

Composite ceramic bone graft substitute in the treatment of locally aggressive benign bone tumours

OS Schindler

Droitwich Knee Clinic and Birmingham Arthritis & Sports Injury Clinic, Worcestershire, United Kingdom

SR Cannon, TWR Briggs

Bone Tumour Unit, The Royal National Orthopaedic Hospital, London, United Kingdom

GW Blunn

Department of Biomedical Engineering, Institute of Orthopaedics, University of London, London, United Kingdom

ABSTRACT

Purpose. To report the use of a composite ceramic bone graft substitute containing calcium sulphate and hydroxyapatite (HA) in the treatment of large expansive osteolytic benign bone tumours.

Methods. 4 women and 9 men aged 8 to 49 (mean, 22) years with aneurysmal bone cysts (n=6) or giant cell tumours (n=7) in the epi- or meta-physeal areas of the lower limbs underwent curettage, phenolisation, and filling with bone graft substitute containing calcium sulphate and HA. The mean tumour size was 38.5 (range, 18–65) ml. The patients were followed up for a mean of 41 (range, 33–52) months. Range of movement, Musculoskeletal Tumor Society Rating Score (MTSRS), and haematological and blood biochemical parameters were measured.

Results. Two patients had recurrence at 7 and 9 months, both progressed to grade-III giant cell tumours. One underwent revision with an iliac crest autograft, whereas the other underwent *en bloc* excision and prosthetic replacement. The 11 other lesions displayed clinical and radiological consolidation

at a mean of 4.6 (range, 3–7) months. No restriction of range of movement was observed, except in the patient undergoing prosthetic replacement. The mean MTSRS was 96% (range, 83–100%) of that expected for normal function. During the follow-up period, haematological and blood biochemical parameters stayed within normal limits.

Conclusion. Composite bioceramic osteoconductive grafts, which combine porous HA with calcium sulphate, provide a framework for human osteogenesis and avoid donor-site morbidity (autologous bone graft harvesting). Tumour recurrence remains a major concern especially in young patients, as revision invariably requires removal of additional bone, potentially compromising joint integrity.

Key words: bone cysts, aneurysmal; bone neoplasms; bone substitutes; giant cell tumor of bone

INTRODUCTION

The peri-articular areas of the femur and tibia are common sites for the occurrence of semi-malignant (locally aggressive but non-metastatic) bone tumours,

such as aneurysmal bone cysts (ABCs) or giant cell tumours (GCTs). These tumours, usually appear as osteolytic, cystic lesions, are locally aggressive and have a high rate of recurrence. Traditional treatment involves thorough curettage, autologous bone grafting, and various adjuvant therapies. The additional use of phenol or liquid nitrogen has been reported to reduce recurrence.¹⁻⁷ Large amounts of bone graft are required to achieve biological reconstruction. Joint stability may be at risk even if an appropriate amount of bone graft is inserted. Harvesting of autologous bone graft is difficult and frequently associated with considerable donor-site morbidity.⁸⁻¹¹

In the adult skeleton, injection of bone cement (methylmetacrylate) provides instant stability and has been an alternative to bone grafting.^{12,13} Although bone cement does not provide biological reconstruction, it causes thermo-necrosis of superficial tissue layers, thereby destroying remaining tumour cells in the capsular lining of the lesion.¹⁴ Bone cement appears to be well-tolerated in the long term, but problems may occur in cases of osteolysis, tumour recurrence, or if the patient develops osteoarthritis, joint arthroplasty becomes necessary.^{15,16}

In the immature skeleton, the use of non-resorbable material may affect skeletal growth. Hence osteogenetic repair using autologous bone graft has been the treatment of choice.¹⁷⁻¹⁹ As children can only provide a limited amount of autologous bone graft, biocompatible bone graft substitutes resembling physiological bone have been developed.²⁰⁻²² They have unlimited availability, preserve physiological surroundings, reduce operating time and blood loss, and avoid donor-site morbidity. Calcium-sulphate-hemihydrate ($2\text{CaSO}_4\cdot\text{H}_2\text{O}$), known as 'gypsum' or 'plaster of Paris', is by far the most popular of all synthetic materials.^{23,24} Other graft materials include β -tricalcium-phosphate and hydroxyapatite (HA).^{25,26}

Plaster of Paris was first used to fill bone defects caused by tuberculosis,²³ and later in the treatment of lytic lesions of benign bone tumours.²⁷ Its safety and efficacy in the treatment of various bone defects, including benign bone tumours such as simple bone cysts, giant cell tumours, and fibrous dysplasia, have been confirmed.²⁸⁻³⁵ It does not disturb the proliferation of bone marrow or alter the normal growth pattern of bone. An increase in blood calcium levels, noted in animal studies, has not been encountered in humans.^{34,35} Histological investigations of bone marrow harvested from areas of previous calcium sulphate applications revealed normal bone structure. The calcium sulphate graft had been completely resorbed and replaced by physiologically regenerated bone.^{30,36}

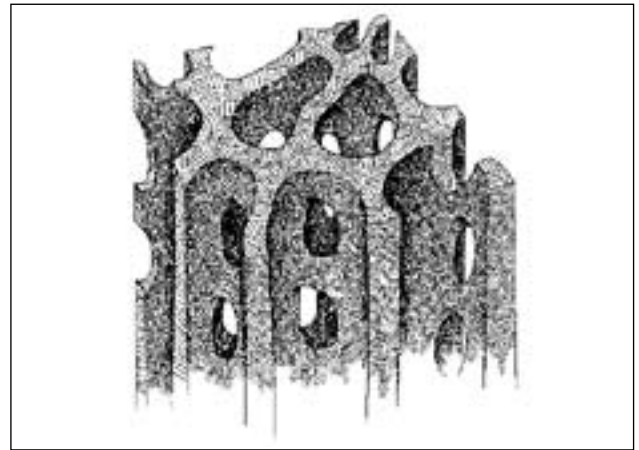


Figure 1 A ceramic bone graft substitute scaffold showing porosity and channels of osteonic diameters mimicking the interstitial matrix of cortical bone.³⁷

HA is a bone mineral, which comprises 90% of the inorganic matrix of bone and is osteoconductive.³⁷ It is widely used in surface coating of joint replacements, as it facilitates direct bone ingrowth onto the prosthetic component.^{38,39} It has also been used as a bone graft substitute but is poorly resorbed (compared to calcium sulphate).⁴⁰⁻⁴⁷

Calcium sulphate and HA have pure osteoconductive qualities, thus creating a suitable environment for new bone formation. As they are unable to promote osteoinduction, the speed of bone ingrowth and repair depends on the host and the delivery of osteoinductive mediators such as bone morphogenic protein, transforming growth factor, and platelet-derived growth factor, from the haematopoietic cells of the surrounding marrow. Although the process of osteoinduction is not yet fully understood, it is generally believed that mediators that activate progenitor cells within the trabecular bone are responsible for osteoinduction.^{21,48-55}

The combination of calcium sulphate and HA enables rapid resorption of calcium sulphate but leaves a coral matrix of porous HA behind (Fig. 1). This osteoconductive scaffold has a large surface area, which further enhances ingrowth and formation of new bone.⁵⁶ Such composite grafts have been used in oral surgery and reveal an increase in bone ingrowth compared to calcium sulphate alone.⁵⁷ Numerous studies have demonstrated the biocompatibility, bioactivity, and osteoconductivity of ceramics such as calcium sulphate, β -tricalcium phosphate, and HA.^{37,58-61} However, the long-term results of such treatment for benign bone tumours are still limited.^{30,45,62}

Table
Patient demographics and clinical details

Patient No.	Sex/age (years)	Tumour grade*	Location	Tumour size (ml)	Follow-up period (month)	Time to consolidation (weeks)	Recurrence (month)	MTSRS [†] (%)	Comments
1	M/14	ABC-I	R proximal femur	44	38	24	-	97	-
2	F/11	ABC-I	R proximal tibia	29	33	16	-	97	-
3	F/8	ABC-II	L proximal tibia	36	34	12	-	97	Postoperative fracture healed
4	M/10	ABC-I	L proximal tibia	18	36	12	-	100	-
5	M/36	GCT-II	L proximal tibia	45	40	20	-	100	-
6	M/49	GCT-II	R proximal tibia	24	42	14	-	97	-
7	F/35	GCT-II	R distal femur	48	42	28	-	94	Reduced range of movement of knee (0°–5°–130°)
8	M/21	GCT-II	R distal femur	52	48	-	GCT-III (7)	83	Distal femoral resection and prosthetic replacement
9	M/27	GCT-II	R distal femur	36	36	16	-	100	-
10	M/30	GCT-II	L proximal tibia	65	48	-	GCT-II (9)	86	Successful re-curettage and autologous bone grafting
11	M/23	GCT-I	R distal femur	45	36	18	-	97	-
12	M/12	ABC-II	L proximal femur	40	48	24	-	100	-
13	F/9	ABC-I	L proximal femur	18	52	18	-	100	-
Mean	22	-	-	39	41	18	-	96	-

* ABC denotes aneurysmal bone cyst, and GCT giant cell tumour; grading according to the Campanacci classification

† MTSRS denotes Musculoskeletal Tumor Society Rating Score, indicating the percentage of the expected normal function

MATERIALS AND METHODS

From May 1996 to January 1998, 4 women and 9 men aged 8 to 49 (mean, 22) years with expansive, osteolytic, benign bone tumours in the lower limbs were treated with a composite ceramic bone graft substitute containing calcium sulphate and HA. The inclusion criterion was the presence of such a tumour, which was too large for autogenous bone grafting. All patients underwent preoperative core needle bone biopsy.⁶³ Histology revealed 6 patients had aneurysmal bone cysts and 7 had giant cell tumours. All tumours were graded according to the Campanacci classification,⁶⁴ based on radiological features (grade I=5, grade II=8; Table). There were no pathological fractures within or around any of the tumours, which were located in epi- or meta-physeal areas of the lower limbs near the hip or knee joint (proximal tibia=6, distal femur=4, proximal femur=3; Figs. 2–5).

The surgical sites were approached through the original biopsy tract. A cortical window was cut into the bone to open the tumour cavity, allowing visualisation of the whole cavity. After thorough curettage, a swab soaked with 20% phenol was placed into the cavity and left *in situ* for approximately 3 minutes to ensure impregnation of the tumour lining. After swab removal, the cavity was further washed



Figure 2 Anteroposterior radiographs of a 12-year-old boy showing (a) an aneurysmal bone cyst located within the greater trochanter of the left proximal femur. (b) At postoperative one month, the typical radiolucent halo surrounding the opaque bone graft substitute during the initial period of graft resorption is demonstrated. (c) At postoperative 16 months, implant margins become indistinct indicating osseous integration through bone ingrowth.

out with 0.9% saline solution. The tumour size was estimated by the volume of liquid injected; the mean volume was 38.5 (range, 18–65) ml.

The bone graft substitute contained 65% HA granulate and 35% calcium sulphate hemihydrate



Figure 3 Anteroposterior and lateral radiographs of a 49-year-old man showing (a) a giant cell tumour located within the lateral aspect of the right proximal tibial epiphysis. (b) At postoperative 2 years, signs of bone ingrowth and consolidation are obvious, with no signs of re-recurrence.

and was mixed with 10 to 20 ml of autologous venous blood. After thorough drying of the tumour cavity, the bone graft substitute was injected and firmly impacted.

Radiographs were taken pre- and post-operatively, and during follow-up at 1.5, 3, and 6 months and 6 months thereafter. A final radiograph was taken at 3 years. The necessity and indication for further reviews beyond 3 years was decided on an individual basis.

All patients were instructed to not or partially weight bear (5–10 pounds) for 2 to 3 months in order to protect the grafted area. Weight bearing was gradually increased depending on the degree of radiological consolidation. Haematological and biochemical blood analysis was performed preoperatively, and also at 3 and 12 months postoperatively. All patients were assessed according to the Musculoskeletal Tumor Society Rating Score (MTSRS), which provides a percentage value of expected normal function.⁶⁵



Figure 4 Anteroposterior and lateral radiographs of a 35-year-old woman showing (a) a giant cell tumour located within the medial femur condyle displaying signs of expansive growth and cortical erosion around the posterolateral aspect. (b) At postoperative 2 years, although the radio-opacity of the bone graft substitute is still visible, the implant margins become indistinct indicating bone ingrowth.

RESULTS

The mean follow-up period for the 13 patients was 41 (range, 33–52) months. One patient had a fracture of the metaphyseal cortex but healed uneventfully, and none developed any noticeable deformity. Tumour recurrence was observed in 2 patients at 7 and 9 months respectively. In one of these cases, signs of tumour growth were seen beyond the original borders of the tumour cavity with breaching of the femoral cortex (Fig. 5b). The tumour was classified as a Campanacci grade-III (G_0T_2) lesion. Due to such destabilising joint destruction, anatomic reconstruction did not seem feasible and a prosthetic replacement was performed (Fig. 5c).^{66,67} In the other case, the lesion was successfully treated with re-curettage, phenolisation, and packing with autogenous bone graft harvested from the iliac crest.

The remaining 11 patients showed clinical and



Figure 5 Anteroposterior radiographs of a 21-year-old man showing (a) the curretted tumour cavity packed with radio-opaque bone graft substitute within the lateral femoral condyle. (b) At postoperative 7 months, the tumour recurs and shows aggressive transformation through expansion beyond the cortical borders of the distal femur; (c) *en bloc* excision and custom-made prosthetic replacement are performed.

radiological signs of consolidation and were able to bear full weight by a mean of 4.6 (range, 3–7) months. No restriction of range of movement was observed, with the exception of the patient who underwent prosthetic replacement. During the early postoperative period, a radiolucent zone (halo) surrounding the graft material became visible, indicating graft resorption (Fig. 2b). During the period of 3 to 24 months after operation, bone density increased and tumour demarcation disappeared, indicating osseous-integration and consolidation of the graft-filled cavities (Fig. 2c).

The mean MTSRS was 96% (range, 83–100%) of the expected normal. The 2 patients with recurrence had lower MTSRS (83 and 86%) values than the others. Haematological and blood biochemical parameters during the follow-up period remained within normal limits.

DISCUSSION

Despite ongoing improvements in tumour surgery, the treatment of locally aggressive but non-metastatic bone tumours remains a challenge. Success is compromised by a relatively high rate of tumour recurrence and difficulty of establishing subchondral bone stability, particularly when treatment is intra-lesional or intra-capsular. The aim of such treatment is to re-establish skeletal stability and bone morphology, without compromising axial growth, joint function,

and overall mobility.

Some of our patients presented with lesions expanding into subchondral areas, placing the integrity of the joint surface in jeopardy. Although synthetic bone graft substitutes using calcium sulphate and HA may provide a physiological reconstruction,^{31,33,42,45,46,68} so far they have only been used in experimental animal studies and in maxillofacial surgeries.^{21,37,57,69}

Calcium sulphate in the form of plaster of Paris was administered to 26 patients with unicameral bone cysts; 24 of them did not require further surgery and displayed evidence of consolidation 3 to 6 months later.³³ Nonetheless in earlier studies, results were inconsistent and probably attributable to variations in particle size and crystalline structure of the plaster of Paris used.^{30,34,70}

In a large multicentre trial, surgical-grade calcium-sulphate pellets (Osteoset; Wright Medical Technology, Arlington [TN], US) were used in 46 patients with benign bone tumours (mean size, 3.2 ml; range, 0.15–112 ml).³² In 36 of 42 patients, a mixture of additional graft materials including demineralised bone, bone marrow aspirate, and autograft were used. 100% pellet resorption and 96% bone ingrowth were reported at 12 months, with no significant difference between patients receiving Osteoset alone or in combination with other graft materials.³²

Osteoset with or without demineralised bone matrix was used in 23 patients with bone cysts or benign bone tumours (mean size, 23 ml). Healing was observed in all patients and the rate and amount of bone regeneration was not dependent on the addition of demineralised bone matrix to the calcium sulphate granules. Osseous repair of the lesions was considered complete by 6 months, and all but one patient resumed normal functional activities by 12 months.⁷¹

Porous blocks of calcium HA ceramic were used in 60 patients with benign bone tumours, including 8 giant cell tumours and 5 aneurysmal bone cysts (mean size, 78 ml; range 2–180 ml).⁷² The lesions were curretted and if necessary stabilised with plates and screws. No adjuvant agents were used and no recurrences observed. The radiographic density of the implant increased and the margins abutting the host bone became indistinct, which was considered indicative of bone regeneration. Biopsies obtained during metal-ware removal around 12 months after surgery confirmed widespread bone ingrowth into the calcium HA pores in the absence of fibrous tissue. However, no signs of biodegradation of the HA graft material were seen.

Similar findings were found in 75 patients with benign bone lesions implanted with a combination of HA and tricalcium phosphate. No adjuvant therapy

was used. Radiolucent zones surrounding the bone graft substitute disappeared at a mean of 4.2 months,⁶² which was in keeping with our own results.

Another osteoconductive substance, β -tricalcium phosphate has also been used successfully as a space filler in the treatment of benign bone lesions, and henceforth may represent a viable alternative ceramic graft material to calcium sulphate and HA.^{25,47,73,74} However, comparative studies looking into a potential advantage of β -tricalcium phosphate over other grafting materials are scarce.⁴⁷

One of the major factors determining the quality of bone graft substitutes is the speed with which the graft material integrates into the host bone. It is difficult to compare the rate of graft incorporation reported in various studies, as no quantitative measures are available for evaluation of bone ingrowth into porous material. Histological analysis could provide such information but appears impractical, due to the requirement of bone biopsies (unless performed during associated procedures).⁷² Hence radiological assessment has been widely accepted as the method of choice, but standardised assessment guidelines have not been defined. In our study, disappearance of the radiolucent zone or halo surrounding the graft material was taken as an indicator that defined the degree of consolidation.^{47,62,72} However, the high calcium content and characteristically high-density ceramic bone graft substitute make a judgment on the degree of consolidation difficult. Reported figures for completion of osseous repair are size dependent and range from 3 to 24 months.^{32,33,47,72,73}

Once the bone graft substitute is placed into the tumour cavity, the process of calcium sulphate resorption is initiated leaving behind a 3-dimensional construct of HA.³⁷ It is believed that calcium sulphate is replaced by newly formed bone, in a process called creeping substitution, by which resorption takes place at the same rate as consecutive bone ingrowth. Calcium sulphate, which is known to support the ingress of blood vessels and osteogenic cells, acts as a space filler, and by doing so prevents the ingrowth of fibrous tissue.⁷⁵ During this process HA functions as a scaffolding, which provides temporary structural stability. The highly crystalline, porous HA scaffold is brittle and carries little tensile strength.³⁷ Due to its weak mechanical properties, load bearing should be delayed until evidence of graft consolidation is present, especially if the implant is used in peri-articular areas. Once the graft is incorporated, its mechanical strength equals that of normal bone. Six months after graft implantation, no significant difference in mechanical strength was noted between HA and autologous cortical bone.^{76,77}

In our study, after a mean of 4.5 months, bone integrity and joint stability were regained in 11 out of 13 patients, without compromising tumour control. Tumour recurred in 2 of the 7 patients with GCTs. One of them was locally aggressive and perforated into the knee joint, necessitating prosthetic replacement.

Curettage and bone grafting alone, as the traditional treatment for ABCs and GCTs, confer recurrence rates of 37% to 71%.⁷⁸⁻⁸¹ The use of liquid nitrogen and/or phenol as adjuvant treatment has decreased recurrence to between 0% and 34%.^{4-7,64} Nonetheless, 2 (40%) of 5 GCTs (mean size, 7.8 cm) recurred after filling with HA porous cubes.⁴⁷ Whether an adjuvant agent such as phenol was used was not specified.

It is possible that recurrence is affected by the type of filling material used. However, it is more likely dependent on the thoroughness of the curettage and the effectiveness of any adjuvant agent used prior to implantation of the graft material.⁸² A recurrence of 28% in the sub-section of our GCT patients is in keeping with the results of others who have used phenol in the tumour cavity. However, statistical analysis of such a small sample size should be interpreted with caution.

Apart from phenol, many other adjuvant agents have been advocated, including: liquid nitrogen,⁷ hydrogen peroxide,⁸³ and heat cauterisation with electrocautery, argon beam coagulation or polymethyl-methacrylate polymerisation.^{12,64,84} Controversy exists regarding the efficacy of the various agents and some authors consider that the recurrence rate is not affected by the type of adjuvant used.^{82,85}

In 47 patients with GCTs, recurrence was noted in 11 patients, 3 of whom also developed pulmonary metastasis.⁸⁶ Within the group where recurrence was observed, 88% presented as a grade-III lesion. Tumour-suppressing phosphoprotein (p53) as expressed by mononuclear stromal cells was present in 66%, which included all the patients with metastasis. It was concluded that patients with grade-III tumour and/or those in whom the tumour expresses p53 have a higher chance of pulmonary metastasis and recurrence. There was a positive correlation between the presence of matrix metalloproteinase (MMP-9) expressed by mononuclear histiocytic stromal cells in GCTs and the development of lung metastasis.⁸⁷

It is unclear why aggressive transformation occurred. It has been proposed that 'tumour secreted basement membrane degrading enzymes' may play an important role in tumour invasion and malignant behaviour.⁸⁸ Conceivably, some of the answers about tumour behaviour and rate of local recurrence may

depend on the tumour's biochemical make-up.

Composite ceramic bone graft substitutes containing a mixture of calcium sulphate and HA for the treatment of benign bone tumours have provided encouraging clinical results similar to those achieved through autologous bone grafting. Being synthetic materials, they avoid the risks of disease transmission associated with allografts and the donor-site morbidity associated with autografts.⁸⁹ They are suitable for growing individuals in whom autograft resources may be limited. We demonstrated the ability of such a bone graft substitute to re-establish normal biomechanical properties, through bone reconstruction in large peri-articular lesions of load-bearing joints. Despite concerns about a possible increase in serum calcium levels, such changes in blood chemistry were not encountered during the follow-up period.³⁵ There is always a risk of recurrence, which presents as focal areas of lucency close to the margin of the treated lesion. Timely recognition of recurrence may be difficult, as during the initial healing phase graft resorption usually creates a radiolucent halo surrounding the periphery of the implant. It is important that during the early

follow-up period regular radiographic examinations are undertaken in at least 2 planes. In cases of recurrence, further resection of bone is almost always required, which may very well create the need for a prosthetic replacement if the tumour is located within the proximity of a weight-bearing joint.⁶⁶

Results from larger trials encompassing clinical and histological investigations are needed. Questions on the effect of different combinations of bone graft substitutes have to be addressed before a wider recommendation for the use of composite ceramic bone graft substitutes can be given.

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