

Bioactive Glass and Autogenous Bone as Bone Graft Substitutes in Benign Bone Tumors

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Abstract: In a prospective randomized study, 25 patients with benign bone tumors were surgically treated with either bioactive glass S53P4 (BG) or autogenous bone (AB) as bone graft material. X-rays were taken preoperatively and postoperatively at 2 weeks and at 3, 8, 12, 18, 24, and 36 months. In addition, for most of the patients, CT scans were performed at the same time-points. No infections or material-related adverse reactions occurred in any patient. The filled cavity was replaced faster by new bone in the AB group than in the BG group ($p = 0.0001$). However, at 36 months, no statistical difference in cavity volume between the two groups was observed on X-rays ($p = 0.7881$) or on CT scans ($p = 0.9117$). In the BG group at 3 years, the filled cavity appeared, however, dense on X-rays, and glass granules on CT scans were observed. During the follow-up period, the cortical thickness seemed to increase more in the BG group than in the AB group ($p < 0.0001$). © 2008 Wiley Periodicals, Inc. *J Biomed Mater Res Part B: Appl Biomater* 90B: 131–136, 2009

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INTRODUCTION

To treat benign bone tumors, many different methods, including curettage with or without bone grafting, percutaneous sclerotherapy, corticosteroid injections, subtotal or total excision with or without reconstruction, and irradiation, have been reported.¹ Simple bone cysts are also known to regress spontaneously after fracture healing.

Autograft bone (AB) with its osteoinductive potential is the material of choice when bone graft is needed. Morbidity at the donor site and availability of graft material must, however, be considered, especially in children and adolescents.

The increasing use of graft materials in orthopedic surgery has resulted in the foundation of allograft bone banks. Fresh allografts are, however, associated with a marked immune response. Other problems associated with allografts are resorption, fractures, nonunion between the graft and the recipient bone, and the spread of infections.² The availability and poor supply of allograft bones may also limit their use in orthopedic surgery.

Bioactive glasses (BGs) have proven to be biocompatible materials with documented bone bonding capacity. The behav-

ior and reactions of BGs are composition dependent. The first BGs were composed mainly of SiO₂, CaO, Na₂O, and P₂O₅. Compared with the conventional soda-lime-silica glasses, they contain less than 60 mol % SiO₂, have a high CaO and Na₂O content, and a low CaO/P₂O₅ ratio.³ Traditional soda-lime-silica glasses are easy to melt, homogenize and form into objects, as the viscosity of the glass melt changes over a wide temperature range. In alkali-silicate glasses, an increase in alkali leads to a decrease of viscosity, resulting in a glass with a narrow working range. These glasses can only be used as bulk or crushed glasses. The BG, S53P4, which was used in this study, is composed of 53% SiO₂, 23% Na₂O, 20% CaO, and 4% P₂O₅. This BG, which today is manufactured as BonAlive[®], Vivoxid, Finland, gained European approval for orthopedic use as bone graft substitute in 2006.

The bonding occurs as a complex series of reactions in the glass. As the glass is implanted in the bone, reactions start at the glass surface, with subsequent formation of a Si-rich layer. On top of this layer, a stabilizing layer of hydroxyapatite (HA) is formed. This HA layer has been demonstrated to chemically bind to the bone.⁴

Cancellous bone defects filled with BG granules in rabbit femora have revealed new bone formation with an intimate contact but without intervening soft tissue between new bone lamellae and glass granules.^{5,6}

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Clinically, BGs have shown good results, for instance, in repair of orbital and facial bone defects, in middle-ear implants, in alveolar ridge maintenance, and in obliteration of frontal sinuses.⁷⁻⁹ However, limited strength and degradation of the material have restricted its use to low loading conditions, for example, as a filling material for benign bone tumors.

The aim of this randomized study was to compare BG and AB as bone graft materials, in benign bone tumors over a 3-year follow-up.

MATERIALS AND METHODS

Twenty-five patients (9 females, 16 males) with a radiologically diagnosed benign bone tumor participated. The tumors were found either after a pathological fracture or on X-rays taken because of local pain. All pathological fractures ($n = 13$) were treated conservatively with an immobilization cast, before any bone filling operation was performed. The tumors were located in the humerus ($n = 6$), proximal tibia ($n = 7$), phalanges of the fingers ($n = 9$), navicular bone of the foot ($n = 1$), patella ($n = 1$), and talus ($n = 1$). The mean age of the patients was 25.5 years (SD 10.2).

The patients were randomized into one of the two groups, BG or AB. In the BG group, BG S53P4⁶ (BonAlive[®], Vivoxid, Finland) was used as a bone graft substitute (14 patients); and in the AB group, AB from the iliac crest was used (11 patients). In both the groups, 64% of the bone tumors were classified as large (mean 23.4/28.8 cm³) and 36% as small (2.3/1.1 cm³). The volume of the cavity was estimated from both X-rays and CT scans by measuring three orthogonal diameters. An ellipsoidal volume was used.

The patients were operated on at the Department of Surgery, Turku University Hospital. During the operation, the lesion was opened by detaching the cortical lid. A biopsy was then taken to confirm the preoperative clinical and radiological diagnosis. The tumor was meticulously removed, and the inner wall of the cavity was refreshed using bone drills. The cavity was filled with either BG granules or AB. In small bone tumors ($n = 5$), the size of the glass granules was 1–2 mm and in larger tumors ($n = 9$), 1–2, 2–3, or 3.15–4 mm. The filled cavity was covered with the cortical bone fragment that had been detached to access the tumor. Routine antibiotics, and antithromboembolic prophylaxis, and anti-inflammatory drugs were provided. The follow-up scheme included visits at the outpatient department at 2 weeks and at 3, 8, 12, 18, 24, and 36 months. X-rays and CT scans were taken for evaluation of the bone lesion. Blood samples (B-Hb, B-Hkr, B-Eryt, B-MCV, fB-leuk, B-Tromb, P-CRP, P-K, P-Na, fP-Krea, fP-Ca, and P-AFOS) were obtained for standard examination at every visit.

The type of tumor classified by histopathological examination was as follows: aneurysmal bone cyst ($n = 3$), enchondroma ($n = 8$), nonossifying fibroma ($n = 5$), sim-

ple cyst ($n = 7$), epidermal cyst ($n = 1$), and desmoplastic fibroma ($n = 1$).

The local ethics committee approved the study protocol, and patient-informed consent was obtained.

Statistical Analysis

All primary and secondary outcome statistical analyses were performed by an independent source (Medikalla Oy, Medfiles, Turku, Finland). The intent-to-treat populations, which included all randomized patients, were used in all tables and analyses. Descriptive statistics were calculated for all variables. Categorical variables are presented in frequency tables (PROG FREQ in SAS[®]) (number of cases and percentages) by treatment. The numerical variables were tabulated by treatment (PROG UNIVARIATE in SAS[®]).

CT and X-ray measurements were evaluated with analysis of variance for repeated measures (ANOVA) when treatment, size of the bone tumor, time, and treatment-time interaction were included in the model (PROC MIXED in SAS[®]). Thickness of the cortex (thick vs. normal) was analyzed by Fisher's Exact Test (PROC FREQ in SAS[®]).

All statistical evaluations utilized SAS Procedures in SAS[®] system for Windows (version 8.2)

A p value of <0.05 was considered significant.

RESULTS

The BG was tolerated well. No infections were detected in any patient. All patients in both groups, except those with a postoperative complication, described the bone tumor region as painless at 3 months. Blood samples showed no difference between the two groups.

The preoperative calculated mean volume of the bone tumor on X-rays was 20.7 cm³ (SD 17.7) in the AB group and 19.5 cm³ (SD 20.2) in the BG group, compared with the postoperative CT findings at 2 weeks, 22.5 cm³ (SD 16.0) and 26.2 cm³ (SD 16.0), respectively.

A significant difference was presented between the AB and BGs group in how the bone cavities remodeled over time ($p = 0.0001$). Neither the small nor the large filled cavities were measurable on X-rays at 12 months in the AB group, and compared with the preoperative situation, this was statistically significant ($p = 0.0003$, $p < 0.0001$). In the BG group, the volume of the large bone cavities started to diminish after 12 months, and compared with the preoperative situation, a significant difference was presented at 24 months ($p = 0.0195$). However, at that time, the difference between the AB and BG groups remained ($p = 0.0129$), but at 36 months, no difference in volume of the cavity ($p = 0.7881$) could be seen. The small bone cavities began to disappear earlier than the larger cavities, and at 24 months, no difference in cavity volume between the AB and BG groups was detected ($p = 0.2106$). However,



Figure 1. Postoperative image of a nonossifying fibroma in the distal tibia filled with BG.

in the BG group, the regions of both small and large filled cavities appeared dense on X-rays (Figures 1–4).

CT also revealed that the filled cavities in the BG group started to diminish after 12 months. For the large bone cavities, a difference in disappearance between the two groups was noted at 12 and 24 months ($p = 0.0005$, $p = 0.0092$). At 36 months, no difference between the AB and BG groups remained ($p = 0.9117$). The volumes of the bone cavities evaluated by CT during the follow-up are shown in Table I. In the BG group, glass granules incorporated in new bone were, however, still observable. The new bone grew centripetally from the inner walls of the cystic lesion between the slightly rounded granules (Figures 5 and 6).

Cortical thickness was evaluated from X-rays by a radiologist as thin, normal, or thick. The cortical thickness seemed to increase over time more in the BG group than in the AB group (Figure 7). This difference was significant ($p < 0.0001$).

Postoperative complications in the BG group were as follows:

In one male patient with an aneurysmal bone cyst in the proximal humerus, a small residual cyst was observed im-

mediately postoperatively. The cyst started to grow, and 2 years later, the patient was reoperated and the recurrent cyst was filled with additional BG. During the second operation, the BG granules that had been used as filler material in the previous procedure were observed to be well incorporated in the bone. The glass granules were surrounded by a bone that appeared to be harder than normal. After the second operation, the patient became painless.

Three fractures occurred postoperatively. A female patient with an enchondroma in the third finger had undergone surgery 10 years before this study. In the operation, AB graft had been used as a bone substitute. A residue had been observed and the patient was randomized to the BG group. Postoperatively, no splint was used and the patient sustained a fracture in the untouched cortex, which was missed at the control visit. Subsequently, a radial deviation of 20° of the finger was observed, and X-ray confirmed that the enchondroma had not been properly filled and a small residual cyst remained. In a reoperation, a correction osteotomy was performed and the residual enchondroma was filled with AB. At 3 months postoperatively, the patient was painless.



Figure 2. A nonossifying fibroma in the distal tibia filled with BG at 36 months.



Figure 3. An enchondroma in the proximal phalange of the hand filled with BG at 2 weeks.

One male patient with a nonossifying fibroma in the tibia sustained a fissural fracture at 3 months. This fracture healed well with mature cortical callus and no complications.

Another male patient who also had a nonossifying fibroma in the tibia sustained a fissural fracture while dancing 1 month postoperatively. The leg was put in a cast for 6 weeks. The fracture healed well, and at 3 months postoperatively, the patient was painless.

The following postoperative complications were presented in the AB group:

A female patient with a patellar bone cyst sustained a fissural fracture in the patella 4 weeks postoperatively while dancing. The leg was immobilized in a cast for 4 weeks. Four months postoperatively, the knee was painless.

Another patient in the AB group with an epidermal cyst in the distal phalange of the hand had suffered long from postoperative pain. At 2 years, a residue cyst was observed



Figure 4. An enchondroma in the proximal phalange of the hand filled with BG at 36 months.

TABLE I. Postoperative Volume of Bone Cysts Evaluated from CT

Months	AB (cm ³) (SD)	BG (cm ³) (SD)
1	22.5 (16.0)	26.2 (16.2)
3	12.5 (10.3)	26.6 (13.9)
8	2.1 (5.1)	26.4 (12.7)
12	0.2 (0.2)	24.5 (14.7)
24	0.0 (0.1)	16.4 (13.0)
36	0.0 (0.0)	9.1 (14.1)

AB, autogenous bone group; BG, bioactive glass group.

and the patient was reoperated on using AB. At 3 months, the patient was painless.

A male patient with a bone tumor in the proximal humerus also suffered from long-lasting pain in the iliac crest at the donor site and was unable to run at 3 months. The pain disappeared over time.

DISCUSSION

In this randomized study, BG S53P4, was used as a bone graft substitute. It was well tolerated, and no material-dependent adverse effects were observed.

According to X-ray and CT findings, a significant difference was, however, presented between BG and AB groups in how the filled bone cavity disappeared over time. The time for disappearance was significantly longer in the BG group than in the AB group. In the AB group, both small and large bone cavities had remodeled with new bone at 12

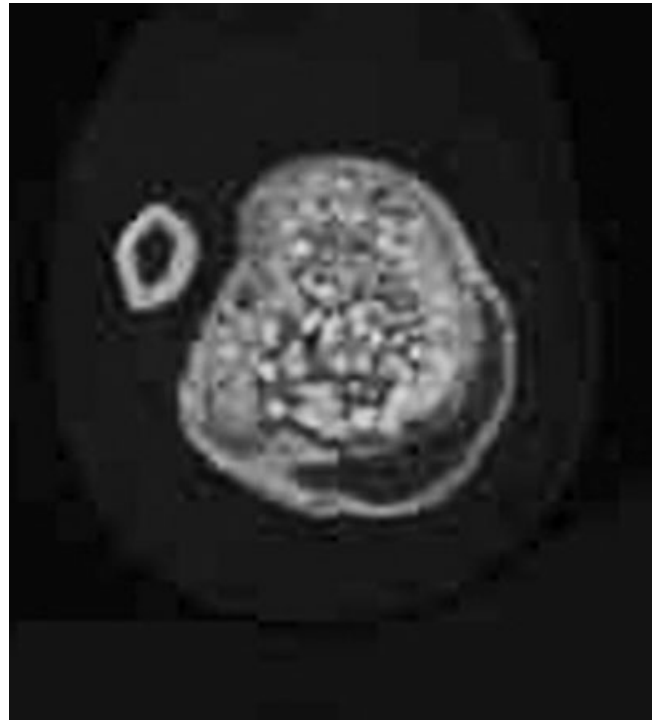


Figure 6. CT scan showing centripetal bone growth from the inner walls of the cavity at 36 months.

months postoperatively. In the BG group, it took 24 months for small cysts and 36 months for large cysts to achieve the same filling level as in the AB group.

In a rabbit model for spinal fusion, it has been shown that the formation of new bone between BG granules increases slowly compared to autograft bone. This is attrib-

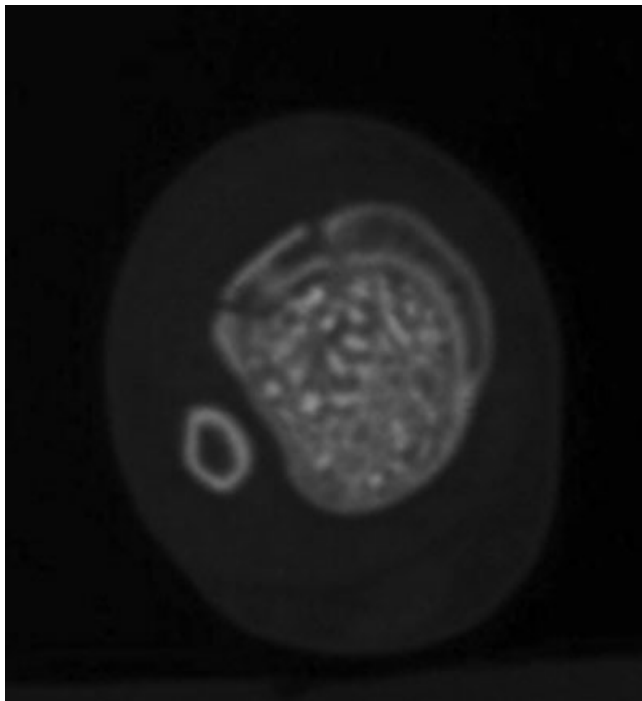


Figure 5. CT scan showing centripetal bone growth from the inner walls of the cavity at 3 months.

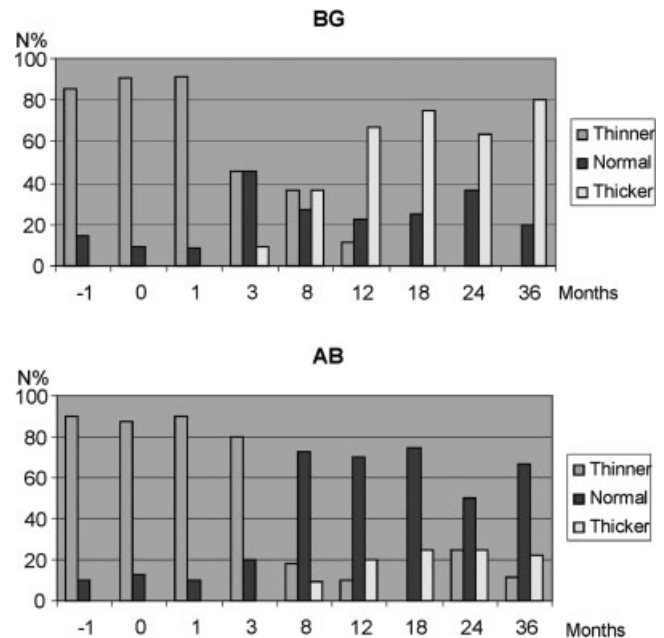


Figure 7. Cortical thickness evaluated from X-rays for BG and AB groups. -1= preoperative status.

uted to the high resorption rate of autograft bone in the beginning of the healing process and the slow remodeling of BGs.¹⁰ In a clinical setting, this observation may limit the use of BGs, for example, in large defects under high loading conditions.

Despite bone remodeling being slower in the BG group, the growing bone was apparently hard. The reoperation of the patient in the BG group with a large bone tumor in the humerus allowed the previously filled cystic cavity to be studied, revealing that the glass granules were incorporated in a cancellous bone tissue that appeared to be harder than normal. This is in accordance with observations on X-rays, where the filled cavity in the BG group seems to be more sclerotic than in the AB group.

At 36 months, glass granules were no longer distinguishable on X-rays, but the region of the filled cavity appeared dense. However, on CT scans, glass granules were still observed, especially in the group of large bone tumors. The bone grew centripetally, incorporating the glass granules, which became rounder and smaller over time. Further investigations are needed to determine how long the glass granules remain visible.

Interestingly, the cortical thickness in the BG group seemed to increase with time. This was observed already at 8 months, and by 36 months 80% of the operated cavities were considered to have a thickened cortex. As the BG slowly dissolves over a long period, new bone formation simultaneously occurs. According to our results, it seems like the remodeling process can stimulate the cortex to grow in thickness. This is in accordance with an earlier observation of cortical thickening in a large BG-filled cavity.¹¹ Compared with AB, BG may also be beneficial in operative treatment of osteoporotic bone. The evaluation of the cortex was, however, rough (i.e. thin/normal/thick), and for better estimation of postoperative thickening of the cortex, further investigations and a longer follow-up period are required.

One problem frequently emerging after treatment of benign bone tumors is the appearance of recurrent tumors. This can result for both technical and biological reasons. Depending on the type of bone tumor, the complication rate has been reported to be quite high. For instance, recurrence rates for aneurysmal bone cysts after curettage and bone grafting have been found to be 30.8–50%.¹² On the other hand, cure rates for nonossifying fibromas have been reported to be 95% independent of any treatment. The indications for operative treatment of these benign bone tumors have been limited to associated pain, fracture, or risk of fracture.¹³

BG was also suitable in which AB graft had previously been used as bone graft material and a recurrent cyst had appeared. The patient with a simple bone cyst in the proximal humerus had earlier been operated on in another hospital using AB as a bone substitute. One year later, a recurrent cystic lesion was observed and a second surgery

planned. The patient was randomized to the BG group, and the cyst was thus filled with BG. No residue was observed during the postoperative follow-up.

A few complications occurred in both treatment groups. Residues in need of reoperation appeared in one patient in both groups. Three fractures in the BG group and one fracture in the AB group were sustained postoperatively. Three of these fractures could probably have been avoided had the postoperative immobilization advice been followed.

In conclusion, the need for bone substitutes in orthopedic surgery is increasing. As new materials and implants are entering the market, evidence-based medicine is important. This prospective randomized study shows that BG S53P4 appears to be a promising bone substitute for the treatment of benign bone tumors.

REFERENCES

- Schreuder HWB, Vert RPH, Pruszczynski M, Lemmens JAM, Koops HM, Molenaar WM. Aneurysmal bone cysts treated by curettage, cryotherapy and bone grafting. *J Bone Joint Surg* 1997;79:20–25.
- Aho AJ, Ekfors T, Dean PB, Aro HT, Ahonen A, Nikkanen V. Incorporation and clinical results of large allografts of the extremities and pelvis. *Clin Orthop* 1994;307:200–213.
- Hench LL. Bioactive ceramics. *Ann N Y Acad Sci* 1988; 523:54–71.
- Hench LL, Paschall HA. Direct chemical bond of bioactive glass-ceramic materials to bone and muscle. *J Biomed Mater Res Symp* 1973;4:25–42.
- Heikkilä JT, Aho HJ, Yli-Urpo A, Happonen RP, Aho AJ. Bone formation in rabbit cancellous bone defects filled with bioactive glass granules. *Acta Orthop Scand* 1995;66:463–467.
- Lindfors NC, Aho AJ. Granule size and composition of bioactive glass affect osteoconduction in rabbit. *J Mater Sci: Mater Med* 2003;14:265–372.
- Suominen EA, Kinnunen J. Bioactive glass granules and plates in the reconstruction of defects of facial bones. *Scand J Plast Reconstr Surg Hand Surg* 1996;30:281–289.
- Peltola MJ, Suonpää J, Aitasalo K, Määttänen H, Andersson Ö, Yli-Urpo A, Laippala P. Experimental follow-up model for clinical frontal sinus obliteration with bioactive glass (S53P4). *Acta Otolaryngol Suppl* 2000;543:166–169.
- Andersson ÖH, Karlsson KH, Kangasniemi K. Calcium phosphate formation at the surface of bioactive glass in vivo. *J Non-Cryst Solids* 1990;119:290–296.
- Lindfors NC, Aho AJ. Tissue response to bioactive glass and autogenous bone in rabbit spine. *Eur Spine J* 2000;9:30–35.
- Aho AJ, Suominen E, Alanen A, Yli-Urpo A, Knuuti J, Aho HJ. Remodelling of the tibia after grafting of a large cavity with particulate bioactive glass—hydroxyapatite—Case report on treatment of fibrous dysplasia with 13 years follow-up. *Acta Orthop Scand* 2003;74:766–770.
- Rastogi S, Varsney MK, Trikha V, Khan SA, Choudhury B, Safaya R. Treatment of aneurysmal bone cysts with percutaneous sclerotherapy using polidocanol: A review of 72 cases with long-term follow-up. *Bone Joint Surg* 2006;88:1212–1216.
- Hollawell S, Pfeiffer D. Technique for curettage and grafting of an intramedullary tibial bone cyst. *J Am Podiatr Med Assoc* 2006;96:351–355.