRI whereas only 35 patients had a CT scan after 1 year. All CT scans showed a satisfactory filled mastoid and epitympanic cavity with 45S5 BG without any migration of the bioactive glass material in the middle ear (Fig. 1). Likewise, all post-operative MRIs revealed no sign of enclosing cholesteatoma within the obliterated cavities or residual disease. Regarding the inflammatory response, two MRIs showed marked inflammation around the obliterated material in the T2 weighted image (T2WI) sequence while the rest were unremarkable. 45S5 BG did not generate any imaging artifacts in the CT-scan or MRIs that interfered with the analysis in relation to the surrounding structure. No major complications were reported in this study such as skull base osteitis, fistulae with a CSF leak or facial palsy.

5. Discussion

The mastoid and epitympanic obliteration technique has gained considerable popularity among otologist and ear surgeons as it provides many advantages in the context of cholesteatoma surgeries. It has been demonstrated to significantly reduce the growth rate of the residual disease as well as the recurrence rate after surgery when using either the canal wall-up or wall-down technique [14]. In addition, it is very effective in the context of rehabilitation surgeries after a canal wall down mastoidectomy, improving chronic ear discharge related to large cavity, the ability to use classic hearing aids, and liberating the patient from ear water restrictions [15]. In this study, we report on our experience performing mastoid obliterations using 45S5 bioactive glass as a bone graft with different otological scenarios. Excellent tolerability and safety after a 1-year follow-up was observed. To our knowledge, this is the first study in the literature that demonstrates tolerance of 45S5 bioactive glass in middle ear cavity.

Mastoid obliteration was described first with autologous materials. Unfortunately, this was limited by the fact that the muscle flaps shrunk over time due to atrophy, rendering impossible to predict the final shape. In addition, there is limited amount of autologous materials to be harvested, especially in case of a revision surgery [16]. Many alternative materials has been described in literature, however bioactive glass substitutes have earned a noticeable reputation due to their unique proprieties. The use of S53P4 bioactive glass had been documented in the literature with noteworthy results and a corresponding positive safety profile [17]. It has long been demonstrated that 45S5 BG can form a direct bond with the hosting bone and soft tissues with added benefit of exhibiting some bacteriostatic activity [12]. However, there is not much evidence related to its clinical usage and safety in ear surgery in the literature. From the senior surgeon's point of view, 45S5 BG, in its putty-like form, is easier to apply and manipulate during the obliteration of the middle ear, especially in the narrow irregular cavity compared to other bioactive glasses. This study shows that 45S5 BG has a satisfactory tolerance, safety profile and clinical results with 95.2% of the patients through different modalities of evaluation. These outcomes are comparable with the reported observations in the literature referring to other bioactive glass types [18].

Mastoid and epitympanic cavities obliterations with 45S5 BG in this

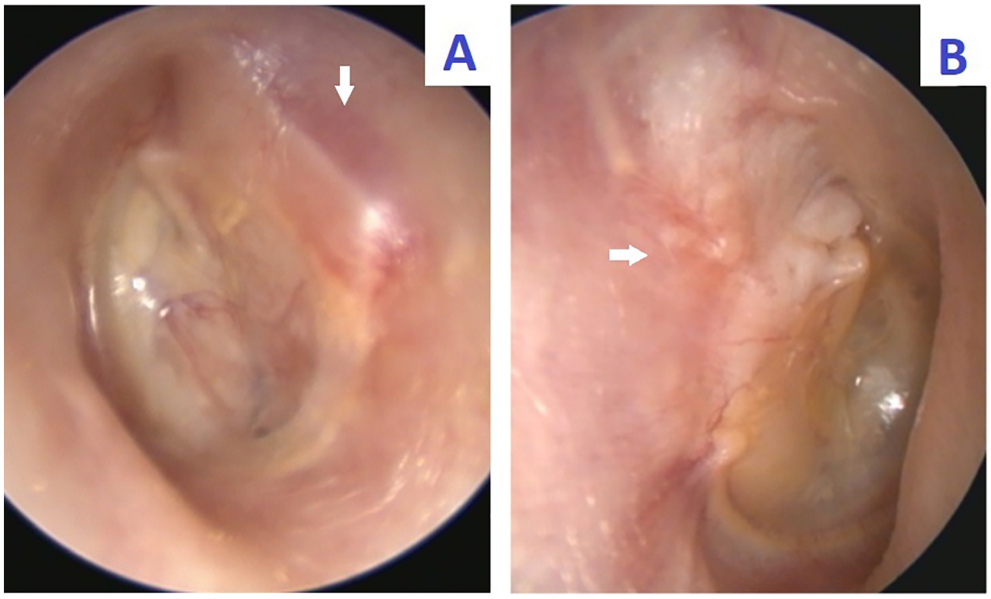

Fig. 3. Otoscopic examinations after 1-year postoperative showing the result of obliteration using 45S5 Bioactive Glass. Note the reconstructed attic with a cartilage (white arrow).
A: An example of a left ear.
B: An example of a right ear.

Table II
MRI appearance of bioactive glass [20].

	T1	T2	T1 + Gadolinum	Diffusion
Cholesteatoma	Hypo-/iso-intense	Hyper-intense	–	Hyper-intense
Granuloma	Hyper-intense	Hyper-intense	–	Variable
Infection	Hypo-/iso-intense	Hyper-intense	Fast	Variable
S53P4	Hypo-/iso-intense	Hypo-intense	Moderated	Hypo-intense
45S5	Hypo-intense	Hypo-intense	–	Hypo-intense

S53P4, 45S5; Bioactive glass.

study showed a well-healed, dry and acceptable external auditory canal and tympanic membrane at the 1-year follow-up in 95.2% of patients (Fig. 3). There were no major complications among the 42 cases, or the need for a revision surgery and the removal of the implanted material. Only 4 patients were found with a local infection of the EAC or the retro-auricular incision site post-surgery, that were managed successfully with classical antibiotics and standard local care. In addition, 1 patient had a persistent wound dehiscence after 3 months and needed surgical closure with a local flap. The nature and incidence of these complications is identical to the standard complications after cholesteatoma surgery without obliteration [17].

There are many concerns about the integrity of the inner ear function when using bioactive glass in an obliteration procedure due to the high osmotic activity of the material that could damage the inner ear when the particles come in contact with round, oval wind or a thin diseased bone of the labyrinthine [19]. During the consolidation process of the bioactive glass with the bone, there is a theoretical risk of particles migration through the attic from the mastoid to the tympanic cavity and potential direct contact with round or oval wind. We assessed the inner ear function integrity in this study by comparing the means of the threshold of bone conduction PTA pre-operatively and post-operatively, which were found to be stable or could it be improved without any statistically significance difference. The results regarding the hearing function in this study are in good agreement with the reported results in the literature. [18,19]

The silent implantation of cholesteatoma within the obliterated cavity is one of the feared complications along with an inflammatory reaction (granuloma) linked to the implanted materials [14]. All MRIs, with a diffusion weighted sequence, performed 1 year after the surgery did not show any evidence of implanted or residual cholesteatoma, although it is too early to evaluate whether there is a recurrence of the disease after 1 year. Furthermore, only 2 patients (4.8%) had a marked inflammatory reaction around the implanted materials on the MRI. Nevertheless, there clinical examination revealed a dry well-healed ears and retro-auricular scars. Table II illustrates the MRI appearance of the bioactive glass compared to the other pathology [20]. All high-resolution CT-scans showed acceptable obliterated cavities with no evidence of particles migration to the tympanic cavity (Fig. 1). We did not observe any imaging artifacts interfering with our ability to analyze the surrounding structure, which is in line with the published observations for other bioactive glasses. [20,21]

Despite the limitation of this preliminary study, such as its retrospective design and the relative short-term follow-up of 1 year, data allows to acceptably demonstrate the safety and tolerance of 45S5 BG in the mastoid and epitympanic obliteration. However, no statement can be made on the eventual recurrence of the pathology as well as the long term efficacity and stability of the 45S5 BG. Authors will continue this study with minimum 5-Year Follow-Up to determine the long term efficacity and stability.

6. Conclusion

This preliminary study reveals that mastoid and epitympanic obliteration with 45S5 bioactive glass is tolerable and safe with favorable outcomes similar to other bioactive glasses, especially S53P4 in the context of middle ear surgery. These outcomes were assessed using clinical, audiological and radiological examinations over a 1-year follow up post-operatively. Larger prospective studies with longer follow-up are recommended to determine the long term efficacity and stability of the 45S5 BG volume inside the obliterated cavity before any generalizations can be made.

Author statement

Nasser Al Tamami: Conceptualization, Methodology, Writing-Original draft preparation.
Naif Bawazeer: Data curation, Writing - Review & Editing.
Maxime Fieux: Software, Validation.
Sandra Zaouche: Conceptualization, Validation.
Stéphane Tringali: Conceptualization, Methodology, Supervision.

Disclosure of benefit

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Bioglass 45S5, a relevant alternative to autogenous harvesting for secondary alveolar bone grafts in clefts? Retrospective study of one hundred surgeries

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ABSTRACT

The secondary alveolar bone grafting (SABG) step restores the continuity of the alveolar bone necessary for dentition. Faced with the complications of autografts, synthetic biomaterials such as Bioglass (BG) 45S5 have been proposed. The objective was to evaluate the success rate of SABG with the addition of BG 45S5 and to highlight the prognostic factors.

Patients who underwent operation between 2015 and 2021 and had follow-up cone-beam computed tomography (CBCT) were analyzed. Multivariate analysis was performed to determine factors influencing radiographic success. A total of 102 SABG were analyzed. They were unilateral total cleft lip and palate (49, 48.0%). The mean age at surgery was 9.32 ± 3.09 years. Surgeries were performed mainly outside a syndromic context and without a family history after orthodontic preparation.

The radiographic success rate at 1 year was 80.4%. Mixed dentition stage (odds ratio [OR] = 7.3, p = 0.024), absence of syndromic context (OR = 20.7, p = 0.024) and female sex (OR = 4.88, p = 0.021) were factors predictive of surgical success.

The use of BG 45S5 instead of autograft is relevant for SABG, with a 1-year success rate of over 80%. The stage of mixed dentition, the absence of syndromic context, and female sex were factors for good prognosis.

1. Introduction

Cleft lip and palate is the fourth most common congenital malformation and the first most common craniofacial anomaly (Ysunza et al. 2015). Cleft lip and/or palate (CL/P) are divided into two groups: isolated cleft palate, and cleft lip without or with cleft palate (Merritt 2005; Shkoukani et al. 2013). In France, the incidence of CL/P in all clinical forms is 1 per 700–1000 births (CCMR MaFace, and Filière de santé maladies rares TeteCou, 2021). Cleft palate is characteristic of over 200 well-defined congenital malformation syndromes (Ysunza et al. 2015). Nearly 70% of cases are considered non-syndromic (Stanier and Moore 2004). At present, the described etiologies are multifactorial and involve genetic and environmental factors (Dixon et al., 2011; Martinelli et al., 2020).

It is not yet possible to completely prevent the onset of these embryopathies, which, if left untreated, have a considerable impact on the quality of life of children (Rando et al., 2018; Karki et al., 2021; Leopoldo-Rodado et al., 2021). In France, to optimize the care pathway, a national diagnosis and care protocol (PNDS) was published in November 2021 (CCMR MaFace, and Filière de santé maladies rares TeteCou, 2021). The goal of cleft lip and palate repair is to restore oral anatomy and velum function (Ma et al., 2021). It takes place through three surgical steps.

The first step is primary cheilo-rhinoplasty associated with intraveloplasty. This takes place between 3 and 6 months of age. The second step is the closure of the residual bone gap, scheduled between 12 and 18 months of age. The third step, called secondary alveolar bone grafting (SABG), takes place between 4 and 6 years of age after orthodontic preparation. This key step provides support to the maxillary arch for dentition and mastication by preventing transverse collapse (Weissler

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et al., 2016; Liu et al., 2017).

The use of bone grafts or synthetic substitutes has been described. They can be of natural origin, such as autografts or allografts. Autogenous harvesting can come from different sites: the most common is the iliac crest, but the tibia, mandible or skull can also be used (Thuaksuban et al. 2010). The inconvenience is due to the complications related to the harvesting: postoperative pain, difficulty in walking, nerve damage, hematoma and infections (Cricchio and Lundgren 2003; Sbitany et al., 2010; Hayes et al., 2011; Chang et al., 2017; Sequera-Ramos et al., 2019; Tache and Mommaerts 2021).

In this context, alternatives have been sought (Liang et al., 2018; Wu et al., 2018). Researchers are proposing the use of various bone substitutes: β-tricalcium phosphate (TCP), bioactive silicates, calcium phosphate, and recombinant human bone morphogenic proteins-2 and 7 (rhBMP-2 and rhBMP-7) (Osorio et al., 2020; Brézulier et al., 2021). Among bioactive silicates, Bioglass (BG) 45S5 provided promising results in a study of 58 cases (Graillon et al., 2018). However, literature is poor regarding its use in SABGs.

The primary aim of this study was to determine the success rate of SABG with BG supply. The secondary objectives were to test the predictive value of different parameters on the success of this approach by univariate and multivariate models.

2. Materials and methods

2.1. Study design and participants

A retrospective cross-sectional observational study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. The approval of the Ethics Committee of the Hospital of Rennes was obtained (opinion n°22.31). Data collection took place from November 2021 to July 2022.

Data from 124 SABG with BG 45S5 (GlassBone, Noraker, France), consecutively conducted in the pediatric surgery department of the South Hospital of the University Hospital of Rennes between July 2015 and 2021, by two surgeons, were used in the study. The surgical technique was always the same. First, a vestibular approach allows exposure of the bony cleft. The nasal mucosal plane is closed tightly in case of a fistula, whether it is known or discovered during surgery. The palatal fibromucosal plane is then closed tightly. The bone margins are then enhanced by corticotomies. Briefly, corticotomies are performed with the tip of an 11-blade scalpel on both bone margins, at a distance from the dental germs, until blood suffusion is obtained, but without bone avulsion. The bony cleft is filled with BG, followed by gingivoperiostoplasty to ensure tight closure.

Inclusion criteria were as follows: (1) SABG of a facial cleft; (2) use of BG 45S5 bone substitute (GlassBone, Noraker, France); and (3) procedure performed in patients with a complete medical and radiographic record.

Exclusion criteria were the following: (1) absence of pre- or postoperative three-dimensional X-ray imaging at 1 year; (2) unreadable postoperative three-dimensional imaging at the six sites evaluated; (3) use of another type of graft; and (4) incomplete medical records.

2.2. Studied variables

The variables were divided into six blocks. The first described the sample: patient age at SABG, sex, syndrome, history of familial clefts.

The second block described the characteristics of the operated cleft: type, laterality.

The third described the dental data in relation to the cleft: orthodontics, formula (normal, lateral incisor agenesis, supernumerary tooth), stage of dentition at the time of SABG (temporary, mixed, adolescent), temporary teeth in the cleft and time of their extraction (pre- or per-operative), preoperative fistula.

The fourth block reported on the surgical procedure: fistula closure, operator, ambulatory character, anesthesia by supra-zygomatic block.

The fifth part consisted of postoperative data: residual fistula, antibiotics, infections.

The sixth section, which develops the radiographic data, is presented below.

2.3. Radiographic evaluation and definition of the operative result

The last set of variables was composed by measurements on cone-beam computed tomography (CBCT) at 1 year. The three planes, orthogonal, 2 mm thick, were selected as follows (Fig. 1). A first plane connected the two teeth adjacent to the cleft. A second described the long axis from the mesial tooth to the cleft. A third traveled the cleft path on an anteroposterior axis.

Scoring by thirds (apical, medial, cervical) was performed in the horizontal and vertical dimensions. Therefore 6 sites were evaluated. The score was a discrete variable with three modalities: "1" for the absence of detectable bone in the area of interest, "2" in the presence of bone not filling the area on either side, "3" in the presence of bone filling the area of interest. In case of artifacts or blurring making the area non-evaluable, the score "NA" was assigned.

Inter- and intra-examiner reproducibility were assessed on 11 CBCT scans by 4 practitioners (OA, TDB, DB, and AS) using Fleiss kappa and Cohen kappa. These were complemented by reproducibility analyses by a pair of examiners. Postoperative CBCT scans were then all read separately by the two practitioners with the highest inter-rater reproducibility. Examinations with score discrepancies were re-evaluated by the two examiners associated with a third in a joint reading.

From these measurements, the outcome of the surgical procedure was defined by a binary variable taking the modalities: "failure" if the number of sites with score "1" was greater than or equal to 3 out of 6; "success" in all other cases.

2.4. Statistical analysis

Data were compiled in a Microsoft Excel spreadsheet. Statistical analysis was performed with RStudio software v1.4.1103 (RStudio-Team) in R language v4.0.2 (RCore Team). Categorical data were reported as proportions and counts. χ^2 Tests were performed for comparison. Univariate and multivariate logistic regression analyses were performed. Covariates from the univariate analysis were entered into top-down stepwise multivariate regression analyses. A p value $\leq$ 0.05 was considered significant.

3. Results

3.1. Descriptive analysis of the sample

3.1.1. Characteristics of surgical procedures

The study included 124 SABG surgeries with BG 45S5 performed in 97 patients. A total of 22 patients were excluded: 16 had no control CBCT scans at 1 year, and for 6 patients, the information was unusable (6 of the 6 sites were "NA"). This left a sample of 102 procedures in 79 patients, performed by two experienced operators with a ratio of 3:7. Of this sample, 95 (93.1%) procedures were a primary SABG procedure and 7 (6.9%) were a revision. The procedures were performed at a mean age of 9.32 ± 3.09 years and carried out 34 times in girls and 68 times in boys (i.e., 33.3% and 66.7%, respectively). In 96 (94.1%) procedures, the cleft was isolated, and 85 (83.3%) patients had no family history. The majority of the procedures were performed under general anesthesia on an outpatient basis (96 cases; 94.1%) with suprazygomatic block for 82 cases (80.4%). The majority of cases received 1 cm^3 of Bioglass (99 cases; 97.1%) and the remaining cases required 2 cc. These procedures were almost all under antibiotic coverage (99 cases; 97.1%). Three procedures (2.9%) developed a postoperative infection. The mean age of the follow-up CBCT for this study was 1.58 ± 0.94 years.

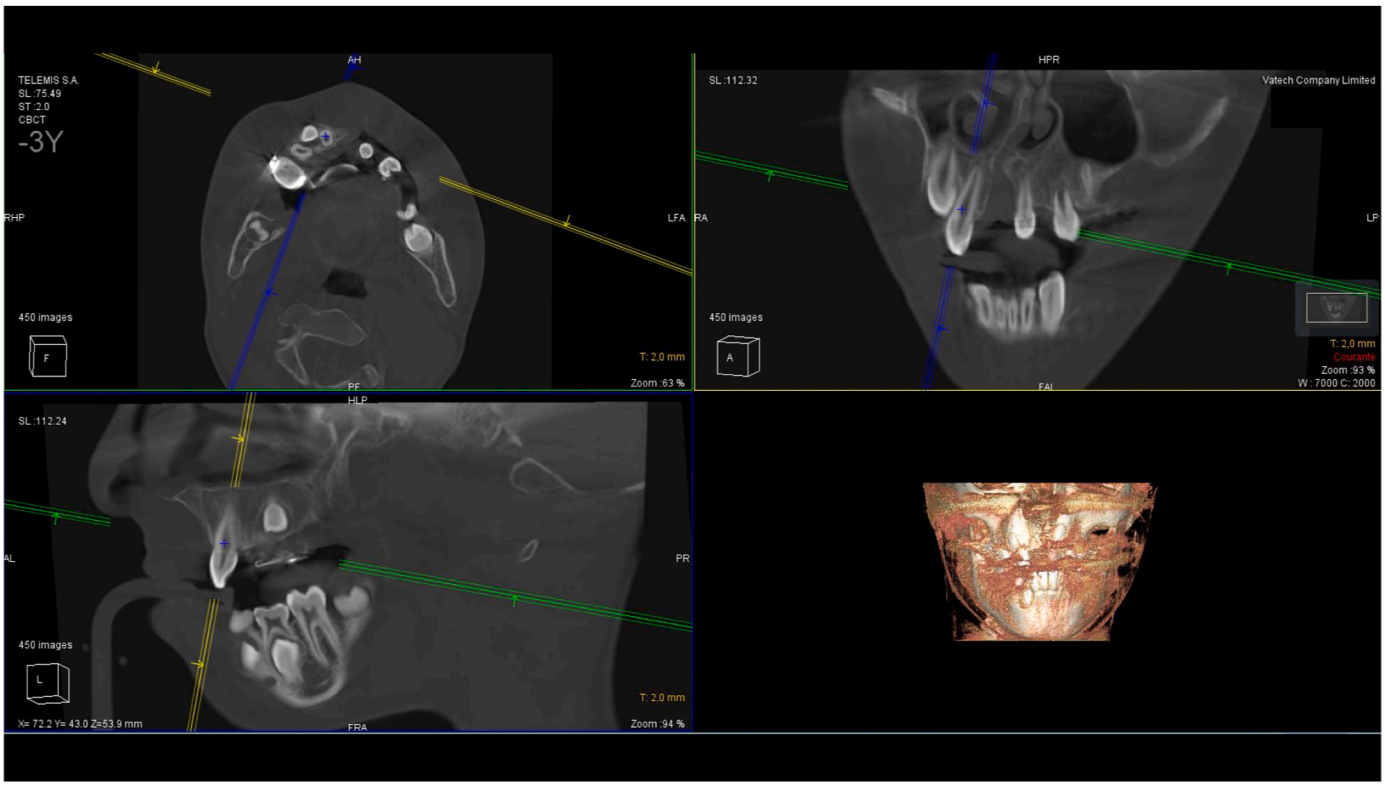

Fig. 1. Positioning of 2-mm-thick CBCT slices in vertical and horizontal dimensions.

3.1.2. *Characteristics of operated clefts*

The majority of the surgeries involved unilateral clefts (57.8%) located on the left in 66 (64.7%) cases. They involved 49 (48.0%) unilateral CLP, 4 (3.9%) bilateral CL, 10 (9.8%) unilateral CL, 4 (3.9%) asymmetrical bilateral CLP and 35 (34.3%) symmetrical CLP.

An orthodontic preparation phase preceded 96 (94.1%) of the surgeries. For all of them and to avoid contraction of the fragments after the graft, the patients were fitted with a Hawley plate or a *trans*-palatal arch or quad'helix after the surgery. In 40 (39.2%) patients, the maxillary lateral incisor was agenesic. In contrast, 15 (14.7%) cases had supernumerary teeth or odontomas near the cleft. 36 (35.3%) cases had a primary tooth in the cleft path. Moreover, in 12 (11.8%) surgeries, a tooth near the cleft was extracted.

Oral-nasal fistulas were visible before the operation in 51 cases (50.0%). They were either closed before the procedure (3 cases; 5.9%) or during the procedure (48; 94.1%). Also, two fistulas (3.9%) of incidental discovery were closed during surgery, leading to 53 closure procedures.

3.1.3. *Assessment of surgical success rate*

First, each rater read 11 CBCT scans twice, 1 month apart. Intra-rater reproducibility ranged from 0.77 to 0.89. Intra-group reproducibility by the Fleiss kappa was 0.71. The pair with the best reproducibility (0.85) then evaluated all CBCT scans.

At the end of the inter-examiner consensus, 9 (1.52%) evaluated sites had artifacts, 8 in the horizontal dimension (1 apical, 2 medial, 5 cervical) and 1 in the vertical (cervical). These were found in 5 patients, respectively 2, 2 and 1 subject with 1, 2 or 3 missing values. For further analysis, the score "1" was assigned to the artifactual sites.

Scores 2 and 3 were most often attained in both dimensions, with one exception in the cervical third, with the minimum score (1) most present in the horizontal dimension (Table 1).

Using the definition of surgical outcome described previously, 82 (80.4%) procedures were successful and 20 (19.6%) were failures. More precisely, among the 95 first operative steps, 77 (81.1%) were successful and among the 7 revision surgeries, 5 (71.4%) were successful ($p = 0.6$).

Considering the orthodontic aspect and the possibility of moving teeth within the graft zone, only 59 of the patients in the cohort were now old enough to receive braces. Of these, 39 (66.1%) are currently being treated without any particular complication regarding tooth displacement.

3.2. *Univariate analysis of factors impacting success*

Initially and after exclusion of the only case with a median cleft

Table 1
Distribution of scores on the six sites evaluated on CBCTs at 1 year after secondary alveolar bone grafting (SABG) in the vertical and horizontal dimensions at the apical, medial, and cervical thirds. Unreadable or artifactual sites were given a score of 1.

Score	Vertical				Horizontal			
	1, N = 76[a]	2, N = 129[a]	3, N = 101[a]	p-value[b]	1, N = 84[a]	2, N = 149[a]	3, N = 73[a]	p-value[b]
Thirds				<0.001				<0.001
Apical	17 (16.7%)	39 (38.2%)	46 (45.1%)		18 (17.6%)	52 (51.0%)	32 (31.4%)	
Medial	16 (15.7%)	47 (46.1%)	39 (38.2%)		16 (15.7%)	61 (59.8%)	25 (24.5%)	
Cervical	43 (42.2%)	43 (42.2%)	16 (15.7%)		50 (49.0%)	36 (35.3%)	16 (15.7%)	

[a] n (%).
[b] Pearson's Chi-squared test.

(surgical success), a univariate analysis was conducted to explain a successful outcome of SABG using the following factors: sex, laterality of the cleft, type of cleft (transformed into "cleft lip/alveolar" or "cleft palate"), syndromic context, surgical step, family history, number of teeth, extraction of teeth, repair of a fistula, and stage of dentition (Table 2). The univariate analysis approach reported no parameters affecting success.

3.3. Multivariate analysis of factors affecting success

Initially, a complete model was used to conduct the multivariate analysis (Fig. 2). Factors predictive of radiographic success were (1) mixed dentition stage (odds ratio [OR] = 7,30, IC 1,67–42,5, p = 0,024); (2) non-syndromic status (OR = 20,7, IC = 1,48–393, p = 0,024); and (3) female sex (OR = 4,88, IC = 1,26–23,2, p = 0,021). The Hosmer-Lemeshow test concluded that the model had good predictive value ($c^2 = 10.55$; p = 0.23).

In a second step, the stepwise top-down selection technique was used to simplify the explanatory model, generating a reduced model (p = 0.74). Only the factors dentition stage, sex, and syndrome were retained in this model. It had an Akaike information criterion (AIC) of 100.33 versus 112.32 for the full model. For this model the Hosmer-Lemeshow test reached ($c^2 = 1.10$; p = 0.998).

4. Discussion

The anterior iliac crest is the preferred donor site for SABG (Schaaf et al., 2010; Gjerde et al., 2020). However, postoperative pain is reported in 38% of cases. Some patients report walking difficulties, haematomas, paresthesias and infections (Eufinger and Leppänen 2000; Nkenke et al., 2004; Swan and Goodacre 2006; Hernigou et al., 2014; Jessop et al., 2015; Brudnicki et al., 2019). This has led to 4.3 ± 3.5 days of hospitalization and 20.2 ± 18.5 days of work absence according to one report (Gjerde et al., 2020). Ultimately, it degrades patients' quality of life (Reissmann et al., 2013).

Table 2
Univariate regression analysis for successful 1-year radiographic outcome of secondary alveolar bone grafting (SABG).

Parameters	N	Event N	OR[a]	95% CI[a]	p-value
Sex	101				0.16
Female		29	–	–	
Male		52	0.45	0.12, 1.36	
Laterality of the cleft	101				0.97
Right		28	–	–	
Left		53	1.02	0.35, 2.79	
Type of cleft	101				0.56
Cleft lip		12	–	–	
Cleft lip and palate		69	0.64	0.09, 2.63	
Syndrom	101				0.086
No		78	–	–	
Yes		3	0.22	0.04, 1.26	
Surgical step	101				0.56
#1		76	–	–	
#2		5	0.59	0.12, 4.36	
Family history	101				0.68
No		68	–	–	
Yes		13	0.76	0.23, 2.99	
Number of teeth	101				0.59
Normal		35	–	–	
Lateral incisor agenesis		33	1.48	0.52, 4.46	
Supernumerary tooth or odontoma		13	2.04	0.46, 14.4	
Tooth extraction	101				0.64
None		72	–	–	
Per-operative		9	0.71	0.19, 3.44	
Oral-nasal fistulas reparation	101				0.80
Pre-operative		2	–	–	
None		37	1.90	0.08, 21.9	
Per-operative		41	2.28	0.10, 26.4	
Stage of dentition	101				0.20
Mixed		33	–	–	
Adolescent		12	0.36	0.07, 1.75	
Temporary		36	0.36	0.09, 1.16	

[a] OR = Odds Ratio, CI = Confidence Interval.

The benefits of using a biomaterial are multiple: no donor site, no limited quantity of material (Janssen et al., 2014), reduction in operating time and the ambulatory nature of general anesthesia. The use of BG 45S5 makes the surgical protocol studied here completely innovative. This synthetic material is a silicate network (45 wt% SiO2) incorporating 24.5 wt% Na2O, 24.5 wt% CaO, and 6 wt% P2O5 (Hench 2006). It binds rapidly to bone and promotes osteoblasts differentiation. Its dissolution of fluids is responsible for the creation of a suitable pH for the nucleation of hydroxyapatite (Sanders and Hench 1973). BG 45S5 also has an inhibitory effect on the activity of osteoclasts (Abstracts of the 35th European Symposium on Calcified Tissues, 2008). This biochemistry makes it an excellent candidate for surgical applications with a limited cost (Graillon et al., 2018; Al Tamami et al., 2020). One of the problems with this type of substitute is its granular form, which does not ensure good mechanical properties. Orthodontic follow-up is therefore necessary.

The main objective of this study was to establish the success rate of SABG with BG 45S5. As this technique is not yet widely used, a retrospective analysis was chosen because it is faster, more economical and easier to implement. This primary objective requires a reliable outcome measure. Although the clinical criterion of success is the placement of teeth in the operated area, a radiographic evaluation is imperative, in particular to argue the need for a surgical revision. The evaluation of the success of the graft have been discussed for a long time, reflecting its complexity due to the radiographic technique and the growth of patients (Kamperos et al., 2020; Shaheen et al., 2022; Stasiak et al. 2021; Chen et al., 2021). The Bergland two-dimensional classification method is historically the most widely used (Bergland et al. 1986; Witherow et al., 2002; Hynes and J Earley, 2003). It gives excellent results (majority of graft height >50% of the cleft height) (Newlands 2000; Matic and Power 2008). However, it does not take into account the sagittal dimension where most of the resorption takes place (Dissaux et al., 2016). Three publications point out that 2D evaluation overestimates results (Van der Meij et al., 2001; Hamada et al., 2005; Feichtinger et al., 2008). These findings make three-dimensional diagnostics an appropriate tool for this purpose. Specifically, cone-beam computed tomography (CBCT) is preferred over computed tomography (CT) because of its lower radiation dose (Amirlak et al., 2013). The evaluation of a percentage or volume of reconstruction during SABG remains extremely complex: first, because percentage ratios do not provide a spatial assessment of the architecture of the bone bridge (Zhang et al., 2012; Dissaux et al., 2016; Stasiak et al. 2019; Liu et al., 2020); second, because this type of evaluation requires defining anatomical landmarks, which are non-standardized criteria and delicate to implement in a growing patient (Feng et al., 2017). Based on these findings, our study replicated the Suomalainen protocol (Suomalainen et al., 2014). It allows the precise localization of the graft in three dimensions. It has been used in a recent study (Padwa et al., 2022). The evaluation was conducted on CBCT taken on average 1 year after surgery as recommended in the literature (Stasiak et al. 2019).

Taking all of these elements into account, the success rate of SABG varies from 32% to 95%. This wide variability is due to the different definitions of success (Tan et al., 1996; Kumar et al., 2017). It is also due to the length of follow-up. Studies conducted in the short term, less than 1 year, show a higher success rate. A study using the same protocol showed a 94% success rate (Padwa et al., 2022). According to a 2022 meta-analysis, the total percentage of SABG success in the follow-up period of at least 1 year according to the Bergland index was 76.52% and the total percentage of bone filling after 1 year and according to CBCT was approximately 63.38% (Jahanbin et al., 2022).

The protocol with BG 45S5 led here to a success rate of 80%, higher than that found in the literature for this type of procedure with autogenous graft. Moreover, this score should be weighted by the fact that the

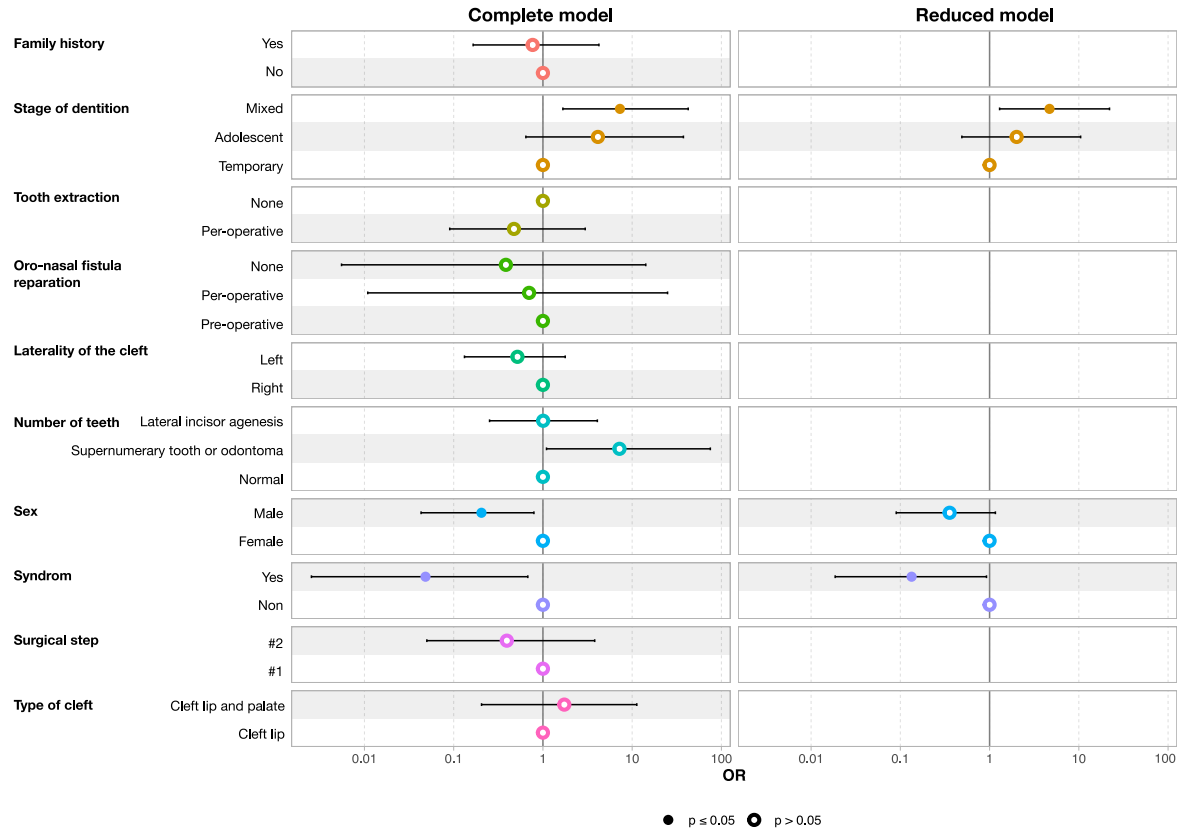

Fig. 2. Complete multivariate analysis model and reduced model using the step-down selection technique for successful 1-year radiographic outcome of secondary alveolar bone grafting (SABG).

artifactual sites were given a score of "1" by default, which leads to an underestimation of the success rate. In addition, the very low complication rate is significantly lower than reported with autografts. Only one other study used the same surgical protocol. In a smaller sample (58 patients) and with an assessment of bone continuity on CBCT at 1 year by linear measurements, the success rate was lower than ours (Graillon et al., 2018). From an orthodontic point of view, the young age of the cohort meant that no reliable long-term conclusions could yet be drawn. However, the first 39 cases showed that it was possible to move teeth through the grafted area.

Second, we sought to establish the parameters influencing the outcome. A univariate and then multivariate approach was conducted. It is regularly used in medicine for these purposes (Bell et al., 2014; Mishra et al., 2021). Nevertheless, a preliminary description of the sample is essential. Concerning the sex of the patients, 66.7% of the interventions concerned male patients, which is comparable that in to a systemic review (Ma et al., 2021). The mean age of 9.32 years at the time of surgery is consistent with another study (Chen et al., 2021). The majority of the clefts were located on the left, in agreement with the literature. One of the particularities here is the high proportion of bilateral clefts (42.2%), since the incidence of unilateral clefts is normally double that of bilateral ones (Martelli-Junior et al., 2007). As in the literature, clefts were associated with a syndrome in 5.9% of cases (Prevalence at Birth of Cleft Lip with or without Cleft Palate, 2011). Van der Woude syndrome was the most common in this sample. It is the leading cause of syndromic cleft lip and palate. It associates clefts, fistulas of the lower lip and sometimes hypodontia (Ural et al., 2019).

The univariate analysis approach reported no parameters influencing surgical success. The data were then included in a multivariate model. The syndromic context was then shown to be an unfavorable element for the success of SABG. The literature on this subject is not abundant. The vast majority of studies exclude patients with syndromes (Chetpakdeechit et al., 2021; Thiruvenkatachari et al., 2021). Concerning the Van der Woude syndromes, a recurrent inflammatory context complicate the care (Dissemond et al., 2004; Etöz and Abdullah, 2009). Another parameter that emerged from this approach was the stage of dentition reached at the time of surgery. The stage of mixed dentition, that is, after evolution of the permanent lateral incisor but before eruption of the canine, offered the best prognosis (Ozawa et al., 2007; Zhang et al., 2012; Borba et al., 2014). The eruption of the lateral incisor would initiate osteoinductive activities resulting in better bone formation and less resorption (Ozawa et al., 2007). In parallel, rapid closure of the space and eruption of the canine through the grafted area were associated with maintenance of the thickness and width of the bone volume (Feichtinger et al., 2006, 2007; Elhaddaoui et al., 2017; Miller et al., 2010). A three-dimensional analysis showed a higher success rate of bone grafting around 5 years of age (Dissaux et al., 2016). This age is younger than those in the study cohort. With the first ones dating back to 2015, orthodontic expansion was complex. The age of surgery is decreasing as advances in orthodontics make it easier to manage very young patients. The impact of the adjacent tooth is essential and directly influences the success rate of the bone graft, regardless of age (Feichtinger et al., 2006, 2007; Pinheiro et al., 2020). Finally, male sex was found to be a factor predictive of failure. Our hypothesis is that young boys tend to have poorer oral hygiene control and inflammatory conditions around the graft. Girls tend to brush their teeth more often and to have better oral hygiene and dental care (Vallejos-Sánchez et al., 2008; Angelopoulou et al., 2015; Costa et al., 2022). Although we did not collect this parameter from patients, several studies have associated poor hygiene with SABG failure (Jabbari et al., 2015; Lundberg et al., 2021; Chalien et al. 2022).

Despite the reported success rate of about 80%, the limitations of this

study should be noted. First of all, radiographic success does not predict clinical success, especially the good evolution of the teeth in the grafted areas with a healthy aspect of the periodontal mucosa. Secondly, the histo-physiology of the newly formed bone remains unknown. Further work in this area is required.

5. Conclusion

We can affirm that the innovative approach to clefts using BG 45S5 substitute offers a very interesting success rate, greater than 80%. A multivariate analysis retained the following predictive factors for a favorable outcome: mixed dentition stage, absence of syndromic context, and female sex. The earlier the SABG was performed, the more favorable the outcome, always before the evolution of the permanent canines. To reinforce these good results, we believe it is essential to implement appropriate oral hygiene measures.

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The authors have the following to disclose: Each of the authors declares the absence of any link of interest with the content of this article. The commercial product used is the GlassBone marketed by the company Noraker (France).

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ORIGINAL ARTICLE

Cone Beam-CT-Based Bone Volume Assessments of Alveolar Synthetic Bone Graft GlassBONE™ in Cleft Lip and Palate Patients: A Retrospective Study

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Abstract

Background Clefts of the lip and palate (CLP) are facial deformities that require multiple surgical procedures during childhood. One of these steps consists of filling the alveolar space with bone graft, traditionally removed from the iliac crest. However, this procedure could be invasive in children.

Aim Here, we aimed to evaluate the outcomes of GlassBONE™ graft, a bioactive glass used as a bone substitute, as an alternative to the deleterious autologous bone graft in children.

Materials & methods Retrospective monocentric study with 17 children aged 7.5 ± 2.2 yo [3.8–13.3 yo] carrying CLP. This technique has been established at La Timone Children hospital (Assistance Publique - Hôpitaux de Marseille) since 2011. Clinical (scar, graft rejection and periodontal status) and radiological (both panoramic radiographs and cone beam-CT) follow-up was conducted one year after the graft. The primary outcome was the reduction of the cleft volume, and secondary was the eruption of the adjacent tooth through the graft.

Results GlassBONE™ permitted a significant reduction in the cleft volume by 42.4 ± 27.7% [0.6–81.1%] ($p < 0.0001$), corresponding to a filling of 57.6 ± 27.7% of the alveolar cleft. GlassBONE™ is well tolerated, ensuring satifactory clinical results (improvement in both scar and periodontal coverage), as well as the physiological evolution of the germs through the biomaterial. GlassBONE™ appears particularly suitable for small volumes, and we were able to determine a minimum volume of approximtely 0.259 + / − 0.155 cc required for a successful bone fusion.

Conclusion The bioactive glass GlassBONE™ could be safely used in children with small CLP cases, providing satisfactory clinical and radiological results.

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Keywords Bone transplantation · GlassBONE™ · Cleft lip · Cleft palate · Oral surgery

Abbreviations

Bioglass 45S5 or calcium sodium phosphosilicate	Bioactive glass specifically composed of 45 wt% SiO_2, 24.5 wt% CaO, 24.5 wt% Na_2O, and 6.0 wt% P_2O_5
BLMPC	Bilateral labio-maxillo-palatine cleft
CBCT	Cone-beam CT
CLP	Clefts of the lip and palate
ESBG	Early secondary alveolar bone graft
GlassBONE™	Bioglass 45S5 or calcium sodiuù phsophosilicate
ICC	Intraclass correlation coefficient
LMC	Labial-maxillary cleft
LMPC	Labio-maxillo-palatine cleft
mths	Months
OP	Occlusion plane
PROMs	Patient-reported outcomes measures
RCT	Randomized controlled trial
ROI	Region of interest
SD	Standard deviation
VOLpost	Postoperative volume
VOLpre	Preoperative volume
wt	Weight
yo	Year-old
yrs	Years

Units

%	Percent or percentage
µm	Micrometer
cm^3	Cube centimeter
d	Day
min	Minute
mm	Millimeter

Introduction

Clefts of the lip and palate (CLP) are the most common congenital anomalies affecting the craniofacial complex [1, 2]. Alveolar cleft repair remains a surgical challenge in the overall management of labio-alveolar-palatal clefts due to its impact on facial growth and dentition development [3, 4]. The gold standard [5–10] for alveolar cleft grafting remains autogenous bone grafts from the iliac crest, typically performed between 6 and 12 years during the mixed dentition stage before canine eruption. This technique relies on autologous immunocompatible bone cells, which promote the phenomenon of osteogenesis. However, it is an invasive procedure that requires hospitalization [11, 12] and can cause postoperative discomfort, including temporary or chronic pain and walking difficulties.

Recently, a less invasive technique has been introduced to reduce postoperative morbidity, notably the early secondary alveolar bone graft (ESBG) with GlassBONE™ (Noraker, Lyon, France), a bioactive glass 45S5 used for alveolar cleft closure in children with labio-alveolar-palatal clefts [13–17]. GlassBONE™ is a 100% synthetic bone substitute that belongs to the family of resorbable bioactive glass ceramics. Bioactive glasses are biocompatible, bioconductive, and absorbable [18]. ESBG in patients with CLP restores maxillary bone continuity, ensuring its stability, closing alveolar fistulas, facilitating its evolution, correcting dental positioning, and enabling orthodontic and surgical movements [19]. Initially performed during the mixed dentition stage between 6 and 10 years, ESBG is now conducted earlier, between 3 and 6 years, to normalize the maxillary arch before the eruption of the permanent teeth, promote tooth eruption trough the graft, secure and enhance orthodontic movements by improving bone support, and close a residual oro-nasal fistula.

Materials & Methods

Experimental Design and Study Population

This retrospective monocentric study included patients aged between 4 and 10 years who had undergone early secondary alveolar grafting (ESBG) with Glassbone™ from January 2011 to December 2015 (a period of 5 years). Procedures were conducted at the Pediatric Plastic Surgery Department of the University Hospital of La Timone Children (Assistance Publique - Hôpitaux de Marseille). The primary evaluation criterion was the reduction in the volume of the cleft, as assessed by preoperative cone-beam CT (CBCT) and CBCT one-year after the operation. The second evaluation criterion was the eruption of the adjacent tooth through the graft.

Surgical Procedure

Bone Substitute

The bone substitute used in this retrospective study was the GlassBONE™, a synthetic resorbable bioactive glass 45S5 ceramic with a grain size of 0.5 mm.

Surgical Steps

Alveoloplasty with the placement of GlassBONE™ was performed under general anesthesia following the Troxell mucoperiosteal flap technique [3]. Depending on the volume of the alveolar cleft, 0.5 to 2 cm^3 of GlassBONE™ mixed with patient's blood was grafted. The same surgical protocol was followed by all four surgeons in the department. In cases of bilateral cleft (4 in total), the alveolar closure of each cleft was performed independently, with a monthly interval for two children and during the same procedure for the other two. The average duration of the surgical was 30 min.

Postoperative Medications and Recommendations

All the patients were discharged the day of the surgery (outpatient basis). Antibiotherapy was continued for 8 days (Amoxicillin + Clavulanic acid). Postoperative pain was managed with level 1 (paracetamol) or level 2 (tramadol) analgesics in case of severe pain. A mixed diet was recommended for 15 days. Mowing was prohibited for 15 days, but the children were allowed to perform nasal washes three times a day. Oral hygiene was prescribed (surgical toothbrush, chlorehexidine mouthwash to promote healing). The children were then scheduled for follow-up appointments at 15 days and 2 months postoperatively. Generally, an eight-day school absence and a 15-day restriction from sports activities were recommended.

Data Collection

Baseline Characteristics

The following parameters were recorded: (1) age, (2) type of clefts (single labial-maxillary cleft (LMC); labio-maxillo-palatine cleft (LMPC); bilateral labio-maxillo-palatine cleft (BLMPC)), (3) dental agenesis, (4) genetic syndrome, (5) bone graft side (right/left), and (6) previous orthodontic treatment (maxillary expansion).

Clinical and Parodontal Assessments

The scar was clinically evaluated at a distance from the intervention by the team of plastic surgeons and maxillofacial surgeons during the multidisciplinary consultation. The recurrence of oral fistula was also clinically evaluated at a distance, as well as the occurrence of partial or total exposure of the graft and the rate of graft failure due to infection or graft rejection. The eruption of teeth through the graft or subsequent to orthodontic tooth movement within the bone graft area was also assessed. Using a periodontal probe, we measured the depth of periodontal pockets, the height of gingival recession if present, as well as the attached gingival height for the teeth at the edge of the cleft and for the contralateral teeth. Oral hygiene was also assessed visually using endobuccal photographs.

Radiological Assessments

X-rays (orthopantomograms) were used to determine the alveolar space according to the Chelsea classification described by Witherow et al. [20]. For bilateral clefts, each side was studied separately.

CBCT imaging (Planmeca® Helsinki, Finland) was conducted at baseline (preoperatively) and 1 year after surgery in each patient to assess the following parameters: (1) preoperative cleft volume (cm^3) and (2) postoperative cleft volume (cm^3). Additionally, the percentage of cleft closure was calculated.

Two senor operators carried out the measurements. The measurement methods were as follows: The percentage of bone filling of the cleft was determined according to the method described by Linderhup [21] on DICOM format files using Osirix7.5® software. The volume of the cleft was determined section by section using the normal opposite site by symmetry. For bilateral clefts, each side was studied independently. Thus, the contour of the cleft was manually delineated by the operator, the region of interest (ROI) tool using the "closed polygon" mode and the "CLUT: Black/White Inverse" mode, which increases contrast to clearly differentiate between ossified or non-ossified areas. The "Volume Calculation" mode added up all the areas and multiplied it by the section thickness (ranging 150 µm to 1 mm), resulting in the final cleft volume expressed in cm^3. The limits of the clipping of the cleft on the pre- and postoperative CBCT were defined as follows: *upper limit*, the floor of the contralateral nasal fossae; *lower limit*, the vertex of the contralateral alveolar ridge; *in vestibular and palatine*, the limits were determined by reconstructing the ideal contour of the side arch reached by symmetry on the healthy side. The percentage of bone filling was calculated using the following formula: $[(VOLpre–VOLpost)/(VOLpre)] \times 100$. VOLpre = preoperative volume, VOLpost = postoperative volume.

The distance between the incisal edge of the central incisor (and lateral if present) and the canine point at the edge of the occlusion plane cleft on sagittal and coronal sections was quantified using the Walker's method [22]. Hence, we objective the progression of the teeth through the GlassBONE™, to ensure that it does not obstruct tooth eruption. When the occlusion plane was cut on CBCT, the top of the alveolar ridge served as a reference point. On the Osirix7.5® software, in "Maximum Intensity Projection" mode and the "thick cut" slider set to maximum, contrast was modulated to provide a clear definition of dental germs and their contours for precise marking of the canine tip and incisor edges, as

well as an extended visualization of the occlusion plane. Once these adjustments were made, the occlusion plane (OP) was drawn in "Length" mode and we measured the perpendicular distance to the OP from the canine point and the incisor edges of the teeth at the edge of the cleft. Inter-rater and intra-rater tests were performed to assess reliability of measurements (ICC and kappa coefficients).

Sample Size Calculation

The primary outcome of this study was the relative reduction in cleft volume after surgery, expressed as a percentage, specifically as $Y = [(\text{preoperative cleft volume} - \text{postoperative cleft volume})/\text{preoperative cleft volume}] \times 100$. Under the null hypothesis (H0), the mean μ of the relative reduction in cleft volume after surgery is zero (H0: $\mu = 0$), and under the alternative hypothesis, the cleft volume is expected to decrease after surgery, resulting in a positive relative reduction in cleft volume (H1: $\mu > 0$). To estimate the required sample size for the study, we aimed to detect a relative reduction in cleft volume μ of at least 20%. We set the standard deviation (SD) of variable Y at 30%, the significance level at 5%, and the power at 80%. Based on these assumptions, the power calculation showed that a minimum of 14 patients would be needed for the study using a one sample one-sided Student's t test. Finally, 17 patients were included in the study.

Statistics

The results were expressed as means and standard deviations (SD) for quantitative variables and as frequency tables for categorical findings. The postoperative relative reduction (%) in cleft volume was assessed using a one-sample one-sided Student's *t* test, with significance set at the 5% critical level. Calculations were performed using SAS version 3.4 (SAS Institute, Cary, NC, USA).

Results

Pediatric Population

Patient characteristics are presented in Table 1. The patients had an average age of 7.5 ± 2.2 years [ranging from 3.8 to 13.3 years] at the time of the surgery. Among them, 4 children had bilateral labio-maxillo-palatine clefts (BLMPC), 6 children had a single labial-maxillary cleft (LMC), and 7 children had a labio-maxillo-palatine cleft (LMPC). Nineteen ESBGs with GlassBONE™ were performed by the four surgeons in the department, following the same surgical procedure. Twelve patients had previously undergone orthodontic or orthopedic management to normalize the transverse direction, two patients had syndromes associated with cranio-facial abnormalities, and seven patients had agenesis of central or lateral incisors. No patients were lost to follow-up (Fig. 1).

Table 1 Study patient characteristics ($n = 17$)

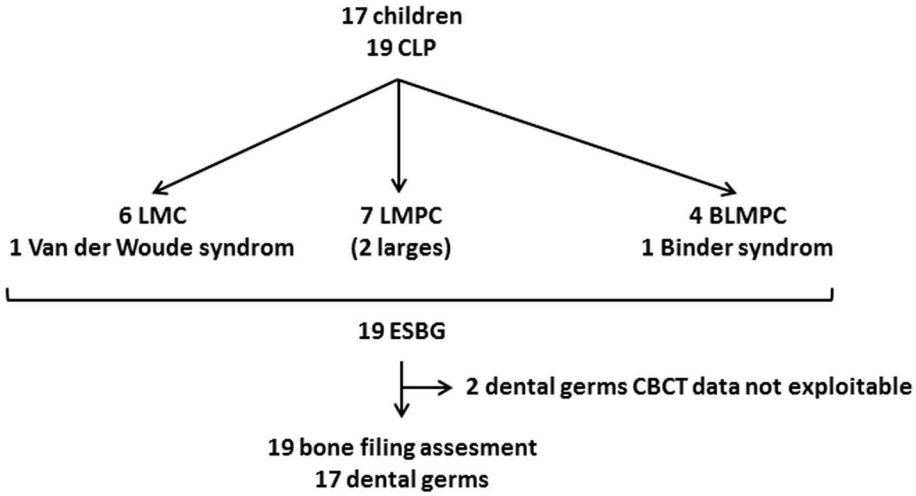
Variable	Category	Number (%)
Age (years)	Mean ± SD	7.5 ± 2.2
Cleft type	BLMPC	4 (23.5)
	LMC	6 (35.3)
	LMPC	7 (41.2)
Side	Right	8 (47.1)
	Left	7 (41.2)
	Both	2 (11.8)
Previous orthodontic treatment	Yes	5 (29.4)
	No	12 (70.6)
Dental agenesis	No	10 (58.8)
	Yes	7 (41.2)
	12	2 (28.6)
	22	3 (42.9)
	12 + 22	1 (14.3)
	21 + 22	1 (14.3)
Syndrome	No	15 (88.2)
	Yes	2 (11.8)
	Binder	1 (50.0)
	Van der Woude	1 (50.0)

Clinical and Parodontal Assessments

The gingival scar was satisfactory in 63% of patients ($n = 14$) (Fig. 2A), while 37% of the patients ($n = 7$) had an unsatisfactory scar, with varying degrees of alveolar space retraction (Fig. 2B). One child with BLMPC had a satisfactory scar on one side and an unsatisfactory scar with significant alveolar space retraction on the other side (Fig. 2C). Two children experienced a recurrence of oro-nasal communication. For the first child, oral hygiene needed improvement (presence of dental plaque and mild gingivitis), but it did not pose a significant problem. Unfortunately, the second child, who had BLMPC, experienced a recurrence of communication despite proper oral hygiene (Fig. 2D). No graft losses due to postoperative infection or partial/complete exposure of the graft were reported.

In all patients surveyed, whether in mixed or permanent dentition, we observed greater pocket depth at the level of the teeth at the edge of the cleft, with an average depth of 4.1 mm [ranging from 3 to 5 mm]. Only three patients (22%)

Fig. 1 Flow chart



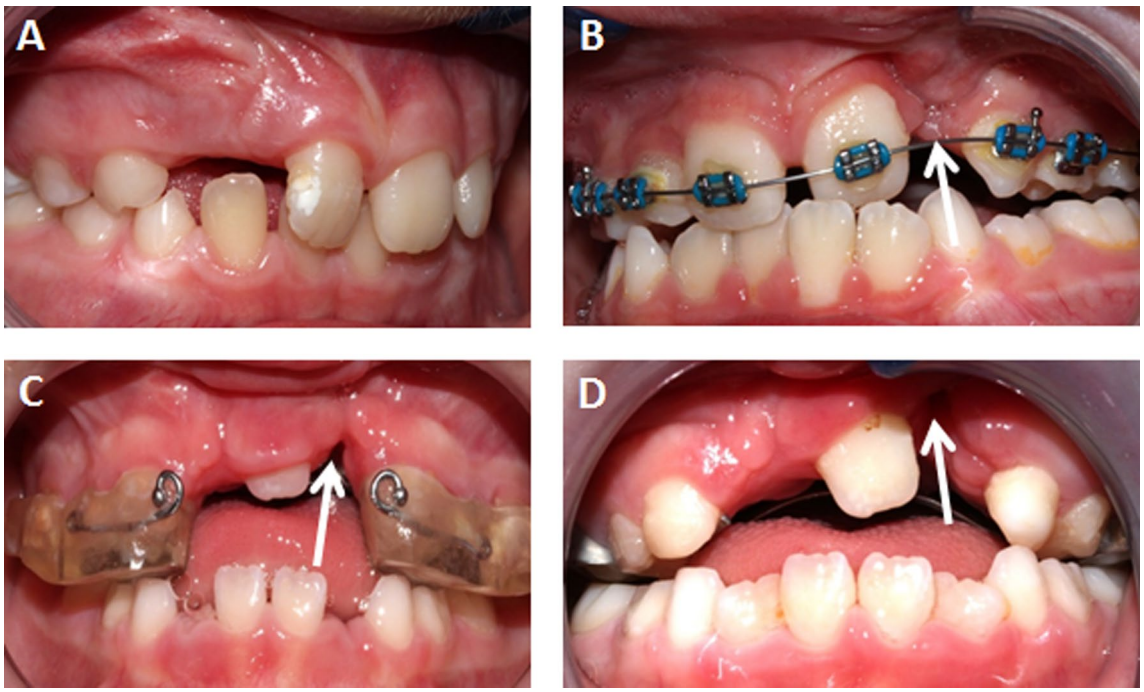


Fig. 2 Endobuccal pictures. **A** Satisfactory gingival scar after bone graft. **B** Unsatisfactory scar (arrows). **C** Satisfactory scar on the right side, unsatisfactory scar on the left side (arrow) with a significant gingival retraction associated to **D** a recurrence of the oro-nasal fistula in a patient with a bilateral CLP

had a gingival recession at the level of the incisors at the edge of the cleft, with measurements of 2 mm for two cases and 1 mm for one case. 60% of the children had a low height of keratinized gingiva, which was associated with the vestibular mucosa near the neck of the teeth at the edge of the cleft. More than half of children (55%) exhibited a poor oral hygiene, characterized by the presence of dental plaque and varying degrees of gingivitis.

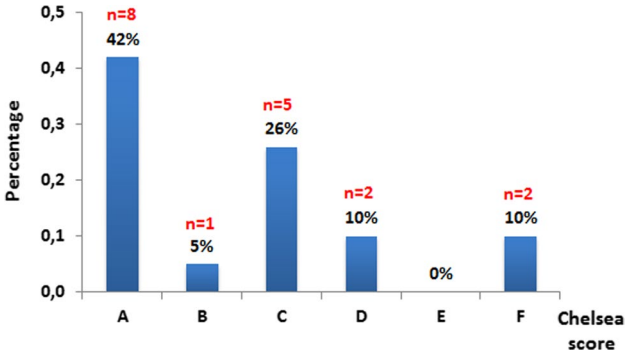


Fig. 3 Distribution of grafted cleft based on Chelsea score

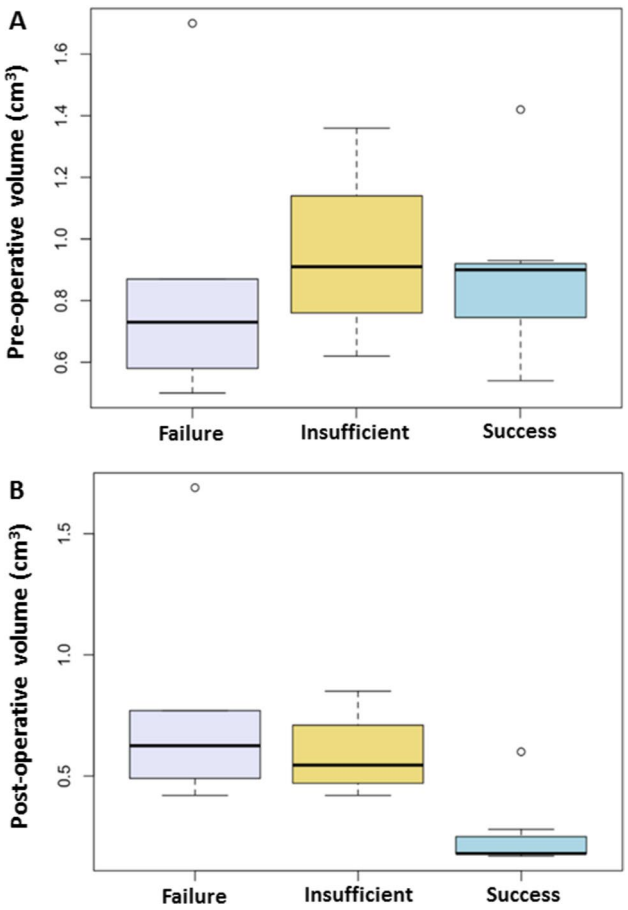


Fig. 4 **A** Boxplot distribution of preoperative cleft volumes according to postoperative results. **B** Boxplot distribution of the volumes of the postoperative clefts according to the operative results. °=significative ($p<0.05$)

Radiological Assessments

Chelsea Score

For bilateral cleft, each side was independently studied; resulting in a total of 19 grafted alveolar clefts being monitored. According to Chelsea's classification, the distribution was as follows: 42% ($n=8$) had an A score, 5% ($n=1$) had a B score, 26% ($n=5$) had a C score, 10% ($n=2$) had a D score, and 10% ($n=2$) had an F score (Fig. 3). No E scores were recorded. Considering A and C scores as indicators of surgical success, the final success rate was 68% ($n=13$).

In 73% ($n=14$) of the grafted clefts, the evolution of the germs through the graft was observed, while in the remaining five grafted sites, the evolution of germs could not be observed. It was for all the lack of evolution of the germs of the canines. In a grafted bilateral cleft, it was the absence of the germs of a lateral incisor.

Bone Filing with CBCT

The osseous volumes obtained before and after the operations are presented in Table 2. The preoperative and postoperative cleft volumes observed for the 17 patients were 0.89 ± 0.33 cm^3 and 0.52 ± 0.37 cm^3, respectively (Fig. 4A &B). The mean relative reduction in cleft volume was $42.4\pm27.7\%$ [ranging from 0.6% to 81.1%] ($p<0.0001$), corresponding to a filling of $57.6\pm27.7\%$ of the alveolar cleft.

Dental Germs

Measurements using the Osirix® software could not be recorded for two patients: In the first patient, the CBCT was readable, but the measurements were not feasible; in the second patient, the field was too small, preventing the determination of the free edge of the incisors or molars and, consequently, the drawing of an occlusion plane (Fig. 5). Regarding the measurements made on the sagittal sections, we observed the evolution of dental buds through the GlassBONE™ graft in 87% patients ($n=14$), as indicated by a decrease in the

Table 2 Clinical evaluation (scar quality, recurrence of the oro-nasal fistula, and signs of reject)

Variable	*N*	Mean	SD	SE	Min	*Q*1	Median	*Q*3	Max	Student *p*-value	Wilcoxon *p*-value
Preoperative cleft volume (cm^3)	17	0.89	0.33	0.08	0.5	0.6	0.87	0.9	1.7		
Postoperative cleft volume (cm^3)	17	0.52	0.37	0.09	0.2	0.2	0.49	0.6	1.7		
Cleft volume close %	17	57.60	27.69	6.72	18.9	33.3	61.96	84.0	99.4	<0.0001	<0.0001
Cleft volume %	17	42.40	27.69	6.72	0.6	16.0	38.04	66.7	81.1	<0.0001	<0.0001

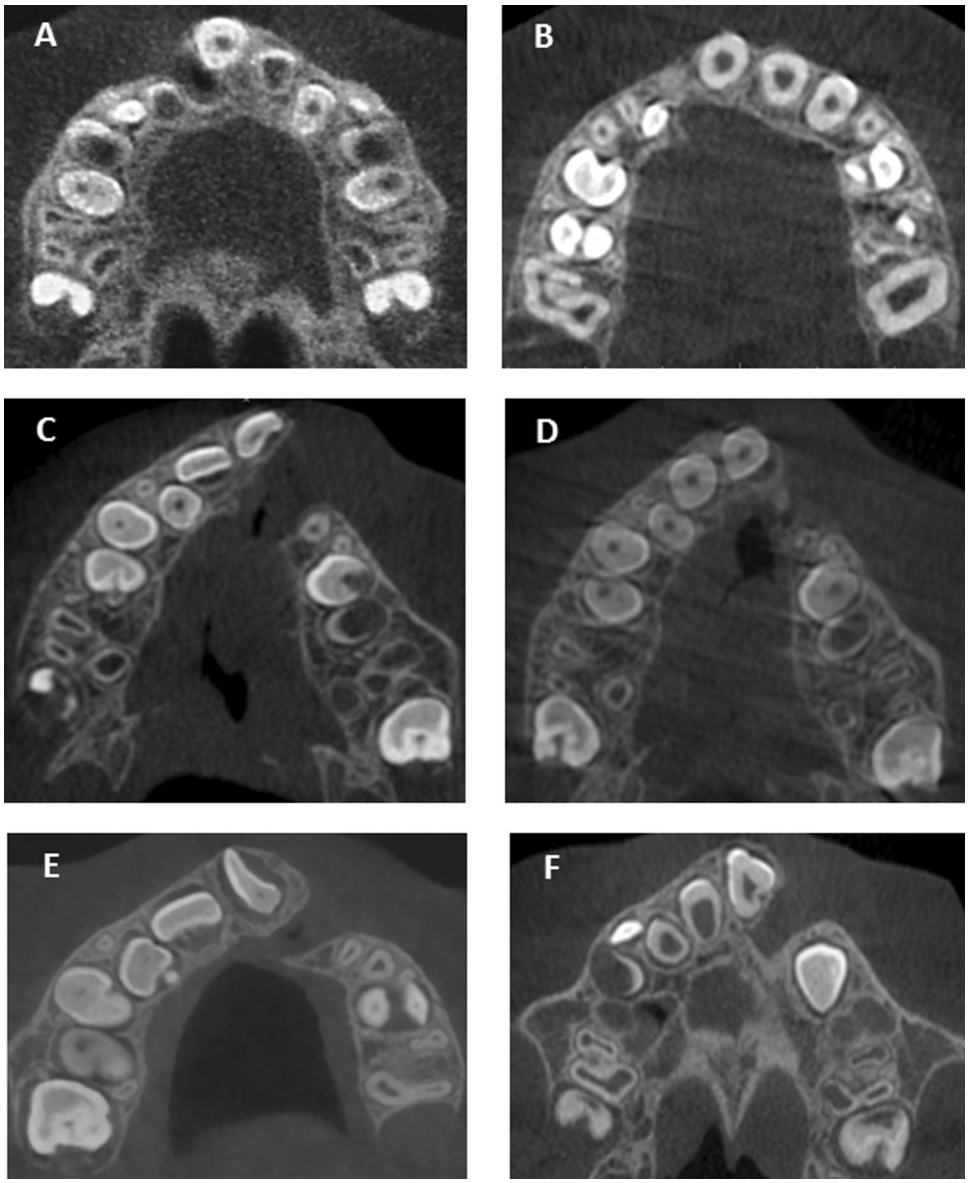


Fig. 5 Cone beam-CT, axial thin sections, bony window. Patient #1: **A** Preoperative, **B** postoperative satisfactory result. Patient #7: **C** Preoperative, **D** postoperative insufficient result. Patient #11: **E** Preoperative, **F** postoperative failure

distance. In 18% of patients ($n=3$) we observed an increase in this distance. For these three cases, the canine at the edge of the cleft was affected. In one case, it was also a central incisor, and in the last case with a bilateral cleft, all the teeth at the edge of the cleft except the central incisors were concerned. For the measurements made on the coronal sections, only two children had an increase in the distance between the canine tip or the incisal edge up to the occlusion plane. These were the same patients who showed an increase in measurements on sagittal sections, and it affected the same teeth.

Determination of the Minimal Volume to Obtain Bone Fusion

Consistency tests yielded favorable results (ICC > 0.9 and kappa coefficient > 0.81).

Table 3 summarizes the results for the 17 patients. Success was consistently associated with arch continuity: Five LMC cases and two large LMPC cases. The mean preoperative cleft volume was 0.88 cm^3, the mean postoperative bone filling volume was 0.62 cm^3, and the mean bone filling rate was 70.5%. The comparison of average cleft palate volumes after surgery illustrates our observation, highlighting that GlassBONE™ is particularly suitable for small volumes. Results are more favorable for small volumes with GlassBONE™. The average cleft palate volumes after surgery significantly differed based on the surgical outcomes (failure, success, insufficient/intermediate) (ANOVA test, $p=0.0313$). Consequently, we were able to determine a minimum volume of approximately $0.259+/-0.155$ cc necessary to achieve successful bone fusion.

Table 3 Radiological evaluation of the alveolar bone filling after the graft

Patients #	Types of cleft	Sides of the GlasBONE™ implantation	Ages at the GlasBONE™ implantation	Maxillary expansion before GlasBONE™ implantation	Agenesia	Syndrome	Preoperative cleft volume (cm^3)	Postoperative cleft volume (cm^3)	Bone filling volume (cm3)	Bone filling rate (%)	Arch continuity	Results
1	**LMC**	**Right**	**7 yrs 7 mths**	**No**	**No**	**No**	**0.84**	**0.18**	**0.66**	**78.5**	**Yes**	**Success**
2	**LMC**	**Right**	**6 yrs 7 mths**	**No**	**No**	**No**	**1.42**	**0.60**	**0.82**	**57.7**	**Yes**	**Success**
3	**Large LMPC**	**Right**	**3 yrs 9 mths**	**Yes**	**No**	**No**	**0.93**	**0.18**	**0.75**	**80.6**	**Yes**	**Success**
4	BLMPC	Left	6 yrs 10 mths	Yes	22	No	0.83	0.77	0.06	7.2	No	Failure
5	**LMPC**	**Left**	**7 yrs 7 mths**	**Yes**	**No**	**No**	**0.54**	**0.18**	**0.36**	**66.7**	**Yes**	**Success**
6	LMPC	Right	9 yrs 7 mths	Yes	No	No	0.87	0.74	0.13	14.9	No	Failure
7	Large LMPC	Left	5 yrs 8 mths	Yes	22	No	0.92	0.57	0.35	38.0	No	Insufficient
8	**Large BLMPC**	**Left**	**8 yrs 6 mths**	**Yes**	**12/22**	**No**	**0.90**	**0.17**	**0.73**	**81.1**	**Yes**	**Success**
9	**LMC**	**Right**	**8 yrs 6 mths**	**No**	**12**	**Van der Woude**	**0.91**	**0.22**	**0.69**	**75.8**	**Yes**	**Success**
10	LMPC	Left	13 yrs 3 mths	Yes, but before iliac graft	12	No	1.36	0.85	0.51	37.5	Thin bone bridge at the apical level	Insufficient
11	LMC	Left	5 yrs 1 mths	Yes	22	No	0.63	0.51	0.12	19.0	No	Failure
12	LMPC	Right	9 yrs 4 mths	Yes	No	No	0.90	0.52	0.38	42.2	No	Insufficient
13	BLMPC	Right + Left	1st: 6 yrs 5 mths (Left) 6 yrs 9 mths (Right) 2nd: 7 yrs 8 mths	Yes (Delaire +)	21/22	Binder	0.50	0.42	0.08	16.0	No	Failure
14	**LMC**	**Left**	**7 yrs 9 mths**	**No**	**No**	**No**	**0.65**	**0.28**	**0.37**	**56.9**	**Yes**	**Success**
15	BLMPC	Right + Left	6 yrs 4 mths	No	No	No	1.70	1.69	0.01	1.00	No	Failure
16	LMC	Right	5 yrs 5 mths	Yes	No	No	0.58	0.49	0.11	15.5	No	Failure
17	LMPC	Right	8 yrs 7 mths	Yes	No	No	0.62	0.42	0.20	32.3	No	Insufficient

Success are presented in bold. *Yrs* Years, *mths* Months

Discussion

This retrospective study demonstrated that alveoloplasty with GlassBONE™ achieved a significant reduction in the alveolar cleft. The reduction in the alveolar cleft volume achieved with GlassBONE™ was comparable to the reductions reported in the literature for iliac bone graft. Indeed, Feichtinger et al. reported a mean preoperative cleft volume of 1.2 cm^3 [0.7–1.7 cm^3] in a series of 20 patients aged 11 years, with a mean postoperative cleft volume of 0.6 cm^3 [0–1.4 cm^3] resulting in a residual bone level of 51% at 1 year [23]. Oberoi et al. measured a mean preoperative volume of 0.61 cm^3 and a mean postoperative bone defect of 0.08 cm^3, associated with a bone filling of 84.1% [61.9–96.5%] [24]. In the study of Touzet-Roumazeille et al., the bone graft volume relative to the initial cleft volume was $61.89 \pm 18.77\%$ [25].

While autogenous iliac bone graft is considered the gold standard, bone substitutes have been recognized as a viable alternative in the literature. Indeed, bone substitutes offer several advantages over autogenous bone grafts and can address economic and social challenges. As demonstrated by Graillon et al., surgical procedures with bone substitutes had shorter durations, allowed for outpatient surgery and analgesia required less painkillers consumption [18]. Hospital stays and periods of exclusion from school were shorter. Moreover, the cost of the bone substitute was largely offset by the reduction of the in procedure duration, hospital stay, analgesic treatment, and the duration of professional exclusion for the patient or their caregivers. Additionally, Janssen et al. also reported that the use of a bone substitute in alveolar grafts simplified the surgical procedure and postoperative management, including subsequent orthodontic and periodontal care. It also eliminated the morbidity associated with harvesting iliac crest bone grafts, reduced hospital stays and social exclusions periods, and allowed for earlier alveolar bone grafting, in line with recommendations from some authors [26–30]. This approach improved the acceptability of the graft for both the patient and their caregivers. Further studies are needed to evaluate the density, volume, height and rate of bone resorption of autologous bone graft substitutes for repairing alveolar clefts [31, 32].

The results presented in this study, along with the findings from the cited literature, suggest that bone substitutes such as GlassBONE™ could be a compelling alternative to the invasive iliac bone graft in CLP surgeries, particularly in cases of small clefts, bilateral cleft and dental agenesis with poor prognosis for grafting.

However, it is important to acknowledge some limitations. This retrospective study was not designed as a randomized controlled trial (RCT), which can reduce the study's statistical power. Nevertheless, these promising results warrant the development of future RCTs that include a control group receiving iliac bone grafts and investigate patient-reported outcomes measures (PROMs) such as pain scores and patient satisfaction. Therefore, while novel techniques like GlassBONETM show promise, it is crucial to exercise caution and continue to consider autogenous bone graft from the iliac crest as the "gold standard" until further evidence is available.

Conclusion

The present retrospective study, which included 17 young patients, has demonstrated a significant 42% reduction in cleft volume using the synthetic alveolar bone graft GlassBONE™ for individuals with cleft lip and palate. GlassBONE™ appears to be particularly effective for small cleft volumes, typically around $0.259 +/- 0.155$ cc. Furthermore, GlassBONE™ facilitates the physiological development of dental germs through the biomaterial.

From a practical standpoint, the use of GlassBONE™ is associated with a reduction in surgical time and a simplification of the surgical process, making it possible to perform the surgery on an outpatient basis. Additionally, the GlassBONE™ graft has been found to improve overall quality of life, as it avoids donor site morbidity and reduces both pain and the duration of school exclusion. For all these reasons, this bioactive glass represents a compelling alternative to iliac bone grafts, especially in cases of small cleft lip and palate.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LF/MS. The first draft of the manuscript was written by LF/NS/MS, and all authors commented on previous versions of the manuscript. Methodology and statistics performed by CC. CPA/NS/JHC supervised the revisions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors have nothing to disclose.

Ethical Approval This retrospective study was submitted to the ethics committee of XXX University for approval. This authorization bears the reference number PADS21-14. Parents of the participants provided written consent for this study after receiving information about it.

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Bioactive glass 45S5 ceramic for alveolar cleft reconstruction, about 58 cases☆

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ABSTRACT

Background: Secondary alveolar bone grafting in patients with clefts lip and palate is usually performed with iliac crest bone harvesting, however using bone substitute allow to avoid harvesting morbidity. The purpose of our study was to assess if the use of a bioactive glass ceramic is an acceptable alternative to iliac crest bone harvesting in alveolar clefts treatment.
Methods: A prospective study including all patients who have benefited of alveolar grafting by GlassBONE™ (Noraker, France), a synthetic resorbable bioactive glass 45S5 ceramic was conducted. The patients underwent clinical assessments and imaging check-up by dental panoramic radiography and CBCT.
Results: Fifty-eight graftings were performed. The mean age at the time of the graft was 7.6 years. Hospitalization, social eviction and antalgic consumption were reduced. Bone continuity was achieved in 63.8% of the cases. Bilateral cleft and dental agenesia increased grafting failure. In the subgroup of 25 patients with isolated unilateral cleft without dental agenesis, 80% had bone continuity at one year. We noted 10.3% of alveolar fistula recurrence.
Conclusion: The use of GlassBONE™ in alveolar grafts simplifies the surgery procedure and the postoperative management, and ensures satisfactory mucosal healing, tooth eruption and bone continuity in two thirds of the followed grafts.

1. Introduction

Secondary alveolar bone grafting in patients with cleft lip and palate restores maxillary bone continuity to ensure its stability, close alveolar fistulas, facilitate its evolution, correct dental positioning, and secure orthodontic and surgical movements (Dissaux et al., 2016). Different autogenous bone harvesting sites are used; the gold standard is the iliac crest bone graft harvesting site (Thuaksuban et al., 2010). However, its resorption rate is high during the first year after grafting (Honma et al., 1999), and this type of sampling may cause postoperative pain, walking difficulties, nerve damage, hematomas, infections, and arterial wounds (Seiler and Johnson, 2000; Cricchio and Lundgren, 2003). In this context, the use of bone substitutes avoids the harvesting morbidity, reduces the length of hospital stays and social exclusions, and allows alveolar bone grafting to be performed earlier, as recommended by some authors (Lilja et al., 2000; Talmant et al., 2002). Bone substitutes, such as bioactive ceramics, are already used in pediatric orthopedics as a substitute for iliac crest bone harvesting in spinal surgeries (Ilharreborde et al., 2008) or in filling bone defects (Balakumar et al., 2014).

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The purpose of our study was to assess if the use of a bioactive glass ceramic is an acceptable alternative to iliac crest bone harvesting in alveolar cleft treatment.

2. Materials and methods

2.1. Bone substitute

The bone substitute used in this study was GlassBONE™ (Noraker, France), a bioactive glass 45S5 ceramic, which is synthetic and resorbable, with osteoconductive and osteostimulating properties. We used a 0.5-mm grain size.

2.2. Patients

We conducted a prospective study from January 2011 to June 2015, including all patients who underwent alveolar bone grafting using GlassBONE™ for unilateral or bilateral alveolar clefts.

2.3. Surgical technique

In our protocol, gingivoperiosteoplasty with the placement of a bone substitute was performed in most cases in mixed dentition (early secondary alveolar grafting) after orthodontic expansion, according to the Troxell mucoperiosteal flap (Troxell et al., 1982). The alveolar cleft was grafted with 0.5–2 cc of GlassBONE™ depending on the volume of the graft. The bilateral alveolar clefts were grafted at a 6-month interval.

2.4. Clinical and paraclinical evaluation

The patients underwent clinical assessment preoperatively, at 1 month, 6 months, and 1 year; imaging check-up via dental panoramic radiography preoperatively, postoperatively, at 1 year and every two years; and maxillary CBCT preoperatively and at 1 year.

Initially, we noted the existence of dental agenesis, alveolar fistula, and syndromic anomalies. After surgery, we quantified hospitalization and school and sports exclusion durations. Clinically, we evaluated the quality of healing, rejection of the bone substitute, recurrence of alveolar fistula, and necessity for a new alveolar graft.

Alveolar ossification was assessed via a maxillary CBCT at 1 year. The data were converted to Digital Imaging and Communication in Medicine format and then transferred to the Osirix software (Pixmeo SARL, Geneva, Swiss). Axial, coronal, and sagittal reconstructions were performed. We searched for bone continuity. The maximum crestal and subnasal thicknesses of the grafts were measured in a plane parallel to the palatal plane. The maximum height of the graft was also measured (Figs. 1 and 2).

The patients were divided into two groups. Group 1 patients had an alveolar bone continuity on the CBCT 1 year postoperatively, while Group 2 patients had no bone continuity.

Dental eruption of adjacent teeth through the graft was evaluated using dental panoramic radiography in group 1.

2.5. Statistical analysis

For the descriptive analyses of the sample characteristics, the data were expressed as proportions for the qualitative variables and as means, standard deviations, medians, and interquartile ranges for the continuous variables. For the univariate analyses, the multiple variables were compared between the presence and absence of a bone arch formation within the sample; the non-parametric Mann–Whitney U test was used for the continuous variable (age) and the Chi–Square test for the qualitative variables, including alveolar cleft characteristics (unilateral versus bilateral cleft), presence of polymalformative syndrome, and dental agenesis.

All the tests were two-sided, and statistical significance was defined as $p \leq 0.05$. The statistical analyses were performed using the SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA).

2.6. Ethical considerations

This study was conducted in accordance with the principles of the Helsinki Declaration (2013). The participants or their parents provided a written consent for this study after having received information.

3. Results

3.1. Patient and cleft characteristics

Sixty-eight patients were included in this study. Thirteen patients were lost to follow-up. A total of 58 grafts were performed; three patients underwent bilateral grafting. The mean age of the patients at the time of grafting was 7.6 years (range, 3–15 years). Forty-one patients had a unilateral cleft, and 14 patients had a bilateral cleft, three of which were grafted with the bone substitute

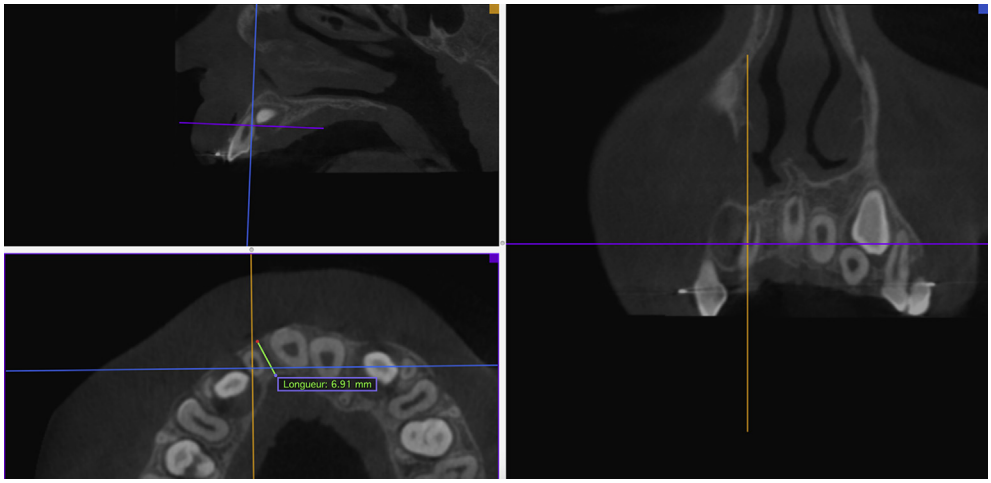

Fig. 1. Measurement of the maximum crestal thickness of a right alveolar bone graft in the parallel plane to the palatal plane on the Osirix software.

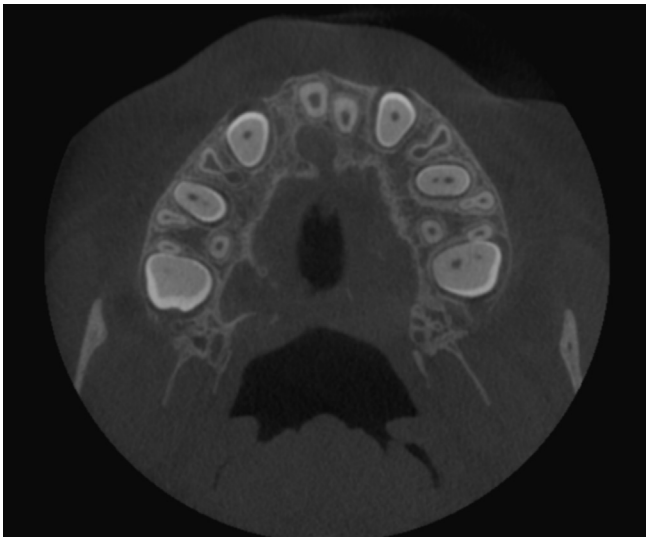

Fig. 2. Maxillary CBCT 1 year after the right alveolar bone grafting using GlassBONE™ showing an alveolar bone continuity.

on both sides and eleven only on one side because the other side was grafted with iliac bone before the beginning of the study. Seven patients had a polyformative syndrome. There were 24 cases of lateral incisor agenesis, one case of central incisor agenesis, and one case of canine agenesis in the patients with lateral incisor agenesis (Table 1).

3.2. Postoperative history and complications

The hospitalization duration was 24 h, while the school and sports exclusion duration was 7 days. Antalgic treatment (level 1), antibiotic therapy with amoxicillin + clavulanic acid (pristinamycin in case of allergy) for 7 days, local site intervention with antiseptic mouthwashes, and antiseptic gel applications according to age were prescribed postoperatively.

Two patients presented delays in wound healing; one was resolved after performing the local site intervention; however, the other presented with a significant exposure of the graft, which caused its exteriorization and complete loss. Alveolar fistula recurred in six patients (10.3%). A patient with Binder syndrome showed a reopening of the cleft after maxillary expansion. Graft revision was performed in 13 cases (22.4%) because of symptomatic alveolar fistula or for securing the bone environment before tooth movements.

Table 1
Characteristics of the study sample.

		M ± S.D., Med. (IQR), or n (%)
Age (y)		7.6 ± 2,9 7 (5–9)
Side	Right	20 (36.4%)
	Left	21 (38.2%)
	Bilateral right-grafted	7 (12.7%)
	Bilateral left-grafted	4 (7.3%)
	Bilateral grafted on both sides	3 (5.4%)
Dental agenesis at the edge of the clefts		24 (41.4%)
Malformation syndrome		8 (13.7%)
Mucosal dehiscence		2 (3.4%)
Substitute rejection		1 (1.7%)
Oronasal fistula recurrence		6 (10.3%)

M ± S.D.: mean ± standard deviation; Med. (IQR): median (interquartile range); n (%): number and percentage.

3.3. Bone evaluation

Bone continuity was achieved in 37 cases (63.8%) (Group 1) (Table 2) but was absent in 21 cases (36.2%) (Group 2).

In Group 1, the mean maximum crestal thickness was 7.76 mm ± 2.30; the mean maximum subnasal thickness was 5.1 mm ± 2.03; and the mean height was 8.9 mm ± 2.60.

Group 1 patients had significantly less dental agenesis than Group 2 patients ($p = 0.026$). Age was comparable in both groups ($p = 0.95$). In Group 1, 8.1% of the patients had polymalformative syndrome compared with 23.8% in Group 2 ($p = 0.124$) (Table 2).

In the subgroup of 25 patients with isolated unilateral cleft without dental agenesis, 80% had bone continuity at 1 year.

3.4. Teeth eruption evaluation

In group 1, after the graft, spontaneous canine eruption was achieved in 6 patients (17.6%) and after orthodontic traction in 2 patients (6.8%). We noticed 24 canine evolutions through the graft without eruption (70.6%) due to the young age of the patients. Only 2 patients did not present canine evolution (6.8%) after the graft. Three patients were not evaluated because the canine was already on the dental arch before the graft. Concerning lateral incisor, spontaneous eruption was achieved in 17 patients (63%), and after orthodontic traction in one case (3.7%). Seven patients presented lateral incisor evolution through the graft without eruption (25.9%) at the time of the evaluation. Two patients presented no lateral incisor evolution after the graft (7.4%). Ten patients were not evaluated, eight cases of lateral incisor agenesis and two cases of lateral incisor extraction.

4. Discussion

The use of a bone substitute in alveolar grafts simplifies the surgical procedure and postoperative management, and ensures satisfactory mucosal healing and bone continuity in two thirds of the followed grafts. To our knowledge, this study presents the largest cohort of patients treated with alveolar grafting using a bone substitute. Several pilot studies presented promising results with small cohorts using rhBMP-7 (Ayoub et al., 2016), micro-structured beta-tricalcium phosphate (de Ruiter et al., 2015).

The use of a bone substitute avoid the morbidity related to iliac crest bone graft harvesting (Janssen et al., 2014). In our center the consumption of analgesics and the hospital stay (by 3 to 1 days)

Table 2
Characteristics comparison of the patients with bone continuity at 1 year (Group 1) and those without bone continuity (Group 2).

Group of subjects			
(Characteristics)	Presence of a bone bridge (n = 37) M ± S.D., Med. (IQR), or n (%)	Absence of a bone bridge (n = 21) M ± S.D., Med. (IQR), or n (%)	p
Age (y)	7.5 ± 2.4 7 (6–9)	7.9 ± 3.8 7 (5–11.5)	0.951[a]
Dental agenesis	13 (61.9%)	11 (29.7%)	**0.017**[b]
Bilateral cleft	6 (16.2%)	9 (42.9%)	**0.026**[b]
Malformation syndrome	3 (8.1%)	5 (23.8%)	0.124[b]

M ± S.D.: mean ± standard deviation; Med. (IQR): median (interquartile range); n (%): number and percentage.
[a] Non-parametric Mann–Whitney U Test.
[b] Chi-Square Test; significance threshold of 5%, significant results in bold.

decreased. Such an intervention is conceivable in ambulatory surgeries. Its use also shortened the duration of school and sports exclusion to 7 days compared with 14–21 days with iliac harvesting. Further, it improves the acceptability of the graft by the patient and his entourage. It has already been used as a complement to iliac samples to reduce its morbidity with results comparable to those of iliac grafts (Takemaru et al., 2016).

Alveolar bone grafting may be proposed at an earlier stage owing to the use of bone substitutes as advocated by some teams to enable a better correction of vertical growth abnormalities of the premaxillary region, graft sustainability that would be favored by dental eruptions, and earlier restoration of nasal ventilation (Talmant et al., 2002).

Our results are similar to those of alveolar cleft reconstruction with iliac bone grafting in terms of mucosal healing quality and alveolar fistula closure. Healing disorders are rare. We noted two cases (3.4%) of mucosal dehiscence, one with graft exposure, leading to its loss. In the context of sliding flaps, the literature reports a 0%–26% incidence rate of dehiscence (Hugentobler et al., 2006). The disadvantage of using a bone substitute is the risk of rejection owing to early exposure, contrary to a bone graft. As for bone grafting, mucosal dehiscence occurs in case of inadequate oral hygiene or periodontal disease. In our study, the two cases were related to poor oral hygiene.

Our study showed a 10.3% rate of recurrence of alveolar fistula. In the literature, the rate is very variable, ranging from 0% to 21.4% for bone grafts (Hugentobler et al., 2006). Late age, notably after canine eruption, would favor fistula recurrence. In our study, two of the six patients with fistula recurrence were grafted after canine eruption.

The early secondary alveolar grafting has to restore bone continuity to ensure the stability of the maxillary arch, closure of alveolar fistulas, dental evolution, and surgical and orthodontic movements. Such a procedure does not require obtaining an immediately implantable bone thickness. A late grafting for pre-implantation is generally necessary after growth. We achieved bone continuity in 63.8% of the cases, and up to 80% in the subgroup of patients with isolated unilateral cleft, without dental agenesis, had satisfactory crestal and subnasal bone thicknesses and height at the graft level, ensuring a good stability of the maxillary and a safe bone dental environment. There is a discrepancy between the quality of mucosal healing – which depends on the quality of the graft taken – and the percentage of bone continuity according to the CBCT. This divergence may be because of a poor evaluation – via the CBCT – of the graft in ongoing transformations or a relatively short time to visualize ossification using CBCT.

We performed biopsies of the graft at one year for two patients, who seemed to present a graft failure on CBCT with a good mucosal healing, that revealed a well-differentiated bone tissue without bone substitute. These histological results suggest that the ossification could be under-rated by CBCT at one year. We did not encounter dental extrusion issues after orthodontic movement or surgical difficulties in the case of maxillary osteotomy after a bone substitute grafting.

The rate of surgical revision was 22.4%. However, most of the revisions were conducted for replacing the bone substitutes during another operation, in particular a cheiloplasty revision or a rhinoseptoplasty, because of the simplicity and the low morbidity of the grafting revision. In case of failure, an iliac crest bone grafting is always possible and accepted by the patient.

Given the early age at the time of the grafting, the rate of lateral incisor and canine eruption could not be evaluated. However, we noted dental eruptions and dental evolutions through the bone substitute (Fig. 3) in 94% of the cases for the canine and in 93% of the cases for the lateral incisor in the subgroup with achieved bone continuity. The possibility of tooth eruption through bone substitute graft has already been demonstrated in several studies (Thuaksuban et al., 2010; Lazarou et al., 2011).

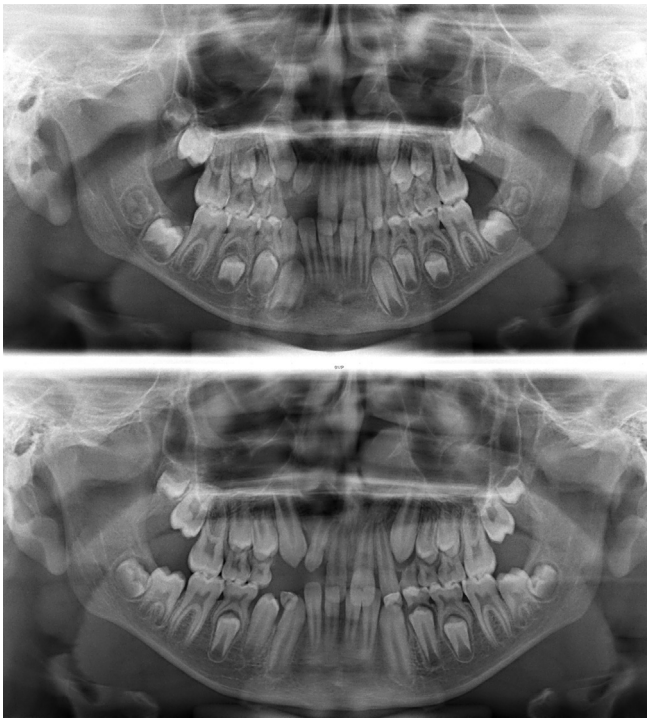

Fig. 3. Dental panoramic view – preoperative (A) and at 1 year (B) – showing the evolution of the lateral incisor and the canine through the right alveolar bone graft with GlassBONE™.

Concerning the cost, the price of the bone substitute is widely compensated by the reduction of the procedure duration, hospital stay, analgesic treatment, and professional exclusion duration of the patient or of his entourage.

5. Conclusion

Alveolar bone grafting using a synthetic bioactive glass bone substitute can be an alternative to iliac crest bone grafting. It simplifies the surgical procedure and outcomes, allows satisfactory mucosal and bone healing, supports tooth eruption, authorizes the performance of the grafting at an earlier stage, and facilitates the acceptability of a late pre-implant transplant because of its simplicity. In case of failure, it does not contraindicate a new grafting using a bone substitute or autologous bone.

Conflicts of interest

The authors do not declare any conflict of interest.

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ASSESSMENT OF THE STICKY BONE PREPARATION OF BIOACTIVE BONE GLASS IN GRAFTING CRITICAL-SIZED SURGICAL BONY DEFECTS

Hesham Elsayed El-Hawary* *and* Mohamed Shawky**

ABSTRACT

Background: Critically sized surgical bony defects after enucleation of cystic bony lesions will not spontaneously heal.

Purpose: This clinical study aimed to assess the osteoinductive potential of bioactive bone glass in the form of sticky bone in critical-sized surgical bony defects.

Patients and methods: the present study is a randomized clinical controlled trial including 24 patients divided into two equal groups. Cystic lesions exceeding 2 x 2 cm were enucleated, and the defect was obliterated with bioactive bone glass particles in group 1 and bioactive glass sticky bone in group 2. Bone density was measured in grayscale units from digital panoramic radiographs immediately, at three and six months postoperatively.

Results: The healing went uneventful, except for the exfoliation of graft particles through the incision line in groups 1. In group 1, the percentage of decrease in the bone density during the first three months is higher in group 1 than group 2 that was then increased by nearly the same percentage at the six months interval although statisticaly there is no significant difference between the two groups through out the study period.

Conclusion: The bioactive glass prepared as the sticky bone has better intraoperative handling and workability, better soft tissue reaction during the healing period and higher bone density values of the grafted defects than when used solely although it hasn't any radiographic statistical significant results regarding the studied parameters.

KEYWORDS: Cyst, Maxillary cysts, Critical size, bioactive bone glass, sticky bone, bone density, osteoinductive, bone substitute.

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INTRODUCTION

Cystic lesions are among the common pathologies known to affect the oral and maxillofacial region. By definition, a cyst is an epithelial lined cavity, filled with fluid or semifluid or gas, as mentioned by **I. Kramer** in 1974. [1] According to **Partsch** [2], there are two proposed treatment lines; the first one entails a complete excision of the lesion and watertight closure to permit immobile and undisturbed healing. However, large lesions that erode the natural bony barriers and encroach the adjacent vital structures may benefit from another line of treatment called marsupialization, which involves creating a decompression window in the cyst wall that reverse the process of cyst expansion, yielding a relatively smaller lesion that could be removed with minimal or no harm to the surrounding structures. [3,4]

The last treatment modality was recommended for lesions exceeding 2 cm in diameter because of the increased risk of infection, wound dehiscence due to retraction of the formed blood clot away from the bony walls. Bony defects exceeding 2.5 cm are critically sized bone defects, as concluded by **Emil H. Schemitsch** [5], and tend to have poor natural healing, which led some authors to use gelatin sponge and thrombin to stabilize the blood clot [6]. In the following decades, different grafting materials were investigated for efficiency as filling materials for the cyst cavity following enucleation regarding infection rate reduction, accelerated healing of a better quality bone, and a reduced soft tissue collapse into the bony defect. Autogenous bone is the gold standard. [7–9] However, it costs an extra donor site morbidity and a longer surgical time for harvesting. The bones harvested from the iliac crest, the mandible, and the tibia were investigated by **Holtgrave and Spiessl** [10]**, Mi Hyun Seo et al.** [11]**,** and **Fethi Atil** [12]**,** respectively.

Studies were conducted to determine the most efficient bone substituting substance. Bone substitutes are used to avoid or minimize the common complications associated with harvesting autogenous bone, beta-tricalcium phosphate (β-tricalcium phosphate) was mixed with blood and used alone **Bicsák et al.** [13] or with the addition of autogenous bone as tried by **Horch et al.** [14] Also, nano-hydroxyapatite was used by **Gerlach and Niehues**.[15] It has a chemical composition resembling bone and teeth, which allows it to release calcium and phosphate ions that bind to the surrounding bone in addition to being a scaffold that is invaded by bone growth. [16] Xenograft mixed with red bone marrow was investigated by **Horowitz and Bodner** [15], he found that the graft was incorporated incompletely after six months. After one year, it was fully incorporated; however, in some cases, it was more radiodense than the surrounding bone, the same density of the surrounding bone was reached after two years.

Bioactive glass is a resorbable, synthetic bone substituting material with osteoconductive, osteoinductive, and bone binding potentials. [17,18] It induces the formation of a silica-rich layer covered by calcium and phosphorous layers on its surface, promoting collagen adhesion, osteoprogenitor cells differentiation [19–22], and acting as a biodegradable framework for the bone to grow on. [19,20] Promising results were encountered upon its employment in the management of osteomyelitis and un-united fractures. [21] It has also been used in maxillary sinus grafting solely in rabbits first [22], then it was mixed with autogenous bone and used for grafting after maxillary sinus floor elevation in a study performed by **J. Menezes et al.** in 2018 [18], and the results were also promising.

The gold standard bone graft should possess the three cardinal characteristics of autogenous bone, osteogenicity, osteoinductivity, and osteoconductivity. The osteogenic property is present only in autogenous bone, so a growth factors rich substance may be added to compensate for the lack of osteogenic potential. The best examples are the growth factors rich platelet derivatives, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and fibrin-rich gel with concentrated growth factors (CGF) that were used to enhance and speed

up new bone formation in sinus floor elevation and guided bone regeneration. [23–25]

Hence, this study aimed to investigate the osteogenic capabilities when a bioactive glass is mixed with platelet rich fibrin containing growth factors and used as a sticky bone to fill bony defects following enucleation of maxillary cystic lesions exceeding 2 x 2 cm in diameter.

MATERIALS AND METHODS

This study was conducted in the department of oral and maxillofacial surgery, faculty of dentistry, Cairo University and was compliant with the Declaration of Helsinki (revised in 1975), and with CONSORT (Consolidated Standards of Reporting Trials) principles and the regional ethical review, the board approved the study. All patients were provided an informed consent and agreed to sign. The inclusion criteria for patient selection were; maxillary cystic lesions exceeding 2 x 2 cm diameter, affecting healthy patients without systemic or local diseases. Exclusion criteria included a history of systemic disease that may complicate bone healing and graft integration, bone metabolic disorders, a history of radiotherapy or chemotherapy.

The recruited patients were interviewed to obtain a thorough medical history, previous dental history, and chief complaint history. During the clinical examination, an aspiration biopsy was done to determine the nature of the lesion being a cyst. A preoperative digital orthopantomogram was requested to exclude other missing underlying diseases (Fig 1). Then an incisional biopsy was done to know the nature of the cystic lesion. According to the biopsy report, patients with lesions that will need bony resection as a definitive treatment were excluded.

Twenty four patients were selected, 14 males and 10 females with ages ranging from 26 to 45 years. They had maxillary cystic lesions exceeding 2 x 2 cm and were free from any systemic diseases (table 1).

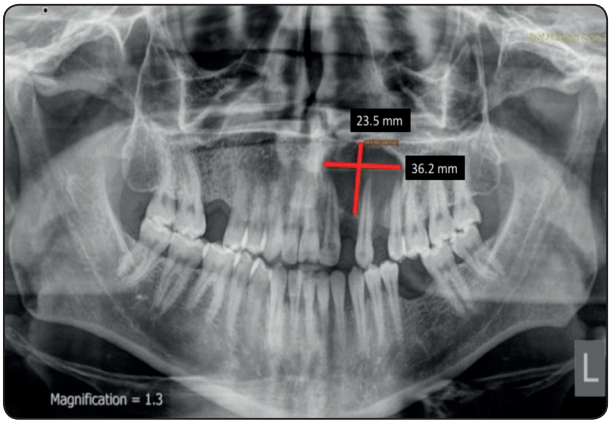

Fig. (1): Preoperative Orthopantomogram with the measurements of the cystic cavity.

TABLE (1) The Demographic Data of the patients.

	Group 1		Group 2	
Patients	12		12	
	9 males	3 females	5 males	7 females
Age range	27-45		22-45	

Study design and Randomization

Patients were randomly divided into two equal groups using a computer permuted block stratified randomization generator (randomization.com).

In group 1, the cyst was enucleated, followed by immediate grafting of the defect using bioactive glass (Noraker, Lyon, France). While in group 2, five males and seven females received a sticky bone prepared from the bioactive glass to and used to obliterated the defect.

Surgical procedure

Under local anesthesia (ARTINIBSA 40mg Articaine hydrochloride / ml + 0.01mg Epinephrine / ml injectable solution, Inibsa Dental S.L.U., Ctra. Sabadell a, Granollers, Km 14,5 (C-155), 08185 Lliçà de Vall (Barcelona) España), the patients were seated comfortably and given infraorbital nerve

block and a palatal block anesthesia as recommended to anesthetise the area of the cyst. A sulcular incision was then commenced extending two teeth beyond the area of interest, followed by two oblique incisions on either side of the flap. A full-thickness mucoperiosteal flap was raised, uncovering the buccal bone, which in all of the cases was thin enough to be breached and removed, exposing the cystic lining. The bony opening was then extended enough to provide adequate accessibility before the lesion was enucleated entirely, followed by peripheral ostectomy using a large-sized rose head bur after resecting the root ends of the related teeth or extracting them if needed to ensure total removal of the lining (Fig 2A).

The defect was obliterated using bioactive glass particles in the first group of patients. In the second group, a sticky bone was prepared from the bioactive glass and used as a filling material (Fig 2 B, C).

To prepare the sticky bone, 20 to 40 CC of the patient's venous blood was withdrawn, injected into an even number of non-coated vacutainers (yellow cap), and centrifuged at 2400 – 2700 RPM for 2 minutes in a special centrifuge with a rotor turning with alternating and controlled speed (Medifuge, Silfradent Srl, Sofia, Italy). The upper layer containing the autologous fibrin glue (AFG) was withdrawn with a syringe and injected over the bioactive glass, left for 8 – 10 minutes to coagulate, forming sticky bone (Fig 2C).

The enucleated lesions' lining was placed in a 10% formalin solution and sent for histopathological examination. Furthermore, the wound was closed primarily using vicryl 3/0 (Assut, Switzerland). A postoperative antibiotic course of amoxicillin + clavulanic acid 1 g tab (Augmentin, Galaxo Smith Kline, Cairo, Egypt) was prescribed for one week and Ibuprofen 600 mg tab (Brufen, Kahira pharmaceutical and chemical industries, Cairo, Egypt) twice daily for one week. One shot of dexamethasone 8 mg vial (Sigmatic, Cairo, Egypt) was administered intramuscularly immediately after the surgery together with ketorolac tromethamine 30 mg (Ketolac, Amriya pharm, Alexandria, Egypt).

Postoperative instructions of ice packs application for 15 minutes every 30 minutes during the first 24 hours were given and replaced by warm fomentations with the same rate for the next two days. A soft diet was recommended for the first forty-eight hours. Strict oral hygiene instructions and chlorhexidine mouth wash (Hexitol; ADCO Pharma, Cairo, Egypt) was used three times daily for 15 days starting from the second postoperative day. An immediate digital panoramic radiograph was requested to be done by the same radiologist using the same machine to deduce the baseline bone density in the

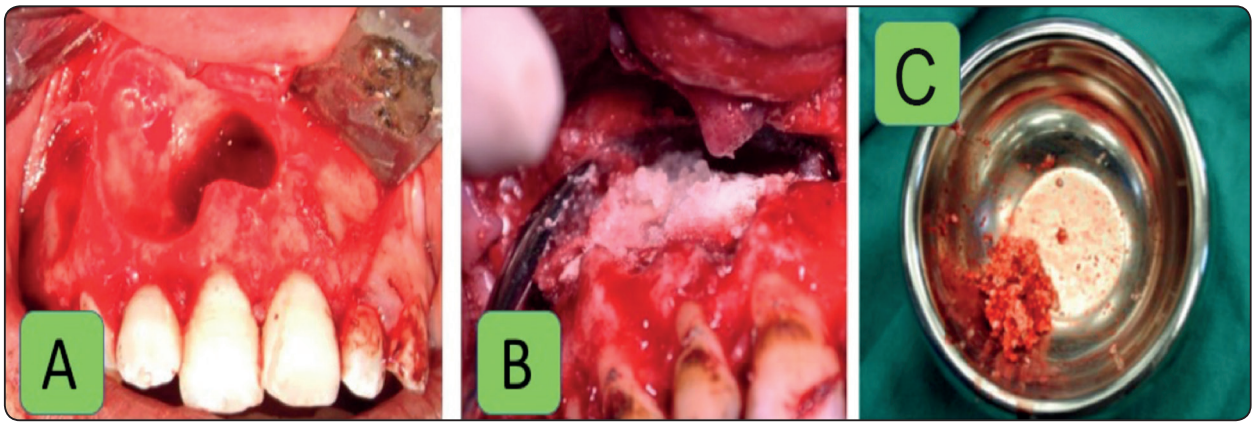

Fig. (2) A: Clinical photograph of the resulted surgical defect after cyst enucleation, B: Clinical photograph of filling the resulted surgical defect with Bioactive bone glass (Group 1), C: Clinical photograph showing the Bioactive glass sticky Bone prior to its use in filling the resulted surgical defect (Group 2).

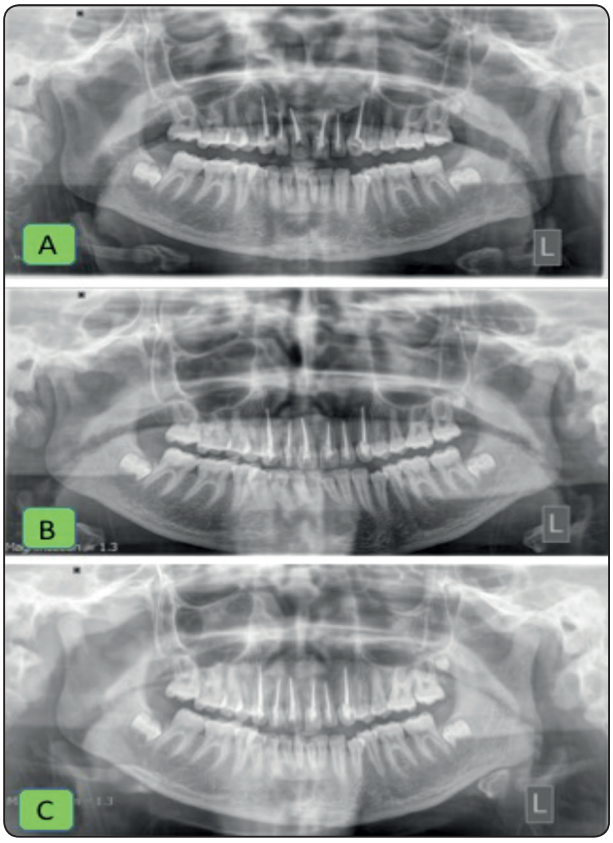

Fig. (3) A: Immediate Postoperative Orthopantomogram, B: 3 months Postoperative Orthopantomogram, C: 6 months postoperative orthopantomograms (Group 2).

grayscale units for the grafted site. It was repeated at 3 and 6 months postoperative (Fig 3A, B, C).

All digital radiographs were taken with the same machine and the same parameters to provide standardization of images. Radiodensitometric analysis was obtained by measuring the relative bone density using the sigma view, Digora software in Gray Scale Units (GSU) (Fig. 04). The obtained measurements were documented and sent for statistical analysis.

The patients were recalled after two days, after one week, at the end of the first month and then at three and six months to monitor the soft tissue healing where the sutures were removed after one week, then at the third and sixth months to evaluate the bony healing.

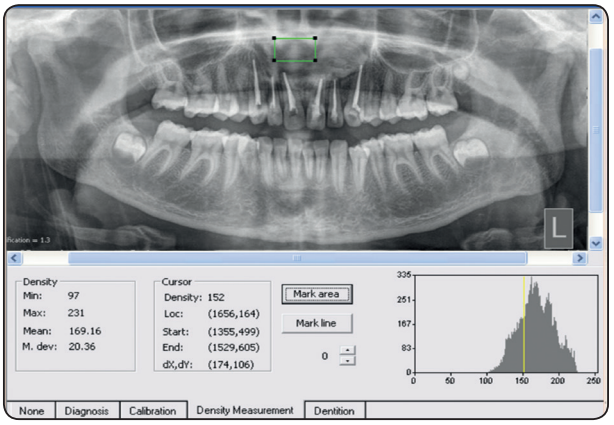

Fig. (4): Photograph showing the screenshot of the bone density measurement from orthopantomogram using Digora software.

Statistical methods

The statistical analysis implemented data analysis using IBM SPSS. (Statistical Package for Social Sciences, Version 22. SPSS Inc., Chicago, IL). The numerical data were described as means and standard deviations, which examined for normality using the Kolmogrov-Smirnov test. The paired student t-test compared the two variables within the same group. The independent samples t-test compared the variables between the two studied groups. The results were considered statistically significant if the computed p-value counted than 0.05.

RESULTS

The current study was conducted on twenty four, 14 males and 10 females patients, ranging from 22 to 45 years old, with a mean age of 33.5. According to the standard techniques, all the cysts were surgically enucleated, and the resulting surgical defects were grafted using the bioactive glass, and bioactive glass sticky bone, according to the study groups. All the patients were included for statistical analysis. Data were reported as mean $\pm$ standard deviation.

Clinical results

Intraoperatively, the surgical elevation of the buccal flaps went smooth in all of the cases. The

cysts were completely enucleated with surgical defect obliteration utilizing the examined materials with adequate unstretched complete soft tissue coverage for the bony defects.

The healing went uneventful through all the cases. All the patients complained of postoperative edema and swelling on the surgical site that resolved at the end of the first postoperative week. The patients suffered from pain that was controlled by the prescribed NSAID drug.

At the 48 hours follow up, Two patients in group 1 reported a feeling of escape of the grafting material into the oral cavity; checking the flaps revealed the escape of some graft particles from the gingival incisions that were related to extracted teeth during enucleation, the patients were instructed to follow the prescribed oral hygiene protocol strictly. However, the surgically reconstructed defects did not show postoperative infection nor wound dehiscence or graft rejection throughout the healing phase. After resolving the postsurgical phase's signs, none of the patients exhibited any complaint during the whole study interval.

Radiodenisty results

For Group 1, the mean value of the bone density measured immediately postoperatively was 137.92±35.53 GSU. By the end of the third month, it was reduced to 106.55±40.67 GSU. At six months postoperatively, it reached 122.65±33.35 GSU. The bone density decreased by 17.6% at three months' interval then increased by 14% by the end of the study, with a total decrease in bone density by 5.3%. For Group 2, the mean value of the bone density measured immediately postoperatively was 131.78±21.27 GSU. By the end of the third month, it was reduced to 126.42±28.22 GSU. At six months postoperatively, it reached 138.05±14.77 GSU. The bone density decreased by 4.5% at three months, then increased by 8.7% at the end of the study, with a total increase in bone density by 4.5 %. (Fig 5).

TABLE (2) Showing the t-test results and the p-value comparing the three groups.

T-Test	P-Value	Significance
Between G1-G2 immediate postop record	0.846170198	Not Sig
Between G1-G2 3 months' record	0.179986149	Not Sig
Between G1-G2 6 months' record	0.16399939	Not Sig

Comparing all groups along the whole study period, there was a nonsignificant statistical difference in the grayscale measurement.

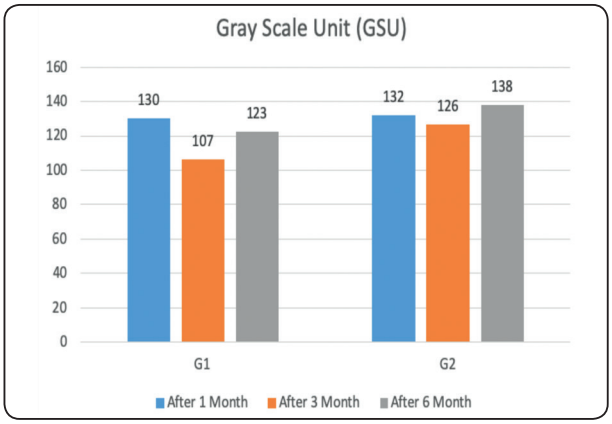

Fig. (5): Diagram Showing the mean bone density for all groups along the entire study period.

DISCUSSION

Bony defects that reach the critical size are not going to heal spontaneously. That is why they are considered clinically problematic. In large defect sizes, the formed blood clot will disintegrate and retract or be superimposed by infection. Moreover, a contour defect arises from the collapse of the surrounding soft tissue into the cavity. Grafting of critically sized surgical bony defects may eliminate or reduce all these potential complications. [5,26] Since alloplasts demonstrated effectiveness in treating postoperative bone defects as suggested by many

authors [5,25–29], the present study aimed to investigate whether optimum osseous healing could be achieved with autogenous bone substitutes.

Among the variety of available substitutes nowadays, bioactive glass has been widely investigated for its biocompatibility, bone binding properties, and acting as an osteoconductive scaffold. Besides, it possesses an osteoinductive potential inducing and speeding up bone formation in the area of interest. It was praised by ***Fetner et al.*** [30] for its workability, convenient handling, and hemostatic properties when he used it in periodontal defects and called it PerioGlas. ***Schepers*** [31] in 1991, ***Furusawa*** [32] in1998, ***Froum*** [32] in 2002, and many other authors [16,19,28] discussed the advantages of using bioactive glass in surgical defects and recommended its use.

In the present study, the defects were all located in the maxilla to standardize the results. The defects' size was regarded as critical, being more than 2 x 2 cm in all the cases. Hence it was indicated for grafting. [5,26,27] All the recruited patients were medically free, which eliminated any underlying systemic condition that may affect healing. As recommended in the literature, aspiration biopsy was done before any intervention to determine the nature of the contents. [33]

The decision to enucleate the cystic lesions was a recommended radical means of treatment to allow the complete histological examination of the full lining and eliminate the need for a close postoperative follow-up in the marsupialization technique. This was preceded by a root canal treatment of the related teeth as recommended in the literature. [33,34]

The application of the bioactive glass sticky bone form in group 2 is easy and convenient than the bioactive glass alone; this is due to the sticky effect of the grafted material that allow to insert it in a bulk form rather than particulate form. Thus the sticky bone form is convenient during its application due to the superior workability. The healing went uneventful through all the cases, except for the exfoliation of the graft particles (popcorn effect) that was reported in the group 1 but not in group 2, which comes in favor of the bioactive glass sticky consistency in that study group. All that in addition to the accelerated bone and soft tissue healing are advantages that come in accordance to ***Sohn et al.*** in 2015. [35]

In both groups, bone density changes were measured using direct digital radiography (DDR) at the specific follow-up appointments, immediately, three then six months postoperatively. DDR facilitated the detection of both the qualitative and quantitative changes of bone density. ***Barbet*** and ***Messer*** [36] stated that it is more accurate and sensitive than conventional radiography, and on the other hand, it offers less radiation exposure than cone-beam computed tomography.[37] Radiodensitometric analysis was obtained by measurement of the relative bone density using the sigma view, Digora software.

The documented data were tabulated as mean and standard deviation and sent for statistical analysis. The computerized image analysis system was an appropriate tool for detecting changes in bone density as it provides numeric values for the progression of the healing process. This goes with the results stated by ***Delano et al.*** in 2001. [38]

A postoperative orthopantomogram was requested immediately postoperatively, after three months and after six months. The bone density measurements revealed a nonsignificant reduction in bone density after three months. Although it is nonsignificant, it can be justified due to the phagocytosis process in the graft core, osteoid formation, and the released silicon rich layer that is readily absorbed and excreted. However, in the six months investigation, the density increased again in both groups, which is explained by the recruitment of osteoblasts, mesenchymal cells and the additional crystallization of the layed down bone matrix thus increasing the radiodensity. This is facilitated by the precipitated layer of calcium and ohosphate over the silicon rich layer. [39]

The statistical results are insignificant along the study period comparing both groups, but regarding the percentage of bone density change; group 2 showed a less percentage in change in the three months interval compared to group 1 but both of them showed nearly the same increase in percentage of bone density change. This might be due to the immediate and early effect of the growth factors and interlukins in the sticky bone which improves its radiographic properties in group 2 than in group 1, thus the sticky bone preparation has a resultant higher bone density regarding the three months bone density.

CONCLUSION

The bioactive glass prepared as sticky bone has better intraoperative handling and workability, better soft tissue reaction during the healing period, and higher bone density values of the grafted defects than when used solely although it hasn't any radiographic statistical significant results regarding the studied parameters.

Recommendations

Bioactive glass prepared as sticky bone is recommended for grafting critically sized surgical bony defects over its use in a particulate form due to its better clinical handling, biocompatibility, soft tissue reaction, and the higher density of the formed bone specialy in the early healing phase.

Further studies are recommended for a histomorphometric analysis of the grafted area to better investigate grafted site histology in different timelines and the bone area percent.

Conflict-of-interest notification

The authors declare that they have no conflict of interest with the contents of this article.

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ARTICLE ORIGINAL

La gingivopériostoplastie avec substitut osseux : technique et premiers résultats

The gingivo periosto plastic surgery with osseous substitute: Technique and first results

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MOTS CLÉS
Gingivopériostoplastie ;
Substitut osseux ;
Glass bone ;
Chirurgie pédiatrique

Résumé
Introduction. — La prise en charge orthodontico-chirurgicale d'une fente alvéolaire est essentielle en raison de ses répercussions sur la croissance faciale et la mise en place de la denture de l'enfant. Notre étude proposait la réalisation d'une gingivopériostoplastie (GPP) précoce dès l'âge de 4 ans, avec comblement par un substitut osseux (SO) afin d'abaisser l'âge de la fermeture des fentes alvéolaires et d'en limiter la morbidité.
Patients et méthodes. — Nous avons mené une étude rétrospective sur une année (janvier 2012 à décembre 2012), avec un recul de six mois, sur 23 cas de GPP avec greffe de substitut osseux de type *glass bone* au service de chirurgie plastique infantile du CHU Timone — Enfants de Marseille en France.
Résultats. — Nous avons retenu 23 patients. Dix-sept enfants dont 12 garçons et 5 filles ont présenté des fentes unilatérales. Vingt patients ont nécessité une quantité de *glass bone* < 1 cc pour les fentes étroites. La prévalence des fissures muqueuses a été faible (4 cas sur 23). La technique de la GPP avec SO est simple et nos résultats sont satisfaisants. Nous avons observé moins de morbidité du site opératoire.
Conclusion. — Les premiers résultats ont permis de noter que la GPP avec SO de type *glass bone* est une technique simple, fiable et reproductible, avec des résultats prometteurs. La réduction de la

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morbidité du site de prélèvement du greffon osseux, le coût d'achat abordable du *glass bone* et la simplicité du geste chirurgical constituent autant d'atouts pour l'adoption de cette technique.

KEYWORDS
Gingivo periosto plastic surgery;
Osseous substitute;
Glass bone;
Pediatric surgery

Summary
Introduction. — Ortho dontico-surgical coverage of alveolar crack is essential in reason of its repercussions on facial growth and implementation of children's teeth set. We proposed to realize a premature gingivo periosto plastic surgery from 4 years old by osseous substitute to lower age of alveolar cracks closure and decrease the morbidity of patients.
Patients and methods. — We conducted a retrospective study over one year (January, 2012 to December, 2012), with six months postoperatively outcomes, on 23 cases of gingivo periosto plastic sugary with osseous substitute type glass by bone transplant at infantile plastic surgery service of Timone — Children teaching hospital of Marseille, France.
Results. — We held 23 patients. Seventeen children, 12 boys and 5 girls presented unilateral cracks. Twenty patients required a quantity of glass bone under 1cc for the narrow cracks. Prevalence of the mucous cracks was low (4 cases on 23). Technique of gingivo periosto plastic surgery with osseous substitute is simple and our results are globally satisfactory. We observed less morbidity of the operating site.
Conclusion. — The first results of this study showed that gingivo periosto plastic surgery with osseous substitute glass bone is a simple, reliable and reproducible technique, with promising results. Reduction of site's morbidity by osseous transplant, accessibility of glass bone cost and simplicity of surgical gesture justified adoption of this technique.

Introduction

La prise en charge orthodontico-chirurgicale d'une fente alvéolaire est essentielle en raison de ses répercussions sur la croissance faciale et la mise en place de la denture de l'enfant. Dans le souci d'abaisser l'âge de la fermeture des fentes alvéolaires et d'en limiter la morbidité chez nos patients porteurs de fentes labio-maxillo-palatines uni- ou bilatérales, nous avons récemment choisi, après une chéiloplastie primaire en condition néonatale et une fermeture palatine par uranostaphylorraphie à 10 mois, de proposer une gingivopériostoplastie (GPP) précoce dès l'âge de 4 ans, associée à la mise en place d'un substitut osseux (SO). Ceci a été rendu effectif par la possibilité de proposer une expansion palatine transverse en denture lactéale dès 3 ans et demi à 4 ans. L'idée première était soit d'éviter une greffe osseuse classique ultérieure, ou de créer de meilleures conditions locales pour la réalisation de celle-ci en absence de ré ossification suffisante du substitut osseux. Séduits par la facilité de réalisation de cette technique, la diminution de la morbidité et l'absence de complication chez nos patients, la technique a été rapidement étendue aux patients âgés de 10—12 ans en attente de GPP associée à une greffe osseuse iliaque. Nous exposons ici la technique de la GPP avec greffe de SO, ainsi que les premiers résultats concernant l'ostéointégration du SO, au travers des 23 cas opérés dans le service de chirurgie plastique infantile du CHU Timone — Enfants de Marseille.

Patients et méthodes

Notre étude a été réalisée dans le service de chirurgie plastique et reconstructrice pédiatrique du CHU Timone — Enfants à Marseille. Il s'agit d'un centre pluridisciplinaire de prise en charge des fentes faciales, où se réunissent mensuellement tous les praticiens impliqués dans la prise en charge globale des fentes (chirurgiens plasticiens, chirurgiens maxillo-faciaux et stomatologues, orthodontistes, orthophonistes, et parfois oto-rhino-laryngologistes). Nous avons mené une étude rétrospective sur une année (janvier 2012 à décembre 2012), avec un recul d'au moins six mois, sur 23 cas de GPP avec greffe de substitut osseux de type *glass bone*. Une fiche d'enquête préétablie nous a servi de support pour la collecte des données essentiellement épidémiologiques, cliniques et radiologiques. Ont été inclus dans notre étude, les enfants des deux sexes, porteurs de fentes alvéolo-palatines uni ou bilatérales, âgés de 4 ans à plus de 10 ans, et ayant bénéficié d'une GPP avec greffe de SO de type *glass bone* au cours de l'année 2012. Tous ces enfants devraient avoir bénéficié d'une préparation orthodontique préopératoire, et avoir un bilan radiologique pré et postopératoire (panoramique dentaire, Denta scanner, ou New Tom scanner 3G). N'ont pas été inclus les patients dont l'un des critères sus-cités au moins était manquant. La préparation orthodontique préopératoire reposait sur la correction des troubles de croissance transversaux du maxillaire à l'aide d'un Quad Hélix scellé sur les molaires, la contention fixe par une barre palatine avec bras d'extension, la correction de l'occlusion croisée antérieure, l'alignement et la préservation du potentiel dentaires. Notre protocole chirurgical était le suivant : l'abord endobuccal réalisait une incision muqueuse aux collets des dents en bordure de la fente au bistouri à lame froide n° 15, puis verticalement sur les berges muqueuses de la fente. Une incision de décharge complétait l'abord dentaire qui allait souvent jusqu'à la première molaire du petit côté de la fente (Fig. 1). Un décollement sous-périosté permettait ainsi une exposition des deux berges osseuses. Ce qui permettait d'obtenir ainsi un lambeau

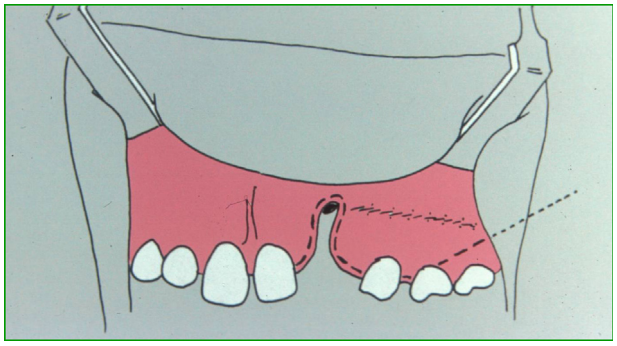

Figure 1 Tracé des incisions muqueuses.

de glissement mucopériosté décrit par Troxell [1], pour la couverture vestibulaire du greffon. Les plans muqueux nasal et palatin étaient ensuite individualisés et délicatement suturés (Fig. 2). Les berges osseuses de la fente alvéolaire étaient avivées, puis un volume de substitut osseux de type *glass bone* équivalent au défect osseux de la fente y était déposé et tassé. Il était préalablement imbibé de sang du patient prélevé sur le site opératoire (Fig. 3). La fermeture muqueuse vestibulaire était assurée par un lambeau de glissement mucopériosté du petit côté de la fente. Toutes les sutures muqueuses devaient être le plus étanches possible, et sans tension (Fig. 4).

Le *glass bone* est un substitut osseux 100 % synthétique ; il s'agit d'une biocéramique faite d'éléments naturels inorganiques (Ca, Ni, Si, P), et obéissant aux critères de biocompatibilité, de résorption et de bio-activité. Le *glass bone* induit la stimulation et la prolifération des ostéoblastes, assurant ainsi la régénération du tissu osseux.

Résultats

Au total, nous avons retenu 23 patients, dont 16 garçons et 7 filles (sex-ratio = 2,9). La répartition des patients selon le type de fentes était comme suit : fentes unilatérales : 17 dont 12 garçons et 5 filles ; fentes bilatérales : 6 dont 4 garçons et 2 filles ; fentes étroites (espace entre les 2 fragments < 5 mm) : 18 dont 12 garçons et 6 filles et fentes larges (espace entre les 2 fragments > 5 mm) : 5 dont 4 garçons et 1 fille. Parmi les enfants de 4—6 ans, il y avait 4 garçons et 2 filles, entre 7—9 ans il y avait 7 garçons et 2 filles et au-delà de 10 ans, 5 garçons et 3 filles. Les consignes postopératoires immédiates en termes d'alimentation et de soins buccaux ont été bien suivies par les parents. Un seul cas de négligence des consignes a été noté, avec comme conséquence un saignement à j2 postopératoire. Le Tableau 1 indique le volume de *glass bone* utilisé selon l'âge des patients.

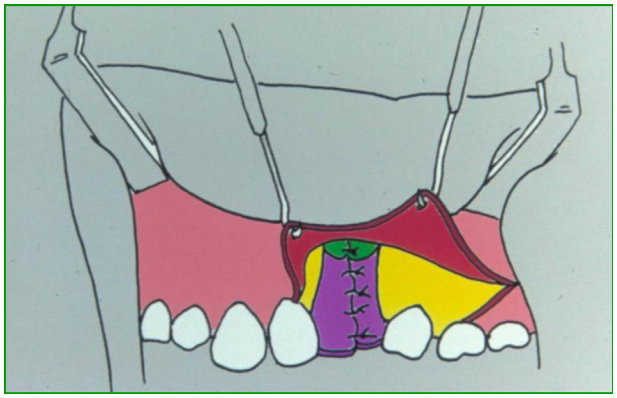

Figure 2 Individualisation des plans muqueux nasal et palatin qui sont suturés ; levée du lambeau de Troxell.

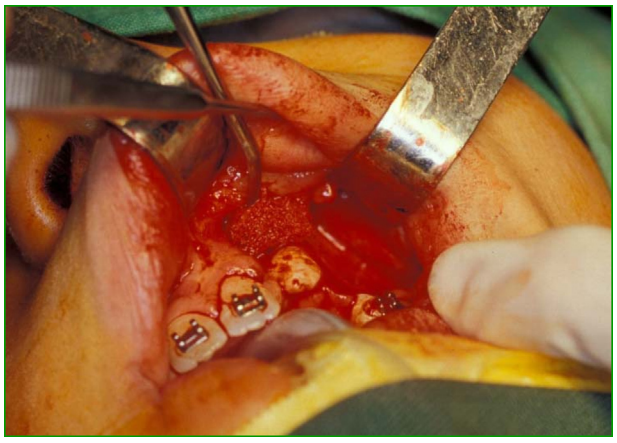

Figure 3 Mise en place du SO (*glass bone*) en peropératoire.

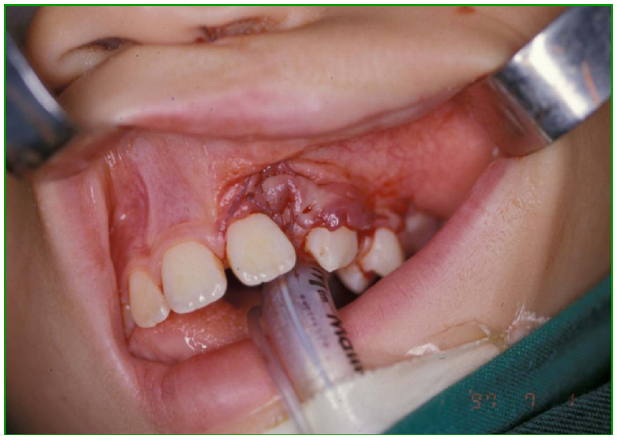

Figure 4 Aspect des sutures en fin d'intervention.

On n'a pas noté de lâchage de suture ni d'infection du site opératoire. Le substitut osseux a été bien toléré au niveau du site, et aucun phénomène inflammatoire n'a été noté. Un seul cas de saignement postopératoire a été signalé à j2 postopératoire, sans lâchage des points de

Tableau 1 Volume de *glass bone* utilisé selon l'âge des patients.

Âge des patients	< 1 cc	> 1 cc	Total
4—6 ans	6	0	6
7—9 ans	6	3	9
10 ans +	8	0	8
Total	20	3	23

Tableau 2 Évaluation de la qualité des sutures muqueuses selon l'âge des patients.

Âge des patients	Suture de bonne qualité	Suture sous tension	Suture impossible	Qualité non précisée	Total
4—6 ans	2	1	1	2	6
7—9 ans	6	2	1	0	9
10 ans +	4	4	0	0	8
Total	12	7	2	2	23

Tableau 3 Évaluation de l'existence de fissure muqueuse peropératoire selon l'âge.

Âge des patients	Présence de fissure muqueuse	Absence de fissure muqueuse	Existence de fissure non précisée	Total
4—6 ans	1	0	5	6
7—9 ans	1	1	7	9
10 ans +	2	1	5	8
Total	4	2	17	23

suture (Tableau 2) ni d'infection du site opératoire. L'existence ou non des fissures muqueuses peropératoires figure dans le Tableau 3. Les orthopantomogrammes sont des radiographies de débrouillage permettant de donner une idée de la denture et de l'environnement dentaire et osseux de la fente. Ils ont été réalisés en denture lactéale ou mixte, en préopératoire et en postopératoire dans le bilan de suivi des fentes. Le scanner du maxillaire en coupes axiales a permis de mieux apprécier l'étendue de la fente, l'environnement osseux et dentaire autour de la fente, et surtout d'évaluer la quantité de substitut osseux nécessaire au comblement au cours de la GPP (Fig. 5, scanner maxillaire). Il était demandé en préopératoire, puis en postopératoire dans le bilan de suivi des fentes. Le scanner ou le New Tom scanner a été demandé à 3 mois postopératoire, puis à 6, 12 et 18 mois. Le New Tom scanner a trouvé ici un grand intérêt du fait de sa dose d'irradiation faible comparée au scanner conventionnel, et de sa précision dans l'analyse des tissus osseux et dentaires. Il a été surtout demandé en préopératoire pour évaluer le volume de substitut osseux à prévoir, et en postopératoire pour évaluer le résultat de la greffe osseuse (Fig. 6, New Tom scanner).

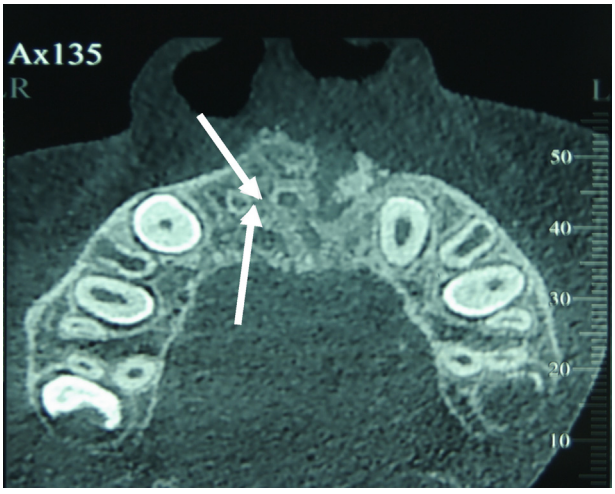

Figure 5 Aspect scanographique de l'environnement osseux et dentaire à 3 mois postopératoire d'une GPP avec *glass bone*.

Discussion

L'objectif de notre étude était d'abaisser l'âge et la morbidité de la prise en charge chez des patients porteurs de fentes labio-maxillo-palatines, en proposant une GPP précoce dès l'âge de 4 ans avec greffe de substitut osseux. C'était soit pour éviter une greffe osseuse classique ultérieure (par greffon de crête iliaque), ou pour créer de meilleures conditions locales pour la réalisation de celle-ci en absence de ré ossification suffisante du substitut osseux. Mais la facilité de réalisation de cette technique, la diminution de la morbidité et l'absence de complication chez nos patients, nous ont conduit à l'étendre aux patients âgés de 10—12 ans ou plus, en attente de GPP associée à une greffe osseuse iliaque. Nos résultats étaient satisfaisants dans le groupe des patients âgés de 4 à 6 ans (6 patients) au même titre que dans celui des patients âgés de plus de 6 ans (17 patients). Une étude antérieure avait été menée afin d'évaluer les résultats d'une alvéoloplastie réalisée avec greffon de crête iliaque chez des patients porteurs de fentes labio-maxillo-palatines. Ceux-ci étaient en denture mixte ou

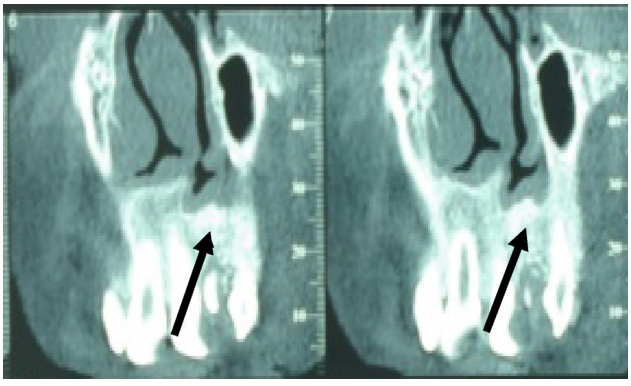

Figure 6 Aspect au New Tom scanner de l'environnement osseux et dentaire à 3 mois postopératoire d'une GPP avec *glass bone*.

lactéale et avaient un âge compris entre 4 ans et 14 ans [2]. Notre prise en charge était identique à celle utilisée dans cette étude, à la différence qu'en lieu et place du greffon osseux iliaque nous avons utilisé dans notre étude, un substitut osseux de type *glass bone*. Ceci, afin de réduire la morbidité liée au site de prélèvement du greffon iliaque. Comme dans notre étude, certains auteurs préconisent l'abaissement de l'âge de la greffe osseuse à 4 ou 5 ans [3—5]. Ces auteurs expliquent leur choix par une meilleure correction des anomalies de croissance verticale au niveau prémaxillaire et une amélioration de la pérennité de la greffe grâce aux éruptions dentaires qui permettraient sa mise en charge. Ils ont démontré une diminution du recours à une greffe ultérieure avant la mise en place d'implants dentaires à visée prothétique. L'action conjointe de l'expansion orthodontique et de la greffe osseuse à cet âge restaurerait plus tôt une ventilation nasale en élargissant l'orifice piriforme et la fosse nasale du côté de la fente. Six cas de greffe par substitut osseux ont été réalisés, avec des résultats précoces satisfaisants. Néanmoins, nous n'avons pas assez de recul suffisant pour prédire de la pérennité du résultat à long terme. Talmant [3], lui, a démontré que ce protocole permettait la réhabilitation prothétique dentaire par implants chez ces enfants dès l'âge de 14 ans, sans avoir recours à une nouvelle greffe. Plusieurs autres alternatives au greffon osseux ont été essayées afin de réduire la morbidité du site de prélèvement. Celles-ci ont d'abord été préconisées en chirurgie reconstructrice maxillo-faciale et en chirurgie orthopédique. Ce sont des techniques d'ingénierie tissulaires utilisant soit un ostéoprogéniteur associé à un support biocompatible, soit un support biocompatible ostéoconducteur seul [6]. Les procédés utilisés comme ostéoprogéniteurs sont les cellules souches mésenchymateuses autologues ou la recombinant *human bone morphogenic protein*. L'ostéoprogéniteur ne devra pas provoquer de réaction inflammatoire majeure, ni de rejet ou de transformation néoplasique. Les supports biocompatibles utilisés sont des polymères naturels, des polymères de synthèse, ou des céramiques phosphocalciques inorganiques. Ces biomatériaux doivent répondre aux exigences de biocompatibilité, d'ostéoconduction et d'ostéoinduction, de résorption avec un équilibre résorption du biomatériau/ostéogenèse, de radio transparence, et avoir un coût acceptable. Utilisé seul, le biomatériau doit attirer les cellules de l'hôte et stimuler la prolifération et la régénération osseuse. Il peut servir aussi de matrice pour l'ostéoprogéniteur en servant de réservoir aux cellules ostéocompétentes, et permettre la différenciation cellulaire [7]. Plusieurs études ont montré une bonne tolérance des biomatériaux utilisés, une ossification rapide de la zone greffée dans les 4 premiers mois, une meilleure reminéralisation comparée au greffon osseux classique, une réduction des douleurs postopératoires et de la durée d'hospitalisation [8,9]. Chez l'enfant, le recours aux cellules souches mésenchymateuses est limité du fait de la multitude de structures en pleine croissance, et aussi des possibilités limitées de prélèvement de la moelle osseuse. Ce qui a poussé certains auteurs à proposer l'utilisation chez l'enfant, de cellules souches de moelle osseuses différenciées in vitro en ostéoblastes, puis le comblement du défect par ces ostéoblastes incorporés dans un substrat biocompatible [10]. Même s'il existe à ce jour plusieurs possibilités en termes d'ingénierie tissulaire pour le comblement de défects osseux, leur application à l'enfant reste encore limitée. De plus, aucune étude ne dispose encore d'assez de recul dans cette population. Les fentes unilatérales ont été prédominantes dans notre série par rapport aux fentes bilatérales ; de même les fentes étroites < 5 mm ont dominé les fentes larges > 5 mm. Les patients d'âge compris entre 4 et 6 ans étaient peu nombreux dans notre série, contre ceux âgés de 7 ans et plus. Ceci s'explique probablement par le fait que la GPP était classiquement réalisée à un âge plus tardif dans le service. Vingt patients ont nécessité une quantité de *glass bone* < 1 cc (fentes étroites essentiellement), contre 3 patients qui avaient besoin d'un volume de *glass bone* > 1 cc (fentes larges). L'analyse de cette quantité de SO nécessaire pour une greffe dans le cadre des GPP oriente notre réflexion sur la pertinence de la réalisation d'un prélèvement d'os autologue chez ces patients, surtout eu égard aux risques liés au site de prélèvement du greffon osseux iliaque. Par rapport à la qualité des sutures muqueuses selon l'âge des patients, nous n'avons noté aucune différence quelque fût l'âge des patients. Ceci témoigne certainement de la maîtrise du geste chirurgical. La quasi-absence de complications postopératoires conforte de plus la faible prévalence des fissures muqueuses (4 cas sur 23). Les cas non mentionnés seraient liés au manque d'attention portée sur les sutures quand elles ne comportaient pas de problème particulier lors de la fermeture muqueuse. L'observance des consignes postopératoires immédiates et précoces était très importante dans l'évolution locale de la greffe. Elles concernaient l'alimentation orale et les soins de la cavité buccale. Le *glass bone*, substitut osseux biocompatible, n'a souffert d'aucune intolérance dans notre série. En témoigne l'absence de cas de rejet du greffon dans notre série. Le bilan radiologique a permis en préopératoire de faire le bilan de la fente et de son environnement dentaire, de quantifier le *glass bone* nécessaire au comblement, et en postopératoire d'évaluer le résultat de la greffe en termes d'ostéointégration du substitut osseux dans la fente, et aussi de la qualité des éruptions dentaires autour de la fente.

Conclusion

Les premiers résultats de cette étude nous ont permis de noter que la GPP avec SO de type *glass bone* est une technique simple, fiable et reproductible, avec des résultats prometteurs. Cette technique pourra être proposée précocement aux patients plus jeunes et également aux candidats d'une greffe osseuse classique. La réduction de la morbidité du site de prélèvement du greffon osseux, le coût d'achat abordable du *glass bone* et la simplicité du geste chirurgical constituent autant d'atouts pour l'adoption de cette technique.

Déclaration d'intérêts

Les auteurs déclarent ne pas avoir de conflits d'intérêts en relation avec cet article.

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RESEARCH ARTICLE Open Access

Effectiveness of bovine-derived xenograft versus bioactive glass with periodontally accelerated osteogenic orthodontics in adults: a randomized, controlled clinical trial

Maha A. Bahammam

Abstract

Background: Periodontally accelerated osteogenic orthodontics (PAOO) combines periodontal therapy with orthodontic therapy, which minimises treatment time. This study compared the effectiveness of a bovine-derived xenograft with that of bioactive glass when combined with PAOO for the treatment of adult patients with moderate crowding of the teeth.

Methods: In this prospective, single-masked clinical trial, 33 orthodontic patients (20 women, 13 men; mean age 21.2 ± 1.43 [18 – 27] years), were randomly allocated to one of three groups. Group 1 underwent a modified corticotomy technique on the labial side only, whereas group 2 was treated with the same technique combined with PAOO using a bovine-derived xenograft and group 3 was treated in the same way but combining PAOO with bioactive glass. The total treatment duration was recorded from the start of active orthodontic treatment, immediately after corticotomy, and at the time of debonding. Probing depth was evaluated clinically and bone density and root length were evaluated radiographically on the day of surgery (baseline, T1), post-treatment at debonding (T2), and 9 months post-treatment (T3).

Results: The duration of orthodontic treatment was markedly reduced to an average of 11.4 ± 0.14 weeks in all groups. All probing depths were < 3 mm, the interdental papillae were well preserved, there was no loss of tooth vitality, and there was no evidence of significant apical root resorption at any time interval. All groups showed a decrease in mean bone density at T2 followed by an increase at T3. The net percentage change that occurred between baseline and 9 months post-treatment was significantly different between the three groups. Groups 2 and 3, where grafts were incorporated, demonstrated a statistically significant greater increase in bone density than group 1 at T3.

Conclusion: Combination of orthodontic treatment and periodontal surgery is an effective treatment for adult patients that decreases the duration of active treatment and reduces the risk of root resorption. Use of a bovine-derived xenograft with modified corticotomy provided superior benefits in terms of increased bone density than did the use of bioactive glass.

Trial registration: The study was retrospectively registered at ClinicalTrials.gov under Clinical Trial Registration Number: NCT02796911.

Keywords: Alveolar bone density, Bone grafts, Corticotomy-assisted orthodontic treatment, Root resorption

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Background

There has been a significant increase in the number of adult patients seeking orthodontic treatment [1]. The average duration of routine orthodontic treatment for adults is considerably longer than for adolescent patients, ranging from 18.7 to 31 months, and even more time is required for extraction cases [2, 3]. Adult patients are also more vulnerable to root resorption and periodontal pathologies during or after active orthodontic treatment, given their narrow, aplastic, poorly vascularised periodontal membrane, and alveolar bone morphology [1, 4]. Hence, it is imperative to modify treatment modalities to reduce the treatment time and achieve optimal clinical results in adults.

Corticotomy and osteotomy have been used in orthodontics primarily to resolve crowding of teeth as rapidly as possible. In published case reports, moderate or severe crowding has been treated without extraction by corticotomy/osteotomy-assisted orthodontics, and in shorter time periods [5, 6]. It has been reported that this approach was efficient for reducing the treatment time to as little as a quarter of that usually required for conventional orthodontics [5, 7–9]. Additional applications for this technique have reportedly facilitated several orthodontic modalities in a short period of time, with greater post-orthodontic stability [7, 10].

A temporary stage of remodelling of localised soft and hard tissue, termed the "regional acceleratory phenomenon" (RAP), results in rebuilding of the sites injured in corticotomy/osteotomy to a normal state by recruitment of osteoclasts and osteoblasts via local intercellular mediator mechanisms that involve precursors, supporting cells, blood capillaries, and lymph. RAP begins within a few days of the insult, typically peaks at 1 – 2 months, and may take as long as 2 years to subside completely [11, 12].

Periodontally accelerated osteogenic orthodontics (PAOO) is a technique involving combination of a selective decortication-facilitated orthodontic technique and alveolar augmentation. Thus, teeth can be moved 2 – 3 times further in one third to one quarter of the time required by traditional orthodontic therapy. Moreover, PAOO provides an increased net alveolar volume after orthodontic treatment and is associated with low morbidity [9, 13]. The greater alveolar volume eliminates bony dehiscence and fenestrations under most circumstances [5]. Likewise, the additional alveolar bone width may be the cause of the enhanced long-term orthodontic stability noted with this technique [13, 14].

Hong et al. conducted a study in 2011 using a Beagle animal model for histologic assessment of the biological effects of PAOO. In the group that underwent corticotomy, no osteoclasts were found on the cementum or dentin, although numerous osteoclasts were detected around the alveolar bone facing the palatal side of the retracted incisor. In addition, a more intact periodontal ligament space of consistent thickness was noted between the surrounding alveolar bone and the root surface. The compression side of the retracted incisor showed no evidence of root resorption [7, 15].

Interestingly, current therapies in both traumatology and tissue regeneration dentistry are based on the use of artificial or natural materials, which produce stimulating signals that trigger physiological regeneration, a process that depends on three mechanisms: osteogenesis, osteoinduction, and osteoconduction [16]. Xenografts and bioactive glass offer such alternatives. A number of previous studies have demonstrated the effectiveness of xenografts as osteoconductive matrices [17–21]. On the other hand, bioactive glass is an alloplastic bone graft and a possible choice for alveolar augmentation in corticotomy-assisted orthodontic treatment (CAOT) [16–25]. Results from clinical studies have indicated that treatment of intrabony defects with bone grafts alone may result in improved clinical outcomes, as evidenced by improvements in probing depth (PD) and clinical attachment [23].

In spite of the advantages of PAOO, assessment of this technique remains challenging in clinical trials, and evidence of the success of these grafts has been evaluated only in a few case reports [5, 8, 26, 27]. Accordingly, the purpose of this study was to evaluate the effectiveness of a bovine-derived xenograft versus that of bioactive glass, using a modified corticotomy procedure, in the orthodontic treatment of adult patients with moderate crowding.

Methods

Sample

The study protocol was approved by the ethics committee of King Abdulaziz University in accordance with the guidelines published by the CONSORT group and the World Medical Association's Declaration of Helsinki, (proposal number 029-16). All research procedures were explained to the patients, who provided signed consent to participate in the study. The study was retrospectively registered at ClinicslTrials.gov under Clinical Trial Registration No. (NCT02796911).

Thirty-three adult orthodontic patients (23 female, 10 male) of mean age 21.2 ± 1.43 (range 18 – 27) years were included in this randomised, prospective, single-masked trial that was conducted between February 2015 and March 2016. The study participants were selected from patients seeking orthodontic treatment at the outpatient clinic in the Orthodontic Department, Faculty of Dentistry, King Abdulaziz University. The criteria for inclusion in the study were as follows: good oral hygiene and systemic health; PD values (measured as the distance from

the bottom of the sulcus to the most apical portion of the gingival margin) not exceeding 3 mm; no radiographic evidence of bone loss; no regular administration of any medication that affects bone metabolism, such as prolonged use of corticosteroids, bisphosphonates, or non-steroidal anti-inflammatory drugs; moderate crowding of the lower anterior teeth only, ranging from 4 – 5 mm; and no previous orthodontic treatment.

Cephalometric analyses were performed to limit patient selection to those with a Class I skeletal pattern and a favourable mandibular incisor plane angle. Orthodontic study cast analyses were used to limit the selection to cases of moderate crowding. Standardised digital periapical radiographs from the left mandibular canine to the right mandibular canine were used and the exposure parameters were fixed for all patients, both initially and during the follow-up period.

Each patient was randomly assigned to one of three groups, masked with respect to assignment and each containing 11 patients. Group 1 (seven women, four men) was treated with a modified technique of CAOT alone, group 2 (six women, five men) was treated with CAOT combined with a bovine-derived xenograft (Bio-Oss, Geistlich, Princeton, NJ, USA), and group 3 (seven women, four men) was treated with CAOT combined with bioactive glass (GlassBone, NORAKER, Villeurbanne, France). Randomisation was performed using a commercially available computer software package (NCSS-PASS, Number Cruncher Statistical Systems, Kaysville, UT, USA).

The proposed treatment procedures along with their advantages and disadvantages were explained in detail to all patients and informed consent was obtained. Initial prophylaxis and periodontal therapy, consisting of full mouth scaling utilising both hand and ultrasonic instruments, were performed under local anaesthesia.

Each participant received orthodontic treatment with a mandibular fixed appliance inserted during the week preceding surgery. In accordance with the treatment plan, the standardised treatment protocol used a pre-adjusted appliance that included direct bond brackets (Roth Prescription) 0.022" × 0.028" in size (Integra Brackets, Rocky Mountain Orthodontics Inc, Denver, CO, USA) from the right mandibular second premolar to the left mandibular second premolar, using a chemical cure orthodontic adhesive (Transbond XT; 3 M Unitek, Monrovia, CA, USA) and banding of the mandibular first molars (Rocky Mountain Orthodontics Inc). The appliance was not activated presurgically. Orthodontic tooth movement was started 2 weeks after the corticotomy procedure; the interval allowed between routine orthodontic adjustments was 2 weeks, which is in line with previous recommendations [5, 9, 27].

During orthodontic treatment, the mandibular arch was initially levelled and aligned using nickel titanium arch wires of increasing size (0.012", 0.014", 0.016", and 0.018"). Thereafter, rectangular stainless steel wires (0.016" × 0.022") were placed. Stainless steel arch wires up to size 0.019" × 0.025" were used for finishing. During the active tooth movement phase, patients were assessed by the periodontist at monthly intervals.

Periodontal surgical procedure

The PAOO technique used for the three groups in the current study was performed under local anaesthesia and is a modification of the basic corticotomy technique described by Wilcko et al. [8, 9, 27]. Intra-crevicular full-thickness flaps were reflected labially only from the distal surface of the lower right canine to the distal surface of the lower left canine while preserving the interdental papilla. The labial flap was reflected beyond the apices of the lower anterior teeth. Selective alveolar decortication was then performed in the form of vertical grooves through the labial cortical plate of bone, using a small round stainless steel surgical bur (number 2) in a low-speed hand piece, under copious irrigation, and extended through the entire thickness of the cortical plate, barely reaching the medullary bone. The vertical grooves started 1 – 2 mm below the alveolar crest and extended 1 – 2 mm below the apices of the teeth (Fig. 1). The lingual flap was not elevated and no horizontal subapical cuts were performed [28].

In groups 2 and 3, after completion of the corticotomy procedure, a bovine xenograft and/or bioactive glass were mixed with blood from the surgical site in a sterile Dappen dish until a sandy consistency was obtained. The resulting coagulum was transferred in increments and applied directly over the decorticated areas (Fig. 1). Next, the flap was carefully repositioned at the original

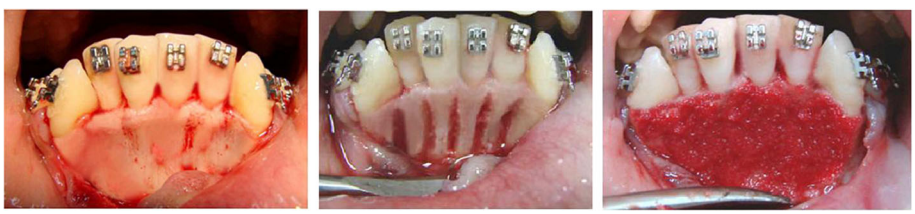

Fig. 1 Surgical procedures

pre-surgical site and sutured with nonresorbable 4-0 silk using the interrupted technique [23, 29].

All patients were provided with oral hygiene instructions and closely monitored to prevent inflammation of the gingival tissues. Antibiotic, diuretic, and analgesic agents were prescribed for 7 days. The efforts to control plaque formation were augmented by antiseptic mouthwash (0.12% chlorhexidine gluconate, for 1 min twice daily for 2 weeks), and the sutures were removed after 10 days. Figure 2 shows representative intraoral images taken before and after treatment.

Data analysis

The total duration of active orthodontic treatment was estimated in weeks for the three study groups from the time of starting active orthodontic treatment, immediately following the corticotomy procedure, to the time of debonding.

Clinical and radiographic parameters were recorded on the day of surgery (T1), post-treatment (at time of debonding) (T2), and 9 months post-treatment (T3) for all three groups. PD measurements were taken using a William's probe 26 from the gingival margin to the base of the sulcus and recorded to the nearest millimetre. Six readings for each tooth were recorded (mesial, distal, and midpoint for both the labial and lingual surfaces).

Radiographic measurements were obtained from standardised digital periapical radiographs from the left mandibular canine to the right mandibular canine using Digora system software (Orion Corp, Sordex Medical System, Helsinki, Finland). The radiographic images for each patient were saved and analysed to record bone density and root length, and the mean of the readings was calculated (Fig. 2).

To measure the bone density, the mean grey value in each region of interest was calculated (256 grey levels of colour resolution) by assigning the grey value of 0 to black, and a grey value of 256 to white. Linear density was measured by drawing a line parallel to the root surface, extended from the apex of the alveolar crest to the level of the apex of the root. A line was drawn midway between every two lower anterior teeth. Five lines were drawn (between the lower right canine and lateral incisor, between the lower right lateral incisor and central incisor, between the two lower central incisors, between the lower left lateral incisor and central incisor, and between the lower left canine and lateral incisor).

The grey level along each line was recorded at the beginning, middle, and end of the line, and the average of the three readings was calculated to obtain the mean average density (grey level) along this line. The mean value of the readings of the five lines was calculated to present the density value.

The root length was assessed by measuring the distance between the cemento-enamel junction (as a reference point) and the apex of the root in millimetres.

One operator (MB) performed all the surgeries and was informed of group assignment after corticotomy just before placing the graft material. Another calibrated operator, who was not involved in the study, performed all the clinical and radiographic measurements without knowledge of group assignment. Intra-examiner calibration was evaluated before starting the study by examination of 30 sites on two separate occasions 48 h apart.

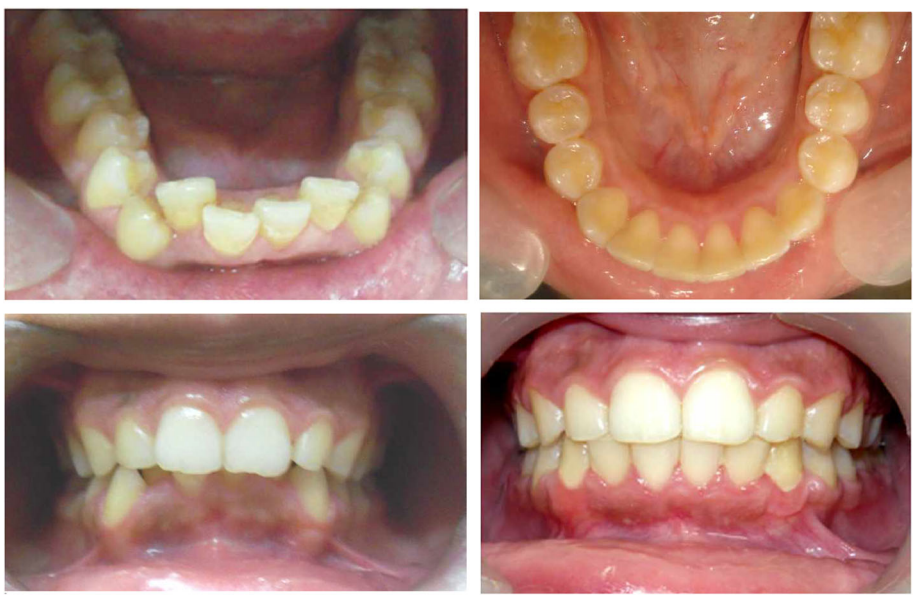

Fig. 2 Occlusal and frontal Pre and post treatment intraoral pictures

Calibration was only accepted if 90% of the readings could be reproduced within a 1 mm difference.

The primary outcome of the study was duration of orthodontic treatment from baseline to the time of debonding. Secondary outcomes included changes in PD, bone density, and root length up to 9 months post-treatment.

Statistical analysis

The collected data were tabulated and statistically analysed using Statistical Package for the Social Sciences version 20 (IBM Corp., Armonk, NY USA). Descriptive statistics (mean, standard deviation, range) are presented. One-way analysis of variance was used to compare data between the three groups, and a post-hoc (Tukey's) test was used for pair-wise comparisons between the groups when analysis of variance test were significant. The Student's *t*-test was used to compare the mean differences within each group for each time interval.

Results

The total treatment time was calculated in weeks from the time of activation of the orthodontic appliance immediately following the corticotomy procedure to the time of debracketing. The treatment duration for patients in all groups ranged from 12 to 20 weeks, with a mean of 15 weeks for group 1, 16.8 weeks for group 2, and 14.4 weeks for group 3. Figure 3 shows representative intraoral images before and after treatment.

Clinical parameters

Probing depth

There was no significant difference in PD at baseline between the three groups ($P > 0.05$; Table 1). Within each group, there was a significant difference between the participants in terms of the net amount of change in PD that occurred between the start of treatment and 9 months post-treatment ($P > 0.05$; Table 2).

There was a statistically significant difference between the three groups regarding the change that occurred in PD during each time interval. Nine months post-treatment (during the retention period), group 1 demonstrated a mean PD of 1.18 ± 0.19 mm, while group 2 demonstrated a mean PD of 1.20 ± 0.20 mm and group 3 demonstrated a mean PD of 1.19 ± 0.18 ($P > 0.05$; Table 1).

Bone density

Within the three groups, there were significant differences in the amount of change that occurred in bone density during the different time intervals. During the period of active tooth movement (from pre-treatment to post-treatment), all groups demonstrated a decrease in bone density; the mean decrease was -29.82% in group 1, -14.43% in group 2, and -24.04% in group 3. The amount of increase in bone density from post-treatment to 9 months post-treatment was also significantly different between the three groups; the mean increase was 0.87% in group 1, 31.99% in group 2, and 13.71% in group 3 (Table 1). The net percentage increase in bone density from the start of treatment to 9 months post-treatment (97.53% ± 6.33%) was greater in group 2 than in groups 1 and 3.

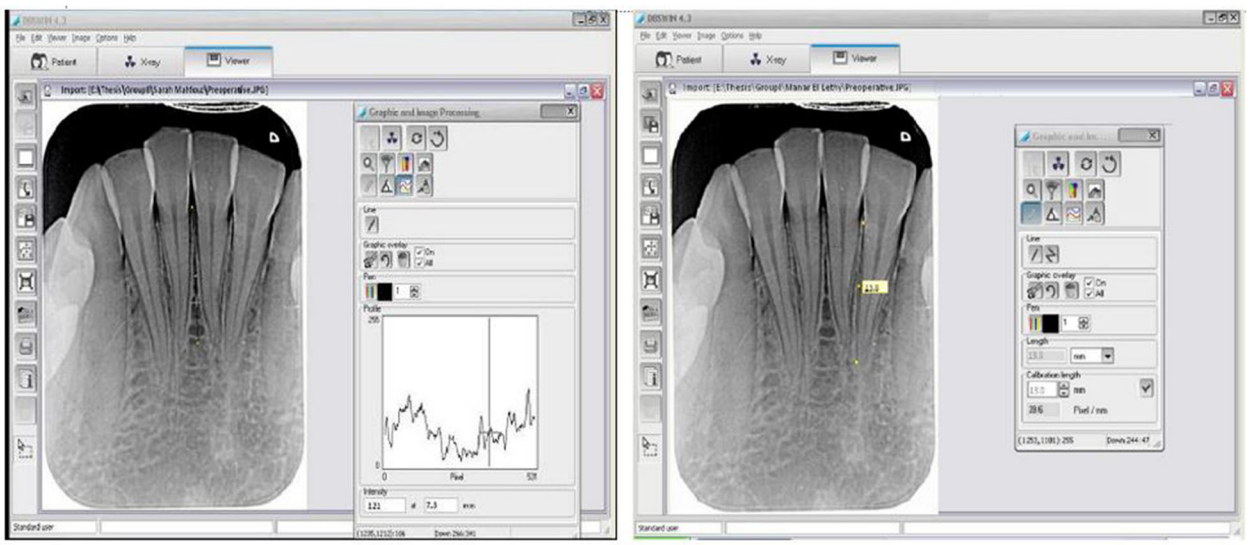

Fig. 3 Radiographic assessment

Table 1 Mean probing depth, bone density, and root length between the groups at each time interval

Parameter	Time	Group 1 (CAOT without graft)		Group 2 (CAOT with xenograft)		Group 3 (CAOT with bioactive glass)		*P*-value
		Mean	SD	Mean	SD	Mean	SD	
Probing depth (mm)	T1	1.54	0.17	1.57	0.13	1.56	0.14	0.054
	T2	1.17[b]	0.16	1.19[a]	0.14	1.19[a]	0.17	0.047*
	T3	1.18[b]	0.19	1.20[a]	0.20	1.19[a,b]	0.18	0.012*
Bone density	T1	63.24[c]	7.21	65.54[b]	6.41	66.41[a]	6.32	<0.000*
	T2	33.42[c]	6.81	51.11[a]	6.21	42.32[b]	6.43	<0.000*
	T3	64.11[c]	6.22	97.53[a]	6.33	80.12[b]	6.31	<0.000*
Root length (mm)	T1	12.81[b]	0.73	12.82[a]	0.54	12.82[a]	0.51	0.037*
	T2	12.79	0.71	12.79	0.64	12.80	0.53	0.968
	T3	12.78	0.64	12.78	0.53	12.79	0.52	0.060

Notes: *P*, probability level; *$P \leq 0.05$; different superscript letters in the same row are significantly different. *n* number; T1, before CAOT (baseline); T2, after debonding (post-treatment); T3, 9 months after debonding. *Abbreviations*: *CAOT* corticotomy-assisted orthodontic treatment, *SD* standard deviation

Root resorption

There was no significant difference between the three groups in terms of the average root length values obtained pre-treatment, post-treatment, and 9 months post-treatment. The difference in the net amount of root resorption between the three groups was also statistically insignificant. The average net decrease in root length was -0.02 ± 0.02 mm in group 1, -0.03 ± 0.11 mm in group 2, and -0.01 ± 0.01 mm in group 3 (Table 1).

Discussion

Most orthodontic patients, and particularly adults, are interested in the possibility of reducing their treatment time. Given this constant demand for shorter treatments, orthodontists have increasingly sought ways and new approaches to shorten the treatment duration without compromising results. CAOT has been suggested for reducing the orthodontic treatment time [5, 6, 8, 9, 28–30]. PAOO can play a major role in the comprehensive treatment of occlusal and esthetic needs in some patients. PAOO is an extension of previously described techniques involving surgical alteration of the alveolar bone to decrease treatment time [5].

In this study there was a significant reduction in the treatment time for adult patients demonstrating moderate crowding to an average of 11.4 (range 10 – 13) weeks. This is in agreement with other reports of CAOT [5–9, 30–32] and agrees with the findings of Wilcko et al., who presented cases treated over short periods with a combination of CAOT and periodontal alveolar augmentation [5, 8, 9, 27].

Table 2 Comparison of mean probing depth (mm) in each group at different time intervals

Group	Time interval	Mean difference	SD difference	*P*-value
Group 1	T1–T2	0.37	0.08	0.002*
	T1–T3	0.36	0.09	0.004*
Group 2	T1–T2	0.38	0.07	0.001*
	T1–T3	0.37	0.08	0.000*
Group 3	T1–T2	0.37	0.08	0.001*
	T1–T3	0.37	0.08	0.002*

Notes: *P*, probability level; *$P \leq 0.05$; T1, before CAOT; T2, after debonding; T3, 9 months after debonding
Abbreviation: *SD* standard deviation

Thirty-three patients were initially enrolled in the present study, but four were excluded because of multiple missed appointments and failure to maintain good oral hygiene, when a considerable amount of patient cooperation was necessary. After 9 months, only 27 patients were available for clinical and radiographic re-evaluation; these patients had a good clinical outcome and did not experience any relapse.

Interestingly, the current results also showed that the total orthodontic treatment time was markedly reduced when compared with the average treatment time (31 months) for extraction therapy [2, 33]. In a clinical trial, Hajji [7] investigated the effects of resolving mandibular anterior dental crowding by comparing non-extraction, extraction, and CAOT approaches. The mean active treatment time for the CAOT group was 6.1 months versus 18.7 months in a non-extraction orthodontic group and 26.6 months in an extraction group, which is consistent with the findings of the present study.

Several theories have been proposed in an attempt to explain the rapid tooth movement observed after corticotomy. The initial concept, which prevailed in several subsequent reports, was based on "bony block movement". According to this theory, the tooth embedded within a block of medullary bone serves as the handle by which the bands of less dense medullary bone surrounding the teeth are moved block by block [33]. However, the latest concept concerning the rapid tooth movement after corticotomy is supported by RAP, described as accelerated bone turnover and decreased regional bone density [8, 9, 12, 33, 34]. RAP is a local response to a

stimulus, and describes a process by which tissue forms more rapidly than during the normal regional regeneration process. The term "regional" refers to the demineralisation of both the cut site and the adjacent bone and the term "accelerated" refers to an exaggerated or intensified bone response in cuts that extend to the marrow. It is explained as a temporary phase of localised soft and hard tissue remodelling that results in rebuilding of the injured sites to a normal state. By enhancing the various healing stages, this phenomenon causes healing to occur 2–10 times more rapidly than normal physiological healing. The RAP mechanism potentiating tissue healing has been shown to occur in the mandible as well as in the long bones [12, 34, 35].

No hazardous effects on the periodontium were observed after corticotomy in this study. PD in particular was not significantly different between the study groups (Table 1). Not only was there no deterioration in periodontal depth, but patients demonstrated a slight improvement in PD values.

Unlike most of the corticotomy procedures described earlier, the present cortical cuts were made in the labial cortical plate of bone only, without making subapical cuts, and the lingual flap was not reflected. This was performed to support the blood supply of the mandibular dentoalveolar region via the lingual mucosa and to protect the thin roots of the incisors in the region where access is difficult and there is a possibility of damaging the teeth. Labial subapical horizontal cuts were omitted to protect the overlying cortical bone and to maintain the blood supply to the incisors, because the spongiosa bone was not left intact. Furthermore, it was assumed that RAP induced by the buccal corticotomy would readily involve the non-corticotomised lingual side [28, 36]. Moreover, the main purposes of using the present conservative technique were to reduce the duration and extent of surgery and the postoperative discomfort by eliminating exposure of the patient to the risks of additional lingual surgery [28, 36]. In addition, using the current corticotomy technique, the vertical cuts were started 1 – 2 mm below the alveolar crest in an attempt to protect the crestal bone and periodontal membrane, as per previous recommendations [28].

Several reports have speculated that, by avoiding the crest of the marginal bone during vertical corticotomies, there would be less risk of damage to the marginal periodontium [5, 6, 28, 33, 37]. These surgical conservative criteria could explain the absence of detrimental clinical side effects on the periodontium in this study.

The current results are in accordance with other reports of rapid tooth movement and reduced treatment times without clinically noticeable adverse periodontal effects [8, 30, 38]. The fact that the teeth can be moved more rapidly, thus resulting in shortened treatment times, is certainly advantageous for periodontal health, because a reduction of the time that the patient needs a fixed appliance reduces patient "burnout" and substantially reduces the time available for relatively benign commensal bacterial biofilms to undergo qualitative changes and convert to a destructive cytotoxic ("periodontopathic") type, which is often seen when fixed appliances have remained on the teeth for more than a year [9].

The present study revealed a reduction in alveolar bone density at the time of debonding (T2) in all three groups (Table 1). This is in agreement with other reports that have attributed this to the trauma caused to cortical bone, which has been shown to be a potentiating factor in producing localised osteoporosis or reversible osteopenia. For bone, this temporary condition means increased mobilisation of calcium, decreased bone density, and increased bone turnover, all of which would facilitate more rapid tooth movement [28, 39–41]. After an initial reduction, the bone density had increased again at 9 months post-treatment in all three groups (Table 2), which adds further support to the view that the dynamics of tooth movement in these patients might be more appropriately described as a demineralisation/remineralisation process, rather than bony block movement [8, 9, 15, 16, 28, 36, 39–41].

PAOO with bone augmentation was performed in the present study to increase alveolar volume and to avoid the possible risks of the procedure [8, 9]. It was considered that the roots would still have sufficient support if very large expansions were implemented to resolve severe crowding. The reshaped alveolar bone provides additional support for the roots of the teeth after completion of treatment and diminishes potential dehiscence [8, 9, 36]. Two different types of bone grafts, a xenograft (bovine xenograft) and an alloplast (bioactive glass), were utilised in this study. Numerous studies have shown the biocompatibility and effectiveness of a variety of xenografts that incorporate biomaterials derived from bovine bone. Other studies have reached the conclusion that this material has a system of interconnected pores, the structure of which is similar to that of human spongy bone, which may contribute to promoting the close interrelationship between hydroxyapatite and bone during growth [17–25]. Bioactive glass was selected as the second bone graft material because a number of in vivo and in vitro studies have highlighted its potential as a regenerative scaffold [18, 21, 22]. Moreover, highly bioactive glass particles have good clinical manageability and certain haemostatic properties, and showed both osteoproduction and osteoconduction [22].

It is interesting to note that, at the end of the study period, there was a significantly greater increase in bone density in the two groups that had been treated with bone grafting when compared with the group that had

been treated with a modified CAOT alone (Table 1). Moreover, patients who were treated with the bovine-derived xenograft showed a greater (albeit not statistically significant) increase in bone density than those who were treated with bioactive glass. This could be attributed to a different ability of the two biomaterials to promote bone formation. In addition, the composition of animal bone is morphologically more similar than any synthetic product to human bone; a previous analysis of the results of clinical testing and the clinical take-up of different products developed by the biomedical industry has shown the overall superiority of bone substitutes of natural origin over derivative substitutes [40, 42].

In terms of root resorption, the current study revealed no significant difference in root length values between the three study groups (Table 1). Root resorption is a complex process, involving the combination of a multitude of biological and mechanical factors. It is generally accepted that some root resorption is expected with any orthodontic tooth movement [43] Thus, it is believed that the absence of any significant root resorption in this study might be, in part, attributed to the short treatment duration, which is in agreement with previous reports of this advantage of CAOT [22, 29, 31, 32, 44]. However, incorporation of bone grafting appears to have little effect on the incidence or amount of root resorption because of the absence of any statistically significant difference between the three groups regarding the amount of root resorption (Table 1).

Conclusions

The results of this study suggest that PAOO is an effective and promising treatment approach that can decrease the active treatment duration, the risk of root resorption, and/or adverse periodontal effects in adult patients. PAOO may improve the state of the periodontium by increasing bone density and decreasing the risk of root resorption. Use of bovine-derived xenografts provided better results than bioactive glass in terms of increasing bone density. However, further randomised testing in humans is required to shed more light on an expanded use of PAOO, as well as to confirm the claimed advantages of this technique and evaluate the long-term effects and stability of such treatment.

Abbreviations

CAOT: Corticotomy-assisted orthodontics; PAOO: Periodontally accelerated osteogenic orthodontics; PD: Probing depth; RAP: Regional acceleratory phenomenon

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Availability of data and materials

Raw Data will be available on request with permission of Faculty of Dentistry, King Abdulaziz University.

Author information

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Competing interests

Bahammam MA has no conflict of interests, and the work was not supported or funded by any bone graft/pharmaceutical company.

Consent to publish

Signed consent was obtained from all participants to publish their personal details and images.

Ethics approval and consent to participate

The study protocol was submitted and approved by the ethical committee of King Abdulaziz University (proposal number 029-16). All research procedures were explained to the patients, who provided signed consent to participate in the study. The study was retrospectively registered at ClinicsITrials.gov under Clinical Trial Registration Number NCT02796911.

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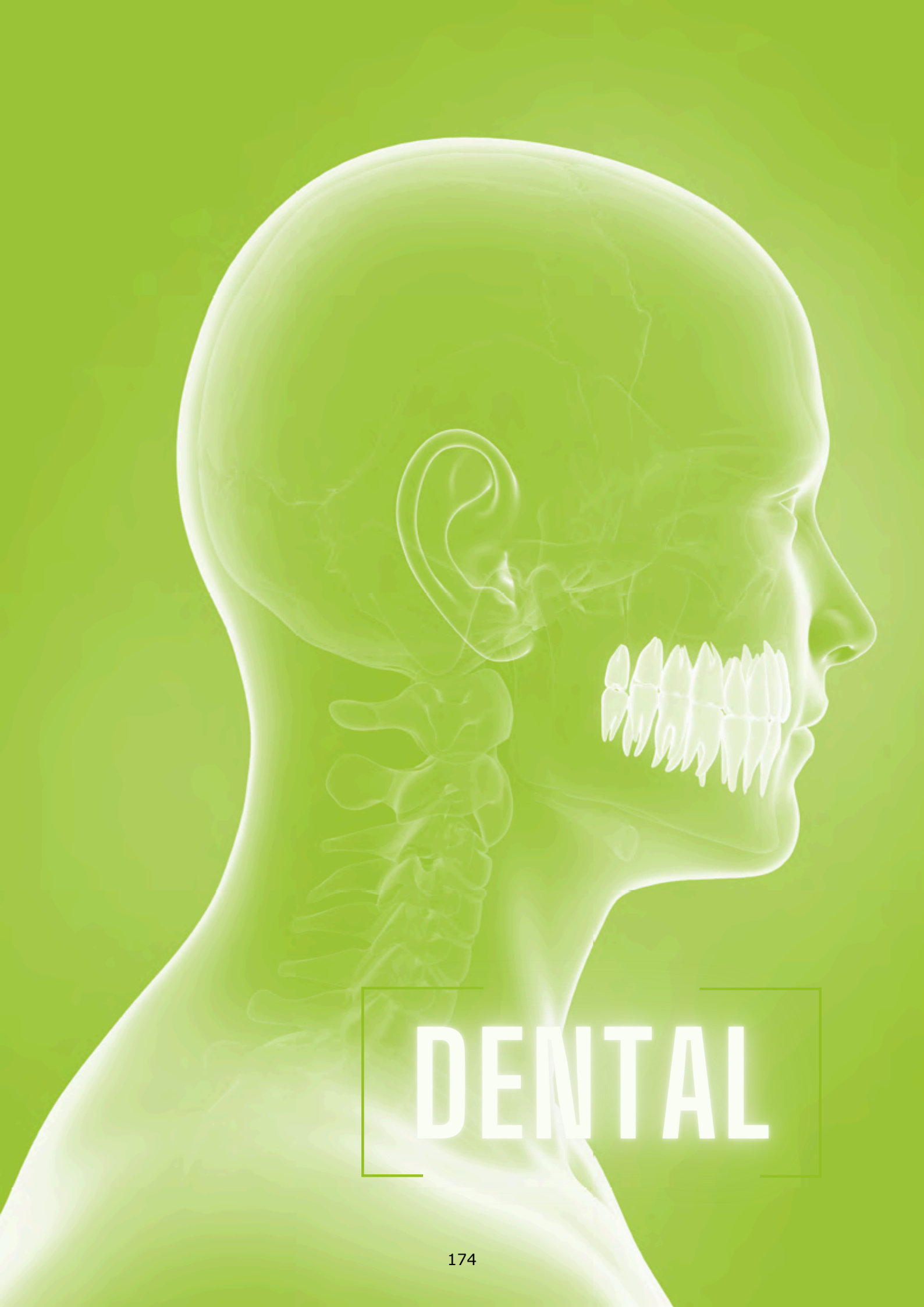

DENTAL

SPINE

ORTHOPEDICS

CRANIO MAXILLO FACIAL - EAR NOSE THROAT

DENTAL

In dental and maxillofacial surgery, the goal of bone defect repair is to recreate a suitable bony site for morphological, prosthetic, or implant-prosthetic rehabilitation. Various factors can lead to bone deficiency, including genetic factors, post-traumatic injuries, tooth extractions, infections, or iatrogenic causes. The amount of bone that needs to be reconstructed varies depending on the specific anatomical situation. The characteristics of the graft material depend on the volumes that need to be filled (e.g., alveolar area) or restored (e.g., vertical or horizontal ridge insufficiency, bone cysts, or sinus lifting) (Guillaume, 2017).

Insufficient bone volume can pose challenges in achieving ideal implant positioning and may compromise long-term peri-implant health, function, and esthetics. To address these limitations, techniques such as alveolar ridge preservation (ARP) or reconstruction (ARR) and implant site development (ISD) are employed. Horizontal and vertical alveolar ridge augmentation (ARA) and maxillary sinus floor augmentation (MSFA) are considered essential ISD interventions in modern clinical practice. These interventions, along with ARP/ARR, can be performed using various techniques and materials, each with its specific characteristics and limitations. Commonly used materials for bone augmentation in ISD and ARP include absorbable and non-absorbable barrier membranes, particulate bone replacement graft materials from different sources, and autologous bone blocks. Despite their proven success in numerous studies, all bone preservation and augmentation protocols have drawbacks and limitations, such as complications during the healing phase (e.g., infections), reduced new bone formation, and delayed healing. To overcome these limitations and increase treatment predictability, the use of biologics has been proposed (Suárez-López Del Amo & Monje, 2022).

Bone grafting is a crucial aspect of regenerative therapy, involving various materials such as autografts, allografts, xenografts, and synthetic materials (alloplasts). Synthetic materials, including calcium phosphate ceramics like hydroxyapatite (HA), tricalcium phosphates (TCP), biphasic calcium phosphates (BCP), and bio-glass (BG), have emerged as effective options for bone augmentation procedures such as sinus lifts and alveolar reconstructions (Liu, 2021). While autografts remain the gold standard due to their innate bone growth properties, they suffer from limitations such as donor site morbidity and availability issues.

Implant therapy is a reliable treatment method known for its favorable and lasting outcomes. When teeth are lost, changes occur in the alveolar process, leading to alterations in its dimensions. These dimensional changes carry significant clinical importance when devising a comprehensive treatment plan. Moreover, factors such as traumatic tooth loss during growth, prolonged edentulism, extensive bone and soft tissue resorption, can pose challenges for implant placement. As a result, implant placement often necessitates additional procedures like alveolar ridge preservation, guided bone regeneration, or sinus floor elevation (SFE) to achieve an optimal position for the prosthetic implant (Stähli, 2018).

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Augmentation osseuse sous-sinusienne à l'aide de verre bio-actif avec repositionnement du volet osseux

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Sinusal bone augmentation using bioactive glass and bone flap repositioning

RÉSUMÉ

L'objectif de cette étude rétrospective est d'évaluer le taux de succès implantaire après augmentation osseuse sous-sinusienne réalisée par la technique modifiée de Tatum avec repositionnement du volet osseux et en utilisant le verre bio-actif 45S5 (Activioss™) comme substitut osseux. La technique opératoire est décrite au travers d'un cas iconographié : la fenêtre d'accès à la membrane sinusienne est réalisée par piezo-chirurgie, et le volet ainsi découpé est repositionné en fin d'intervention, faisant office de membrane de fermeture. Cinquante-huit cas consécutifs chez 58 patients ont été opérés par cette technique. Au total, 111 implants ont été placés soit directement pendant la chirurgie d'augmentation osseuse, soit en différé pour 6 cas présentant un os résiduel trop résorbé. La cohorte de patients a été suivie pendant 12 à 52 mois post-opératoires. Des clichés radiographiques post-opératoires en coupe tomographique sont utilisés pour objectiver le volume comblé, le bon positionnement des implants et l'intégrité de la membrane sous-sinusienne. Les empreintes sont effectuées après validation radiographique de l'ostéo-intégration, à partir de 5 mois. Le succès implantaire est vérifiée une première fois lors du vissage du pilier prothétique qui doit être réalisé entre 25 et 35 N.cm selon les préconisations des fabricants. La survie implantaire est ensuite contrôlée à 12 mois post-opératoires. Dans le cas de poses d'implants différées, des prélèvements osseux sont obtenus lors des

ABSTRACT

The objective of this retrospective study is to evaluate the success rate of implantation after sub-sinusian bone augmentation performed by the modified Tatum technique with repositioning of the bone flap and using the bioactive glass 45S5 (Activioss™) as a bone substitute. The surgical technique is described in an iconographic case: the access window to the sinus membrane is made by piezo-surgery and the flap cut is repositioned at the end of the operation, acting as a closing membrane. Fifty-eight consecutive cases in 58 patients have been operated with this technique. One hundred eleven dental implants were placed either directly during bone augmentation surgery or on a delayed basis for 6 cases with residual bone too resorbed. The patient cohort was followed for 12 to 52 months postoperatively. Post-operative X-ray radiographic images are used to objectify the volume filled, the correct positioning of the implants and the integrity of the sub-sinus membrane. The dental impressions are performed after radiographic validation of the osseointegration, from 5 months. The implant success is verified for the first time when screwing the prosthetic abutment, which must be made between 25 and 35 N.cm according to the recommendations of the manufacturers. The implant survival is monitored at 12 months postoperatively. In the case of deferred implantations, bone samples

chirurgies de l'implant, qui sont intervenues 3 à 30 mois après comblement. Les carottes osseuses ont été analysées par histo-morphométrie, micro-radiographie et micro-dureté, afin d'évaluer la qualité osseuse.
Les résultats de cette étude montre que la technique alliant le repositionnement du volet osseux, l'utilisation de verre bio-actif et le placement immédiat de l'implant permet d'atteindre des taux de succès implantaire de plus de 98 %, identiques aux meilleurs résultats décrits dans la littérature avec des allogreffes ou xénogreffes et, ainsi, de réduire la contrainte physique, temporelle et économique du patient.

MOTS CLÉS

Élévation du plancher sinusal, substitut osseux, verre bio-actif, implant dentaire, histologie régénération osseuse.

are obtained during implant surgeries, which have taken place 3 to 30 months after filling. Core samples were analyzed by histomorphometry, microradiography and micro-hardness to evaluate bone quality.
The results of this study show that the technique combining the repositioning of the bone flap, the use of bioactive glass and the immediate placement of the implant makes it possible to achieve implant success rates of over 98%, identical to the best results described. in the literature with allografts or xenografts and thus reduce the physical, temporal and economic stress of the patient.

KEYWORDS

Sinus floor elevation, bone substitute, bioactive glass, dental implant, histology bone regeneration.

Introduction

Bien que le traitement implantaire du secteur postérieur présente peu d'exigences esthétiques, il peut être problématique de par ses caractéristiques anatomiques et prothétiques.
Afin d'optimiser le succès implantaire, il est important de bien évaluer la quantité et la qualité osseuses disponibles. Dans les secteurs postérieurs tout comme antérieurs, la pose d'implants doit avoir lieu dans un tissu osseux présentant des quantité et qualité osseuses suffisantes (Ulm *et al*., 1995) pour garantir l'ostéointégration et la pérennité de l'ancrage osseux. L'augmentation sous-sinusale avec une greffe d'os autologue, effectuée pour la première fois par Boyne et James en 1980, est une méthode couramment utilisée d'augmentation de la hauteur verticale de l'os pour l'insertion immédiate ou retardée d'implants dentaires.
Afin de solutionner le problème d'insuffisance osseuse dans la région maxillaire postérieure, les greffes osseuses sous-sinusiennes sont devenues prédictibles depuis les années 2000, qu'elles soient d'abord crestal ou par volet latéral. Le recours à cette technique est d'usage dès lors que le volume osseux résiduel est inférieur à 6 mm au-dessus du sinus maxillaire. En effet, de nombreux implants courts (< 8 mm de longueur) commercialisés aujourd'hui permettent de s'affranchir de greffes osseuses préalables, lorsque le projet occluso-prothétique final est adapté à l'indication de ces nouveaux implants. Dans les autres cas, le volume osseux devra être augmenté.

Les techniques dites « de Tatum », par abord latéral du sinus, par création d'un volet permettant l'accès à la membrane sinusienne et son décollement permettent de régénérer des volumes osseux importants avec des risques réduits de perforation de la membrane de Schneider.
Cette technique étudiée a été modifiée par le repositionnement du volet osseux en fin de chirurgie du comblement sous-sinusien, au lieu de placer une membrane de collagène résorbable.
Cette solution a été rendue intellectuellement acceptable pour plusieurs raisons. L'utilisation de la scie de piezo-chirurgie permet un trait de découpe très fin et a-traumatique (pas de chauffe, donc pas d'ostéolyse consécutive). Ensuite, le repositionnement du capot offre une plus grande rigidité par rapport aux membranes collagènes, permettant de réduire le déplacement du comblement dû aux variations des flux d'air sinusaux, ainsi qu'une économie de membrane. Enfin, l'utilisation de verre bio-actif 45S5, dont le mécanisme d'action est décrit ci-après, conduit à une accroche rapide du volet osseux dès la fin de la chirurgie.
Le verre bio-actif 45S5 est un substitut osseux synthétique à base de silicium, calcium, sodium et phosphate qui a la capacité de conduire et stimuler la formation osseuse. Ce biomatériau, utilisé en chirurgie orale depuis le début des années 90 (Hench, 2016), est entièrement résorbable, se transformant et disparaissant au fur et à mesure que l'os envahit la zone à combler.
L'implantation de granules de verre bio-actif 45S5 **(fig. 1 à 3)** au sein de tissus vivants provoque sa

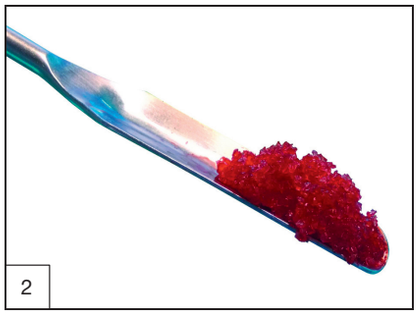


Fig. 1 et 2. Activioss™, matériau de comblement utilisé en chirurgie dentaire **(fig. 1)** et mouillé de sang **(fig. 2)**.
Fig. 1 et 2. Activioss™, filler used in dental surgery **(fig. 1)** and wet with blood **(fig. 2)**.

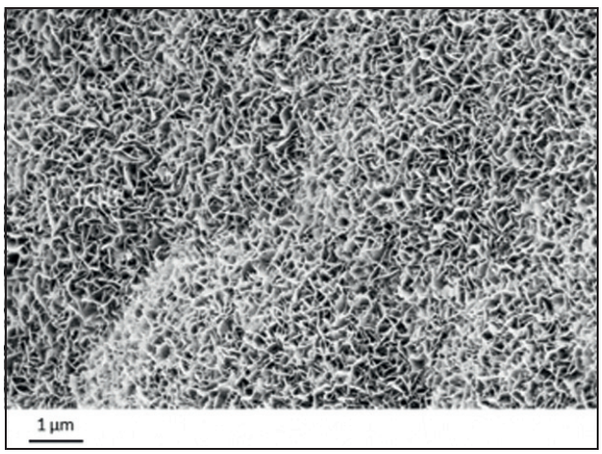


Fig. 3. État de surface de granules de verre bio-actif Activioss™ après 15 jours d'immersion dans une solution de fluide biologique simulée observé au microscope électronique à balayage.
Fig. 3. Surface condition of Activioss™ bioactive glass granules after 15 days of immersion in a simulated biological fluid solution observed under a scanning electron microscope.

dissolution et sa transformation graduelle *in situ* en apatite biologique, équivalente en composition et en structure au minéral osseux, qui est ensuite colonisée et métabolisée pour former un os nouveau.
L'apatite biologique, en se formant, incorpore des fibrilles de collagènes et fournit une interface naturelle avec l'environnement biologique qui lui permet de se lier avec les tissus environnant en quelques jours (6 à 12 jours). Les produits ioniques issus de la dissolution du verre bio-actif participent également au mécanisme de guérison tissulaire en stimulant au niveau génétique l'activité des cellules ostéo-progénitrices.
Simultanément, les échanges ioniques entre le verre bio-actif et les fluides biologiques provoquent une augmentation locale du pH et de la pression osmotique, ce qui permet de créer un environnement défavorable à la prolifération bactérienne. Des études *in vitro* ont également prouvé que les ions du verre bio-actif sont capables de stimuler des marqueurs liés à l'angiogenèse et la production de médiateurs anti-inflammatoires et curatifs, ce qui rend la chirurgie plus sûre pour le patient et le chirurgien.
Ce biomatériau synthétique est donc placé entre la membrane de Schneider et la corticale maxillaire résiduelle. Il permet un « collage » du volet sur le volume osseux comblé, évitant tout risque de séquestre de ce fragment osseux cortical.
Une fois le comblement osseux effectué, la pose immédiate de l'implant est possible si la hauteur de crête résiduelle le permet (chirurgie en 1 temps). Seule la finesse extrême de la crête osseuse résiduelle indiquera de différer le placement de l'implant à une seconde étape de chirurgie après régénération osseuse pré-implantaire (chirurgie en 2 temps), car il sera délicat de garantir un axe implantaire stable pendant la phase d'ostéo-intégration.
L'objectif principal de cette étude est d'évaluer cliniquement l'utilisation d'Activioss® comme substitut osseux dans les greffes sous-sinusiennes avec repositionnement du volet osseux et placement concomitant de l'implant.
L'utilisation d'analyses histologique et histo-morphométrique de carottes osseuses obtenues lors du forage implantaire des cas nécessitant un placement en 2 temps permet de compléter cette étude en accédant à des données sur le remodelage osseux.

Matériel et méthodes

Cas iconographié – Protocole chirurgical

Cas de Mme X, 71 ans, arrêt du tabac depuis plus de 2 ans, projet d'implants en 14 et 15 intercalés **(fig. 4 et 5)**.

Dans un premier temps, une anesthésie locale est effectuée, depuis la région 2e molaire, jusqu'à l'incisive latérale.

L'incision est réalisée de façon arciforme pour respecter les papilles et les collets des dents antérieures, tout en donnant de la laxité au lambeau. Une incision de décharge est réalisée en mésial de l'incisive latérale. Une erreur fréquente consiste à ouvrir une fenêtre osseuse trop distale et ainsi compliquer le comblement dans la zone antérieure. Naturellement, les biomatériaux iraient vers le fond de cette cavité, donc vers la 2e molaire et le palais.

L'anatomie du sinus à opérer est importante pour prédire le volume nécessaire et l'approche de la coupe osseuse. Un sinus avec un angle α aigu nécessitera moins d'apport de volume mais une position du trait de coupe crestal le plus proche possible du plancher du sinus, pour éviter de créer des zones inaccessibles avec les curettes sinusiennes, même à double courbure. Un angle β obtus va augmenter aussi le volume à combler mais la membrane à son contact sera plus facile à décoller **(fig. 6 et 7)**.

La limite haute de la cavité doit correspondre idéalement à la limite de la hauteur de soulèvement de la membrane. Toutefois, nous privilégions les petites ouvertures afin de limiter la zone d'exposition, de faciliter une reprise en cas d'échec et de conserver un maximum d'os natif non travaillé.

La découpe de la fenêtre, réalisée ici par scie piezochirurgie Mectron®, est volontairement asymétrique **(fig. 8)** pour faciliter son repositionnement. Elle est « réservée » dans un godet rempli de sérum physiologique et de métronidazole.

Les copeaux osseux produits par la découpe et le forage des néo-alvéoles sont récupérés à l'aide d'un filtre à os à usage unique (Aspeo, Anthogyr®).

La membrane est largement décollée, au-delà de la taille de la fenêtre, et le forage des zones implantaires est réalisé en protégeant la membrane à l'aide d'une curette interposée dans le sinus. Le comblement osseux s'effectue d'abord dans la région antérieure dans la zone médiane du sinus, puis dans la région palatine **(fig. 9 et 10)**.

Le mélange d'os autogène récupéré – souvent 0,3 cc et rarement plus sur les sinus très procidents – et 1 cc de verre bio-actif 45S5 (Activioss® Noraker) – en granulométrie moyenne (0,5 à 1 mm) et humidifié à l'aide de sérum physiologique 9/1000 et d'antibiotique (métronidazole) – est placé presque intégralement dans le volume. Seulement 20 % du mélange est conservé pour recouvrir d'éventuelles spires de l'implant qui pourraient être apparentes dans le sinus avant de replacer le volet osseux. Si aucun manque n'est décelé, le vissage de l'implant fait refluer une partie du volume vers l'extérieur de la fenêtre ; l'excédent de biomatériaux sera appliqué par-dessus le capot osseux **(fig. 11)**.

Le placement des deux implants – Anthogyr, Axiom Reg 4 mm (diamètre) × 10 mm (longueur) en 15 et

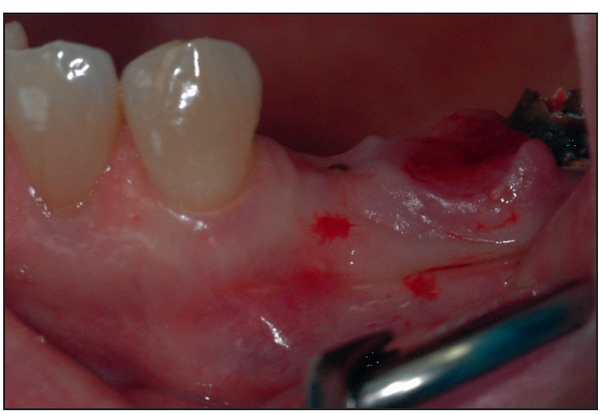


Fig. 4. Site pré-opératoire.
Fig. 4. Pre-operative site.

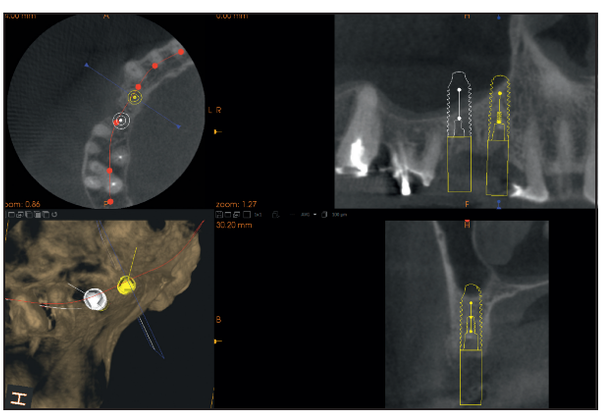


Fig. 5. Scanner pré-opératoire et planification de la pose des implants.
Fig. 5. Pre-operative scanner and planning of implant placement.

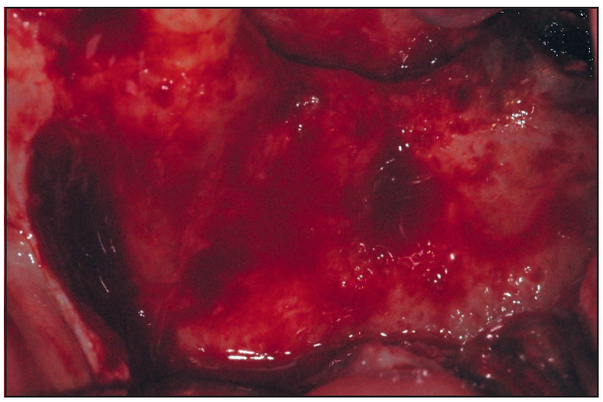


Fig. 6. Lambeau décliné, détermination de la forme de la fenêtre.

Fig. 6. Shred declined, determining the shape of the window.

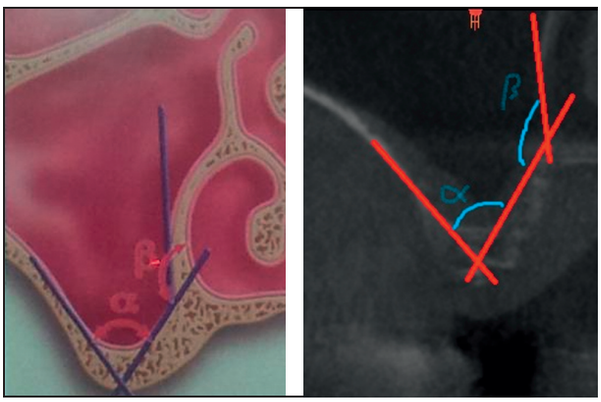


Fig. 7. Coupe frontale du sinus maxillaire.

Fig. 7. Frontal view of the maxillary sinus.

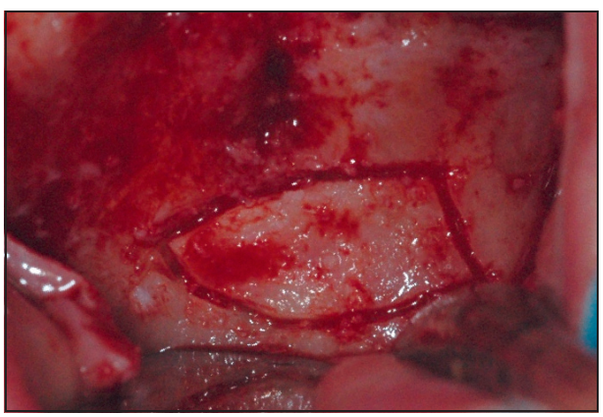


Fig. 8. Fenêtre découpée à l'aide d'un piézotome. Noter la forme volontairement asymétrique pour faciliter son repositionnement.

Fig. 8. Window cut using a piezotome. Note the deliberately asymmetrical shape to facilitate its repositioning.

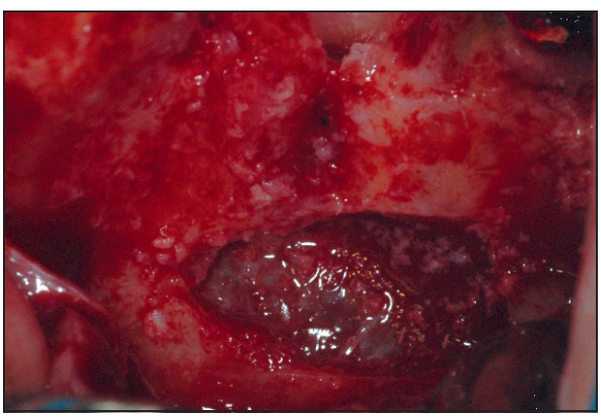


Fig. 9. Vue de la membrane de Schneider désolée, contrôle de son intégrité.

Fig. 9. View of the Schneiderian membrane, checking its integrity.

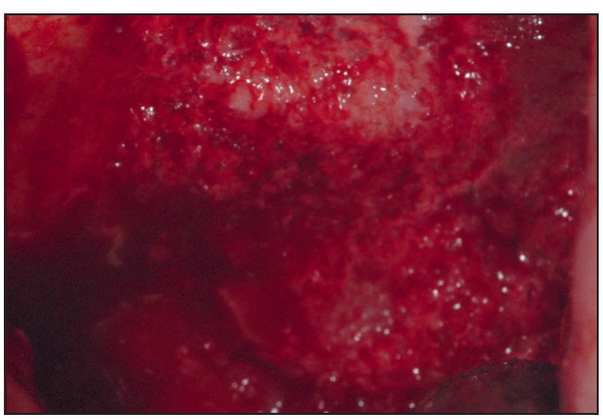


Fig. 10. Après comblement par des granules d'Activioss GM (Granulométrie Médium : 0.5 à 1 mm de diamètre) + métronidazole.

Fig. 10. After filling with granules of Activioss GM (Medium particle size: 0.5 to 1 mm in diameter) + metronidazole.

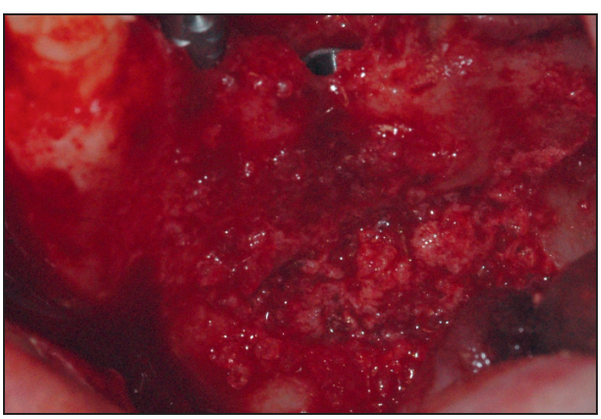


Fig. 11. Les excès de granules sont appliqués sur le site, en apposition simple, afin de compenser la concavité du site.

Fig. 11. The excess granules are applied to the site, in simple apposition, in order to compensate for the concavity of the site.

4,6 mm × 10 mm en 16, avec piliers de cicatrisation (hauteur : 3 mm) – est effectué en 1 temps chirurgical. Le couple d'insertion des deux implants est situé entre 10 et 15 N.cm.

Le capot osseux a été remis dans sa position initiale, par petites vibrations sur une surface comblée et dense, sans espace **(fig. 12 et 13)**.

Les sutures étanches sont effectuées sans tensions. La dépose des points est faite 10 jours après l'intervention afin de supprimer les risques d'inflammation liés à la présence de nœuds retenant la plaque dentaire **(fig. 14)**.

Une radiographie est réalisée à la sortie de la chirurgie **(fig. 15)**.

Les empreintes ont été effectuées après validation de l'ostéo-intégration, à 6 mois et demi **(fig. 16)**.

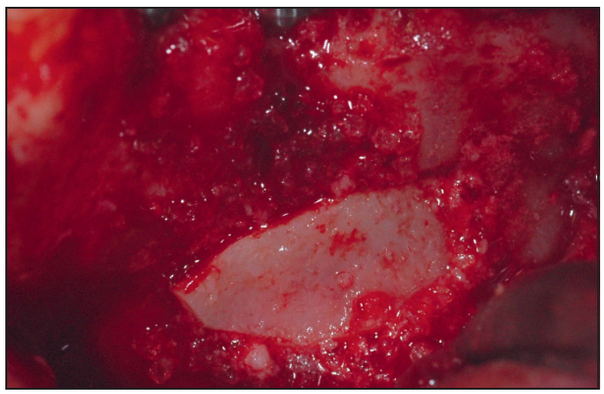


Fig. 12. Vue du site avec son volet repositionné, ajusté par vibrations sur sa zone de découpe.

Fig. 12. View of the site with its repositioned shutter, adjusted by vibrations on its cutting area.

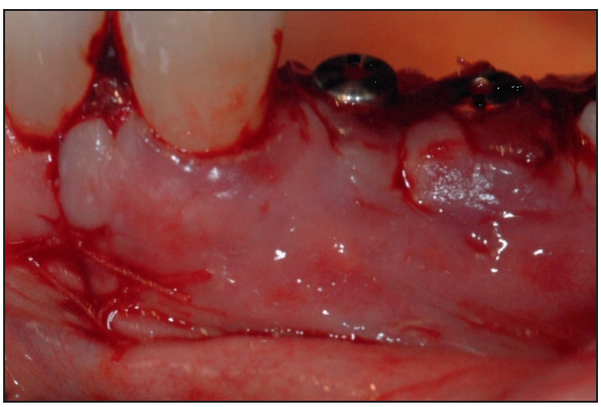


Fig. 13. Sutures sans tensions, en 1 temps chirurgical autour des piliers de cicatrisation.

Fig. 13. Sutures without tension, in 1 surgical step around the healing abutments.

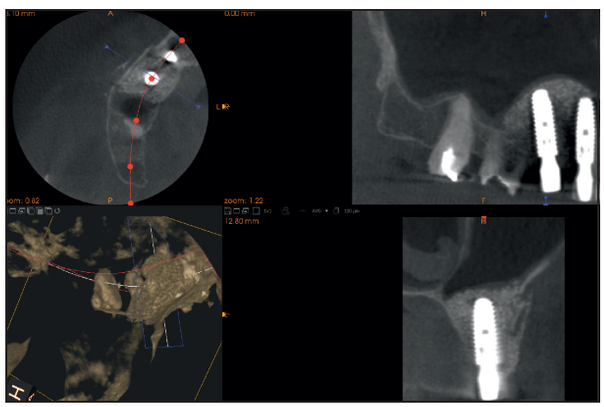


Fig. 14. Cliché tomographique post-opératoire objectivant le volume reconstruit et le placement tridimensionnel de l'implant dans cet espace.

Fig. 14. Postoperative tomographic image showing the reconstructed volume and the three-dimensional placement of the implant in this space.

Fig. 15. À 6 mois post opératoire, lors de l'empreinte pour la réalisation des prothèses.

Fig. 15. Six months postoperative, during the impression for the realization of the prostheses.

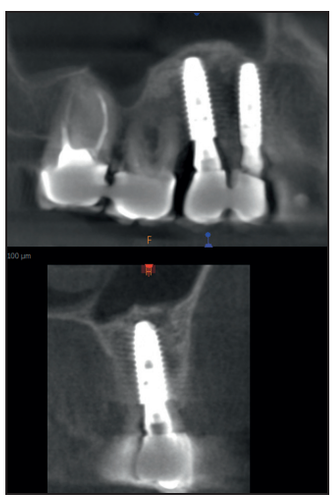


Fig. 16. 24 mois post opératoire, contrôle de l'apparente densification osseuse, et de la stabilité du traitement. Noter la disparition de l'effet « volet osseux repositionné ».

Fig. 16. 24 months postoperative, control of the apparent bone densification, and the stability of the treatment. Note the disappearance of the « repositioned bone flap » effect.

Deux séances sont encore nécessaires pour permettre un essayage des armatures des couronnes et la pose des couronnes (ciment carboxylate sur les piliers trans-vissés).

Protocole d'étude

L'étude rétrospective sur le comblement sinusien avec le verre bio-actif Activioss® a été réalisée durant une période de 40 mois sur 52 patients consécutifs avec un suivi post-opératoire entre 12 et 52 mois (40 mois d'inclusion de patients auxquels s'ajoute 1 an de suivi post-opératoire). Les patients inclus sont venus consulter le premier auteur de cet article à son cabinet privé pour une mise en place d'implant dentaire.
Les implants sont choisis parmi les références suivantes : Anthogyr Axiom®, Tekka Progress®, Straumann® SP et BL, selon les références disponibles au cabinet.
Les clichés radiographiques post-opératoires sont réalisés en coupe tomographique à dose faible (Planmeca mode Ultra Low Dose, ou Kodak K9000), permettant d'objectiver le volume gagné, le parfait positionnement des implants et l'intégrité de la membrane sinusienne, avec la même dose absorbée par le patient que pour une radiographie panoramique.
Une fois le comblement osseux effectué, la pose immédiate de l'implant est possible si la hauteur de crête résiduelle le permet (chirurgie en 1 temps). Lorsque les implants sont posés dans un os résiduel de hauteur supérieure à 5 mm, les piliers de cicatrisation trans-gingivaux peuvent être placés immédiatement. Pour un os résiduel inférieur à 5 mm, l'implant reçoit obligatoirement une vis de couverture temporaire et les sites sont fermés. Les piliers seront placés lors d'une séance préalable à l'empreinte, qui aura lieu en principe 15 jours après.
Les empreintes sont effectuées après validation radiotomographique de l'ostéo-intégration des implants, à 5 mois (6 mois dans les cas où le couple d'insertion des implants dans l'os natif était inférieur à 30 N.cm). Le succès implantaire est vérifié une première fois lors du vissage du pilier prothétique qui doit être réalisé entre 25 et 35 $N.cm^{-1}$ selon les préconisations des fabricants. La survie implantaire est ensuite contrôlée à 12 mois post-opératoires.
Dans le cas d'une pose d'implant différée (chirurgie en 2 temps), des prélèvements osseux sont obtenus lors de la chirurgie de l'implant, qui intervient après consolidation osseuse (6 mois selon les indications du fabricant du substitut osseux). L'analyse des carottes osseuses obtenues est décrite dans le paragraphe suivant.

Analyse histologique et histo-morphométrique

Analyses histologiques

Les échantillons d'os ont été fixés dans de l'éthanol à 70 %, déshydratés dans de l'éthanol absolu et inclus dans du méthacrylate de méthyle sans décalcification préalable.
Les blocs ont été ensuite découpés en utilisant un microtome lourd SM 2500 (Leica®, Allemagne) équipé d'un couteau en carbure de tungstène pour obtenir des sections d'os de 8 µm d'épaisseur.
La coloration est utilisée pour la mesure des paramètres de structure (os cortical et spongieux) et des paramètres statiques de formation et de résorption. La coloration par le solochrome cyanine R a été utilisée pour l'identification du tissu ostéoïde et de la matrice calcifiée. La micro-architecture et la présence éventuelle de défauts de minéralisation ont été évaluées. L'utilisation de la lumière polarisée permet d'examiner la structure de la matrice osseuse et l'organisation des fibres de collagène (os lamellaire ou os tissé).

Analyse histo-morphométrique

Des méthodes semi-automatiques ont été utilisées (Chavassieux *et al*., 1997).
Le volume osseux (BV/TV) et les variables reflétant le remodelage osseux ont été mesurés sur les sections colorées par le trichrome de Goldner modifié. L'os régénéré autour du biomatériau partiellement dégradé a été évalué **(tableau 1)**.

Volume total du prélèvement	mm^3
Volume osseux/Volume total	%
Surface ostéoïde	%
Épaisseur ostéoïde	mm
Nombre d'ostéoclastes/surface osseuse	#/mm
Surface ostéoblastique/surface osseuse	%

Tableau 1. Principales variables histo-morphométriques mesurées.
Tableau 1. Main histomorphome variables measured.

Micro-indentation

Les blocs inclus ont été polis en utilisant une suspension d'alumine de 1 µm (Escil, Chassieu, France) et nettoyés dans un dispositif à ultrasons (Elma, Singen, Allemagne).
La micro-dureté a été mesurée selon la méthode décrite par Boivin *et al*. (Boivin *et al*., 2008).
L'analyse de micro-dureté du tissu osseux est faite avec un micro-duromètre composé d'un indenteur Vickers. Les deux angles identiques du pénétrateur Vickers font une impression pyramidale sur la surface de bloc de l'échantillon osseux incorporé. Une charge de 25 g est appliquée sur la surface pendant 10 secondes.
Le paramètre évalué est la micro-dureté Vickers :
HV (kg/mm^2) = (1854,4 × charge appliquée)/(longueur moyenne des deux diagonales)^2. Le logiciel pour évaluer la micro-dureté est Omnimet HMS v.2.31.

Micro-radiographie quantitative numérisée (Montagner et al., 2015)

Toujours à partir des blocs inclus, des sections d'environ 150 µm d'épaisseur ont été découpées à l'aide d'une scie à fil diamantée de précision (Escil, Chassieu, France), amincies à 100 ± 1 µm par usure manuelle entre une lame de verre dépolie et une plaque de verre dépolie en utilisant de la poudre de carbure de silicium (Escil, Chassieu, France). Les sections ont été polies avec une polisseuse (Escil, Chassieu, France) en utilisant une suspension d'alumine 1 µm et nettoyées avec un dispositif d'ultrasons (Elma, Singen, Germany). L'épaisseur a été mesurée en utilisant un comparateur d'épaisseur micrométrique de précision (précision 1 µm, Compac, Genève, Suisse).
L'appareil a été développé en collaboration avec Photonic Science (St Étienne de St Geoirs, France). Il est composé d'un système de rayonnement X Microfocus Hammamatsu L9421-02 avec une puissance maximale de 8 W, une anode en cuivre, un filtre à nickel, une fenêtre de béryllium de 150 µm et une tache focale de 5 µm de diamètre.
Les paramètres d'exposition sont : haute tension (40 kV), courant (50 µA), puissance (2 W). La distance entre la source et l'objet se situe dans une plage de 1 à 25 cm, comme celle entre l'objet et le détecteur.
Le détecteur est une caméra CCD FDI VHR 11 M avec une surface active de 36 × 24 mm (4008 × 2671 pixels). L'étape de numérisation d'image se fait avec un détecteur d'image numérique de 12 bits (taille de pixel : 9 µm ; la taille du pixel de l'objet dépend du facteur de grossissement ; elle est de 0,83 µm au grossissement utilisé = × 10,8).
Pour l'évaluation quantitative de l'absorption des rayonnements X du tissu osseux, un système de référence en aluminium avec un coefficient d'absorption connu est exposé au faisceau avant la section osseuse (l'aluminium est sélectionné car il a un faible nombre atomique proche de celui de l'apatite). Le système est construit sous la forme d'un escalier rectangulaire avec une série de marches constituant une à huit couches d'aluminium ultra-pur (99,5 %, Strems Chemical Ltd, Strasbourg, France). Les niveaux de gris obtenus au niveau des pixels sont donc convertis en degrés de minéralisation osseuse (DMB) après le tracé d'une courbe d'étalonnage [DMB = f (niveaux de gris)] à partir du système de référence en aluminium.
Enfin, les variables reflétant la minéralisation secondaire de l'os ont été mesurées avec un code du logiciel Matlab, exprimées en g minéral/cm^3 d'os. Ces variables sont : valeur moyenne de DMB ; indice d'hétérogénéité (HI = largeur à mi-hauteur du pic de la courbe de distribution de la minéralisation osseuse : plus HI est grand, plus l'hétérogénéité de la minéralisation est élevée) et la valeur DMB la plus fréquente [DMB freq. Max. = pic de la courbe de distribution de la minéralisation osseuse [nombre de pixels = f (DMB)]. Ces variables ont été données pour l'os résiduel et pour l'os formé autour du biomatériau.

Résultats

Population

Au total, 110 implants ont été placés chez 52 patients inclus entre août 2012 et décembre 2015 **(tableau 2)**. Dans cette population, 58 sites ont été opérés dans lesquels une moyenne de 1,88 implant a été inséré. Les patients, âgés de 25 à 83 ans (moyenne 56,7 ans), sont répartis équitablement entre les deux sexes et possèdent une majorité de fumeurs. Tous suivront un protocole de sevrage tabagique temporaire, de 5 à 28 jours selon leurs aveux (28 jours étant la durée préconisée dans ce protocole, 1 semaine avant la chirurgie et 3 semaines après).

Caractéristiques	1 temps	2 temps		Total
	Pose immédiate du pilier	Pose du pilier différée (vis de couverture)	Pose de l'implant en différé	
Nombre de patients	40	12	6	58
Hommes Femmes	20 20	7 5	1 5	28 30
Moins de 50 ans Entre 50 et 65 ans Plus de 65 ans	13 16 11	3 7 2	3 3 0	19 26 13
Fumeurs Non-fumeurs	31 9	9 3	0 6	40 18
Sites (cas)	40	12	6	58
Implants	80	21	9	110
Succès implantaire	79 (98,8 %)	20 (95,2 %)	9 (100 %)	108

Tableau 2. Description de la population étudiée (effectif des patients et des implants).
Tableau 2. Description of the population study (number of patients and implants).

Résultats cliniques

Aucune complication particulière per-opératoire n'a été observée. Les suites post-opératoires sont habituelles, sans anomalie d'inflammation.
L'ordonnance type des patients est : amoxicilline (1 g matin et soir pendant 12 jours, début de prise 48 heures avant la chirurgie) ; cortisone (1 mg par kg de poids corporel en une prise, pendant 3 jours, début de prise le matin de l'intervention) ; métronidazole (500 mg matin et soir pendant 6 jours, début de prise le matin de l'intervention) ; paracétamol (selon douleur) et bains de bouche à 48 heures en post-opératoire.
Les patients présentant des épaississements de la muqueuse de Scheider ou des antécédents de sinusite débutent les prises de cortisone 48 heures avant l'intervention, afin de diminuer l'inflammation des tissus respiratoires.
Quelques rares douleurs, habituelles pour ce type de chirurgie, ont été maîtrisées par traitement médicamenteux (paracétamol et application de poches réfrigérées sur la joue).
En moyenne, une dose de 1,5 cc d'Activioss a été utilisée indépendamment des groupes.
Le **tableau 3** présente les résultats en fonction des paramètres de l'étude.
En moyenne, la validation de l'ostéo-intégration a été réalisée à 6 mois et 11 mois respectivement pour les poses d'implants en 1 temps chirurgical et en 2 temps chirurgicaux.
Les taux de succès implantaire sont de 98,8 % (1 échec) pour le groupe avec pose immédiate du pilier, 95,2 % (1 échec) pour les chirurgies en 1 temps mais avec pose du pilier en différé. Pour les chirurgies en 2 temps, le taux de succès est de 100 %.
Le taux de succès global est de 98,2 %.
Les deux sinus en échec sont dus à une fonte du comblement total et à une infection avec dépose de l'implant. Cependant, dans un autre cas et indépendamment de l'échec de l'implant, le sinus greffé est

Caractéristiques	1 temps	2 temps		Total
	Pose immédiate du pilier de cicatrisation	Pose du pilier différée (vis de couverture)	Pose de l'implant en différé	
Délai de validation	6,4 mois	5,9 mois	10,9 mois	
Succès implantaire	79/80 (98,8 %)	20/21 (95,2 %)	9 (100 %)	98,2 %

Tableau 3. Résultats cliniques.
Tableau 3. Clinical results.

resté sain. Aucun implant n'a été perdu après la mise en fonction mais deux implants ont été perdus lors du contrôle d'ostéo-intégration.
Pour les cas ayant nécessité une pose d'implant en 2 temps, le ressenti clinique est toujours une sensation de vissage dans la zone greffée avec un couple peu élevé, entre 5 et 15 $N.cm^{-1}$. Malgré cela, le contrôle de l'ostéo-intégration 6 mois plus tard est toujours bon. Des prélèvements osseux ont été obtenus lors des chirurgies de l'implant, qui sont intervenues 3 à 24 mois après comblement. L'analyse des carottes osseuses obtenues est décrite dans le paragraphe suivant.
Le couple d'insertion de l'implant dans la greffe semble n'avoir aucun lien avec la hauteur d'os résiduelle. Indépendamment du nombre de temps chirurgicaux, de la valeur du couple d'insertion de l'implant et du délai de cicatrisation, le vissage du pilier prothétique a toujours été effectué entre 25 et 35 N.cm selon les préconisations de la marque d'implants.
Il s'agit là de notre test de validation de l'ostéo-intégration des implants, par l'absence de mouvement ou de douleur lors de l'application de ce couple de serrage (et d'un contrôle radiographique silencieux).

Régénération osseuse

À 3 mois post-comblement, le tissu osseux minéralisé est présent dans tout le volume osseux augmenté. La partie droite de l'image **(fig. 17)** est composée de tissu osseux nouvellement formé en 3 mois autour du verre bio-actif, encore présent après 3 mois. Les granules résiduelles Activioss™ sont ostéo-intégrées sans signe de réaction tissulaire étrangère et la plupart des granules à cette étape ont montré une excavation **(fig. 18 à 20)**. La présence de nombreux ostéoblastes et liserés ostéoïdes est un signe d'une formation osseuse active. De plus, des ostéocytes sont également observés. Ceci montre l'existence d'un processus de remodelage osseux.
À 6 mois post-comblement, les granules à proximité de l'os résiduel sont entièrement résorbées **(fig. 21)**. Dans la partie droite de la section, les granules résiduelles d'Activioss™ sont ostéo-intégrées sans signe de réaction tissulaire étrangère. La présence de nombreux ostéoblastes et d'épais liserés ostéoïdes est un signe de formation osseuse active. Des ostéoclastes sont également observés, ce qui montre qu'un processus de remodelage osseux est en cours **(fig. 22 à 24)**.

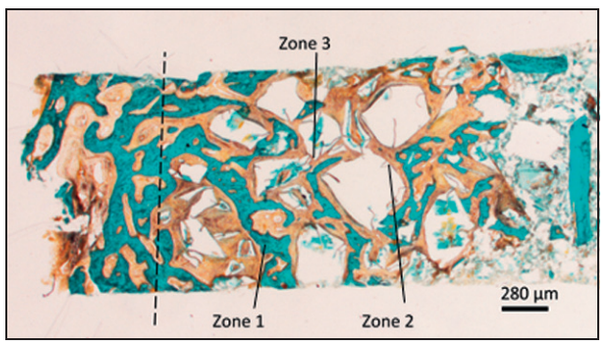


Fig. 17. Histologie à 3 mois post-comblement.
Fig. 17. Three months post-filling histology.

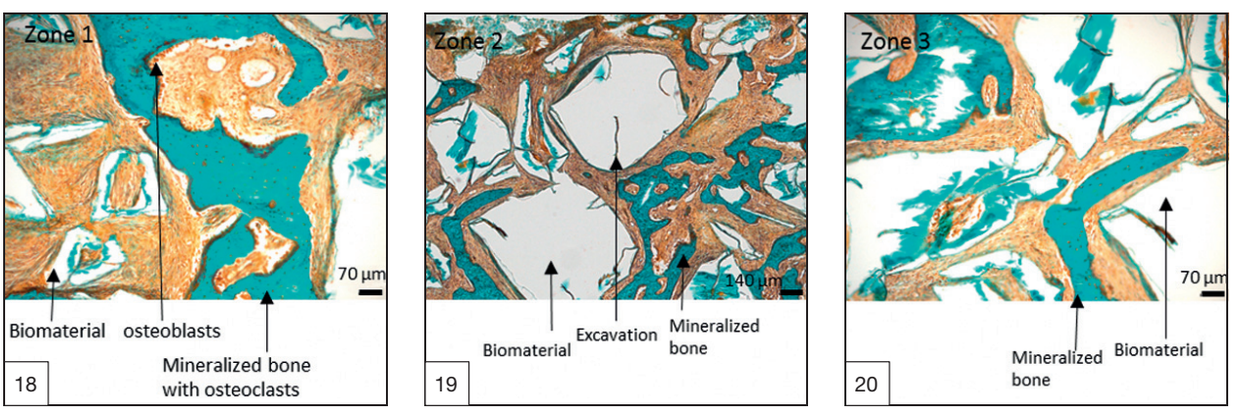


Fig. 18 à 20. Zones d'intérêt de l'histologie à 3 mois.
Fig. 18 to 20. Areas of interest for 3 months histology.

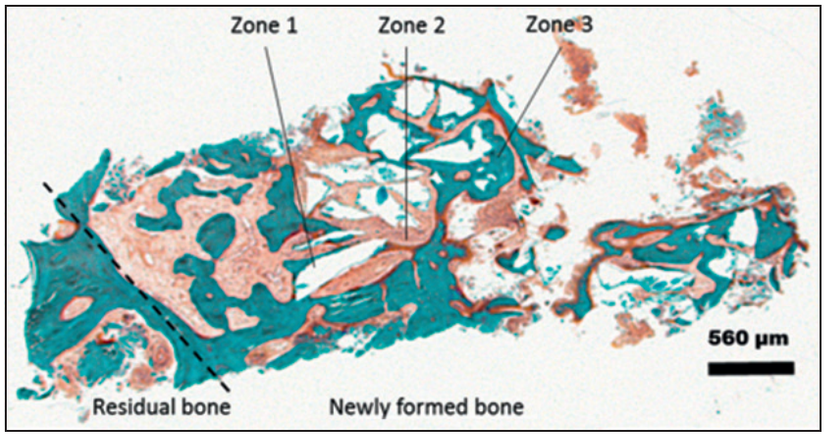
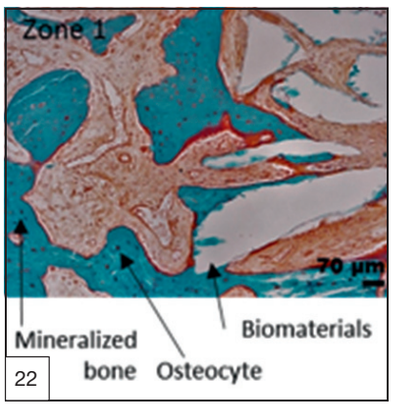
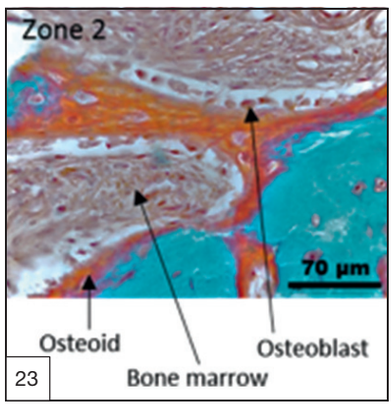


Fig. 21. Histologie à 6,5 mois post-comblement.

Fig. 21. Six and half months post-filling histology.





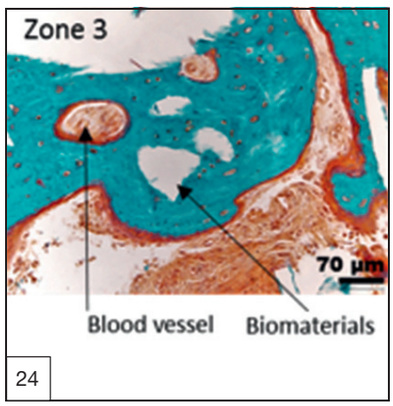


Fig. 22 à 24. Zones d'intérêt de l'histologie à 6,5 mois.

Fig. 22 à 24. Areas of interest for 6.5 months histology.

À 22 mois, le tissu osseux minéralisé est présent dans tout le volume osseux de la biopsie **(fig. 25)**. Les observations sur l'apparence générale n'ont montré aucune différence entre l'os trabéculaire dans les deux zones, bien que quelques fragments de biomatériau soient encore présents dans la région osseuse nouvellement formée. Liseré ostéoïde, ostéoclastes et vaisseaux sanguins montrent un remodelage osseux complet et une vascularisation du milieu nouvellement formé **(fig. 26 à 29)**.

L'analyse quantitative révèle un réseau dense de travées osseuses, des surfaces et volumes ostéoïdes normaux et des surfaces ostéoblastiques normales **(tableaux 4 et 5)**. On constate une augmentation de l'épaisseur de l'ostéoïde par rapport aux valeurs contrôles. Le nombre d'ostéoclastes, reflétant la résorption osseuse, est normal. Comparé à la valeur moyenne des échantillons après 6 mois de comblement, la quantité d'os formée après 22 mois autour du biomatériau est identique (BV/TV à 6 et 22 mois compris entre 4,40 et 54,40). La micro-dureté de l'os néoformé pendant 22 mois autour du verre bioactif est plus faible que celle de l'os résiduel qui est elle-même plus faible que celle des témoins **(tableau 6)**. Cependant, la micro-dureté de l'os néoformé est identique à la micro-dureté mesurée après 6 mois (Hv = 38,96 ± 4,47) et 12 mois (Hv = 40,93 ± 5,47).

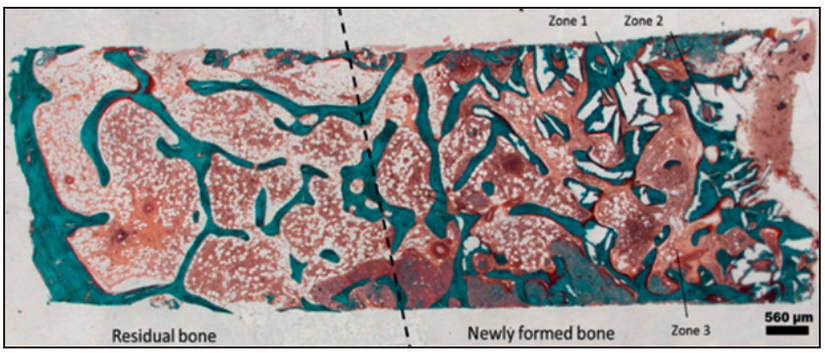


Fig. 25. Histologie à 22 mois.
Fig. 25. Twenty-two months post-filling histology.

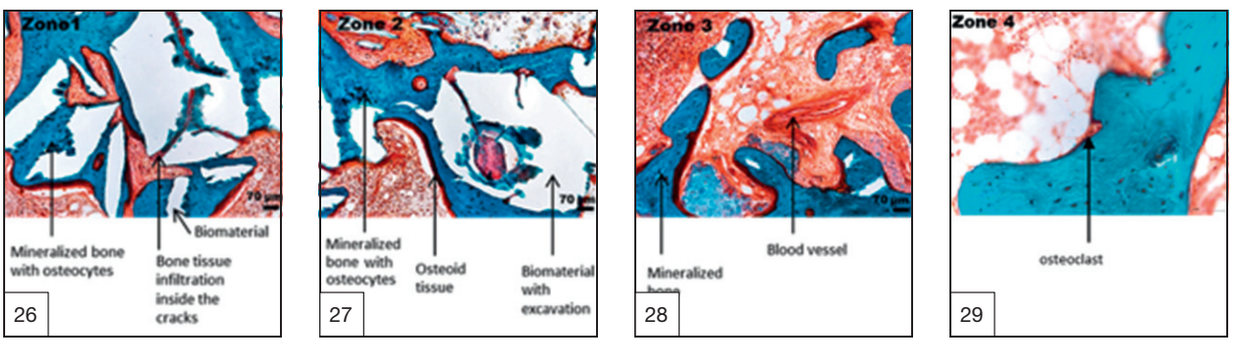


Fig. 26 à 29. Zones d'intérêt de l'histologie à 22 mois.
Fig. 26 à 29. Areas of interest for 22 months histology.

	Variables	3 mois	6,5 mois	22 mois	Témoins
Os total	BV/TV (%)	35,52	41,19	27,44	42,12 (17,58-58,59)
Os résiduel	BV/TV (%)	52,42	63,50		
Os nouveau	BV/TV (%)	29,68	31,67	28,07	
	Volume biomatériau/TV	26	14,68	7,42	
Formation	OS/BS (%)	20,76			17,69 (5,62-33,18)
	OV/BV (%)	7,03			0,04 (0,03-10,32)
	O.Th (µm)	24,94			17,07 (14,87-18,91)
	S.Ob/Bs (%)	2,74			8,05 (0,22-9,63)
Résorption	N.Oc	4			2-4

Tableau 4. Analyse histomorphométrique.
Tableau 4. Histomorphic analysis.

	Variables	3 mois	22 mois	Contrôles
Os résiduel	DMB moyen	0,904 ± 0,104	0,970 ± 0,140	1,125 ± 0,084
	DMB Freq. Max	1,024	1, 061	1,150 ± 0,110
	HI	0,236	0,160	0,190 ± 0,080
Os formé	DMB moyen	0,863 ± 0,166	0,904 ± 0,202	
	DMB Freq. Max	0,867	1,003	
	HI	NM	0,153	

Tableau 5. Microradiographie quantitative.
Tableau 5. Quantitative microradiography.

	3 mois	6,5 mois	22 mois
HV os résiduel	30,98 ± 2,47	36,90 ± 6,74	41,35 ± 4
HV os nouveau	38,53 ± 8,76	36,15 ± 2,44	33,54 ± 3,40
HV contrôles	53,97 ± 9,95	53,97 ± 9,95	53,97 ± 9,95

Tableau 6. Microdureté osseuse.
Tableau 6. Bone microhardness.

Discussion

La technique de Tatum avec membrane collagène a été étudiée dans la littérature. Dans l'étude de Bornstein, 110 implants ont été placés dans 58 sinus comblés avec un mélange 1:1 d'os autologue et de β-TCP (Ceros, 12 sinus) ou de xénogreffe (Bio-Oss, 47 sinus) (Bornstein, ???). Le taux de succès sur 5 ans est de 89 % pour le β-TCP et de 100 % pour DBBM. Dans le groupe β-TCP, 11 implants ont été perdus et 2 autres retirés pour cause de douleurs. De même, l'étude de Tarnow et Wallace présente un taux de succès de 98 % des implants et a été effectuée avec un comblement de DBBM (Bio-Oss) avec ou sans os autologue (Tarnow, Wallace, ???).
Dans notre étude, l'utilisation de la technique de Tatum modifiée par le repositionnement du volet osseux a permis d'obtenir, en moyenne, une augmentation osseuse de 1,5 cc sans complication particulière avec un taux de succès total de 98,2 %.
Les équipes coréennes de Sohn et Moon ont largement démontré que la qualité osseuse le long du volet repositionné et au centre de la greffe était de bien meilleure qualité que lors de l'utilisation d'une membrane de collagène (Sohn, Moon, ???). La propriété ostéo-inductrice du volet osseux accélère la néoformation d'un os plus mature et plus dense.
Cliniquement, l'utilisation de granules de verre bioactif semble aider au recollage du volet osseux ; les réactions de surface permettent une liaison rapide avec les tissus environnants.
Les performances de régénération osseuse des verres bio-actifs ont été démontrées dans plusieurs études cliniques. Comme le montrent les histologies présentées, le tissu osseux est capable de se reformer autour du biomatériau et, à terme, de le remplacer. Ainsi, il n'est pas étonnant de voir que le couple d'insertion des piliers prothétiques est indépendant de la hauteur de la crête résiduelle et que le succès implantaire est élevé (> 95 %), indépendamment des temps chirurgicaux.
De manière générale, le placement de l'implant concomitamment à l'augmentation de volume osseuse sous-sinusienne est toujours préféré : en effet, 6 mois après l'intervention unique, les implants sont mis en charge sans délai supplémentaire alors que, dans la greffe seule, il faut attendre un délai supplémentaire de plusieurs mois pour valider l'ostéo-intégration et réaliser

la prothèse. La seule limite au placement de l'implant pendant la phase d'augmentation de volume sous-sinusienne est le respect de l'axe d'émergence du col implantaire.

Conclusion

L'utilisation de la technique de Tatum modifiée, telle que décrite dans cette étude, sur 58 cas consécutifs et 111 implants posés montre un taux de succès implantaire de 98,2 % à 12 mois post-opératoires, identique aux meilleurs résultats décrits dans la littérature avec des allogreffes ou xénogreffes depuis le début des années 2000. La technique alliant l'utilisation de verre bio-actif, le placement immédiat de l'implant et le repositionnement du volet osseux permet d'assurer un taux de succès implantaire dans les régions sous-sinusiennes et, ainsi, de réduire la contrainte physique, temporelle et économique du patient. □

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