



Biphasic ceramic bone substitute mixed with autogenous bone marrow in the treatment of cavitory benign bone lesions

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A prospective study was performed on 34 patients to evaluate the efficacy and safety of a composite bone substitute formed of hydroxyapatite and tricalcium phosphate (Ceraform®) with or without gentamycin sulphate (Ceraform-Genta®) plus autogenous bone marrow aspirate in the treatment of cavitory bone defects related with benign bone lesions. At the end of the follow-up period, all patients were evaluated clinically for pain and a daily living activity score, and radiologically regarding the time and quality of bone healing, using a modified Neer grading system. Satisfactory clinical outcome without pain or impairment of daily living activities was seen in 97.1% of patients. Radiologically, 70.6% of the lesions were completely healed and 26.5% showed partial healing; one patient had local recurrence according to the modified Neer grading system. The average time to healing was 19.9 weeks and all reported complications were minor, unrelated to the composite graft itself, and did not affect the functional outcome. The composite ceramic used in this study proved to be a safe and effective bone graft substitute; its use appeared at least as effective as other treatment modalities for benign bone lesions.

Keywords: synthetic ceramic; bone substitutes; bone marrow; benign bone lesions.

INTRODUCTION

Bone grafts are widely used to treat bone defects resulting from a variety of causes, including tumours, trauma, and infection. Autogenous bone

remains the gold standard because it does not entail any immunological reaction and is both osteoconductive and osteoinductive (10). Harvesting of autogenous bone, however, can be associated with complications such as donor site pain – in up to 39% of cases –, injury to the lateral femoral cutaneous nerve or the superior gluteal artery, pelvic fracture, haematoma, infection, hernia and gait disturbances (8). Furthermore, the amount of autogenous bone graft available for harvesting is limited and the quality of the harvested autogenous bone is variable (10).

Allograft has been used as an alternative to autograft but its structure, mechanics, and resorption properties may be altered by processing, preservation, and sterilization techniques. There is also the

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potential for disease transmission or immunogenicity when using allograft. This has led to the development of various synthetic bone substitutes (8,10). One of the bone substitutes available is a macroporous biphasic composite ceramic material made of hydroxyapatite (HA) and tricalcium phosphate (TCP), which can be soaked with autogenous bone marrow before implantation.

Many benign pathological conditions can result in osteolytic or cystic lesions which may cause pain or weaken the bone with a risk of pathological fracture. Autogenic, allogenic or synthetic bone grafting may be used to obliterate such bone defects after surgical curettage and debridement.

The purpose of this prospective study was to assess the efficacy and safety of a composite ceramic bone substitute formed of 65% HA and 35% TCP (Ceraform®) or 62.9% HA, 33.9% TCP, and 3.2% gentamycin sulphate (Ceraform-Genta®) soaked with autogenous bone marrow aspirate from the iliac crest as a bone substitute in surgical treatment of benign bone lesions. Healing was graded and results were compared with those of other methods of treatment reported in literature.

MATERIAL AND METHODS

Thirty four patients with various types of benign bone lesions were included in this study. Patients were diagnosed and treated in King Saud Hospital, Unaizah-Al Qassim and King Fahad Specialist Hospital, Al Madina, Kingdom of Saudi Arabia.

Graft material

The biphasic ceramic Ceraform® or Ceraform-Genta® (Teknimed, Vic-en Bigorre, France) is supplied as sterile kits of different shapes and amounts (powder, granules, sticks, blocks, cylinders). TCP is gradually replaced by newly formed host bone within 6-24 months, while resorption of HA is much slower and may take up to five years. Ceraform is a synthetic material (no animal or human organic phase), biocompatible (no biologic reaction or toxicity), and osteointegrable (recognized by bone cells and integrable into the host bone). Its chemical composition is very close to that of the mineral phase of human bone. Its partially inter-connected porosity makes it possible to achieve revascularisation, recolonisation by bone cells and resorption through a process of

creeping substitution. Ceraform® or Ceraform-Genta® is rehydrated or impregnated with the patient's own blood through autogenous bone marrow aspirate from the iliac crest either anteriorly or posteriorly using wide-bore sternal puncture needle and syringes. The composite graft of Ceraform® or Ceraform-Genta® soaked with autogenous bone marrow is used to fill the osseous defect which is left after surgical curettage ; it is slightly impacted without overstuffing. Soaking with bone marrow aspirate drives all remaining air from the Ceraform and enhances rapid exchange of fluid inside the material ; it also eases placement of the material into the cavitory osseous defect.

Patient selection

The criteria for patient selection were : any benign bone lesion which had required surgical treatment resulting in a non structural or marginally structural cavitory osseous defect, regardless of patient's age. We excluded from the study any patient with suspected malignant bone lesion, any patient who had required hardware internal or external fixation in addition to composite ceramic graft, and any patient followed postoperatively for less than two years.

Surgical technique

The surgical technique was essentially similar in all cases and included incising the periosteum, opening the cyst wall, aspirating any fluid content, curetting the cavity wall or any tissue within it, removing any bone trabeculae to achieve a single large cavity, rinsing with diluted hydrogen peroxide, opening the medullary canal proximally and distally, cauterizing the inner wall of the cavity with a diathermy blade and finally filling the cavity with composite ceramic material soaked with bone marrow aspirate. No more than 6-8 ml was aspirated from each iliac puncture site to ensure the highest possible concentration of bone marrow stem cells. Finally the periosteum was sutured over the composite graft.

For cystic lesions close to the epiphyseal plate, curettage was guided by fluoroscopy to avoid injury to the epiphyseal plate. For cases in which a diagnosis of osteomyelitis could not be ruled out, the surgical technique was essentially similar, including guttering, saucerization or excision of the necrotic bone and soft tissue, irrigation with diluted hydrogen peroxide, excision of sclerotic edges or walls until cancellous or haversian bleeding known as "paprika sign" was achieved, and



Fig. 1. — A. Aneurysmal bone cyst in the right proximal humerus in a 16-year-old female patient ; B. Interior of the lesion after removal of cortical window ; C. Post-operative radiograph showing the composite graft (granules and sticks soaked with autogenous bone marrow aspirate), and a non vascularized fibular graft.

finally packing the osseous defect with Ceraform-Genta® soaked with autogenous bone marrow.

Specimens from bone and soft tissue curettage were sent for Gram staining, culture and sensitivity testing for aerobic, anaerobic, acid fast bacilli and fungi when osteomyelitis was suspected. The remaining tissue was sent for pathological examination. No internal or external fixation devices were used in this study ; a non vascularized free fibular graft was used in one patient with a huge aneurysmal bone cyst of the proximal humerus, to support the correction of a previous varus position of the proximal humeral epiphysis (fig 1).

Most patients with benign bone lesions in the lower limb were kept non weight-bearing with or without external immobilisation on crutches for 6 weeks then gradually returned to full weight-bearing. For younger children less than 6 years with cystic lesions of the proximal femur, a hip spica cast was used for 4 weeks. For benign lesions of the upper limb a pop cast, functional cast brace, or sling was used for 4-6 weeks.

Documentation and follow up

For every patient, we recorded name, age, gender, nationality, file number, complaint and their duration, any previous treatment, localisation of bone lesion, provisional preoperative diagnosis, size of the lesion, surgical technique, amount of bone substitute, amount of bone marrow aspirate, nature and duration of post-operative immobilisation, and post-operative pathological diagnosis. The size of the lesion was approximated using the Mirzayan *et al* method by measuring the maximum width multiplied by the maximum height on AP view immediately after surgery and at the end of the follow-up period (19).

All patients were followed up clinically and radiologically every 3 weeks during the first 6 months, then at 2 to 6 months intervals until the end of the follow-up period ; the latter was at least 2 years in all cases (range 24 to 60 months, average 36.4 months).

Assessment

At the end of the follow-up period, all patients were assessed clinically for pain and need for analgesics, and a functional outcome scoring of activities of daily living (ADL) was made according to Chapman *et al* (6). If a patient was able to carry out all ADLs, impairment was rated as “absent”, if he was unable to carry out 2 or 3 activities, this was rated as “slight impairment”, inability to carry out 4 to 7 ADLs was rated as “moderate impairment”, and inability to carry out 8 or more ADLs was rated as “severe impairment”.

Radiological assessment was done to check radiological union and to grade the healing as complete healing, incomplete healing, absence of healing or recurrence after healing, using the modified Neer grading system (table I) (5,23,26).

Statistical analysis

Parametric and nonparametric statistical methods were used to evaluate the results. Data were analysed

Table I. — Modified grading system following Neer *et al* (6)

(1) <i>Complete response</i> : The space occupied by the lesion is completely filled with newly formed bone, with remodeling or integration of the bone substitute.
(2) <i>Partial response</i> : Small radiolucent areas are seen within the boundaries of the previous lesion which otherwise demonstrates complete bone filling and remodeling of the graft substitute with continued radiographic follow-up ; no increase in size of the lucencies is recognized over time.
(3) <i>Local Recurrence</i> : Radiographic lucencies within or adjacent to the prior lesion that enlarge radiologically over time.
(4) <i>No response</i> : No radiographic evidence of bony healing after treatment.

Table II. — Localisation of the benign bone lesions treated

LOCALISATION	N°	%
– Proximal humerus	7	20.4
– Proximal femur	5	14.6
– Distal femur	4	11.6
– Proximal tibia	4	11.6
– Os calcis	3	8.8
– Talus	2	5.8
– Distal tibia	2	5.8
– Proximal tibia and contralateral distal femur	1	2.9
– Femoral diaphysis	1	2.9
– Proximal fibula	1	2.9
– Proximal ulna	1	2.9
– Clavicle	1	2.9
– Metacarpal bone	1	2.9
– Proximal phalange	1	2.9
Total	34	100%

using the SPSS software for Windows, version 8.0. Pearson correlation and one way ANOVA tests were used to define and to compare the relation between the final clinical and radiological results. Statistical significance was set at $p < 0.05$. Results were compared to those reported in literature for other modalities of treatment of common benign bone lesions.

RESULTS

Thirty four cases were analyzed regarding patient characteristics, treatment characteristics, clinical outcomes, radiological outcomes, and any related complications. The average age was 18.8 years with

a range from 4 to 61 years. There were 19 males and 15 females. The localisations of the lesions are shown in table II.

Six patients had received a single intracystic methylprednisolone injection (17.6%) ; in two other patients, this had been combined with intramedullary pinning with K-wires in one, with a titanium elastic nail in the other. The average amount of biphasic ceramic graft used was 19.2 cm³ with a range between 3 to 35 cm³. The average amount of autogenous bone marrow aspirate added to the biphasic ceramic was 25 ml with a range from 15 to 45 ml. In five patients (14.7%), the post-operative pathological diagnosis differed from the presumptive pre-operative diagnosis (table III). The relationship between the nature of the lesion and the amount of biphasic ceramic graft used to fill the defect was found to be of borderline significance using Pearson chi-square test.

Clinical results

All patients were able to carry out all the ADLs investigated (6) without any limitation, except one patient with a large aneurysmal bone cyst (ABC) of the proximal humerus which was treated with a free fibular graft in addition to the composite bone substitute ; she had a preexisting varus deformity which was associated with limitation of internal rotation of the shoulder, resulting in minimal impairment in daily living activity (fig 1).

Two patients were found to have occasional mild pain after sporting activities but did not require analgesics : one of these had a large ABC in the right femoral neck with a calcar defect (fig 2) and the other had osteomyelitis of the distal femoral metaphysis. All wounds healed uneventfully except in three patients ; one had a superficial infection which was cured with local care and 10 days IV antibiotics, another developed a cheloid scar, and the third one had prolonged serous discharge for 3 weeks, which was cured by local care and oral antibiotics (fig 3). One patient had persisting fusiform swelling of the proximal phalanx of the ring finger after treatment of an enchondroma. There were no complications at the bone marrow donor sites. No pathological fractures occurred

Table III. — Preoperative and postoperative diagnosis

		Preoperative diagnosis		Post operative diagnosis	
		No	%	No.	%
1.	Simple bone cyst	13	38.2	14	41.3
2.	Aneurysmal bone cyst	9	26.4	7	20.6
3.	Osteomyelitis	5	14.8	4	11.8
4.	Enchondroma	2	5.9	2	5.9
5.	Non ossifying fibroma	4	11.8	2	5.9
6.	Fibrous dysplasia	1	2.9	1	2.9
7.	Esinophilic granuloma	—	0	1	2.9
8.	Intraosseous ganglion	—	0	1	2.9
9.	Benign fibrous histiocytoma	—	0	1	2.9
10.	Giant cell reparative granuloma	—	0	1	2.9
Total		34	100	34	100



Fig. 2. — 13-year-old male patient with aneurysmal bone cyst of the right proximal femur with calcar defect. A. Pre-operative AP radiograph of the pelvis showing the lesion in the proximal femur ; B. Plain radiograph of the pelvis at follow-up showing the lesion packed with composite graft.

during the follow-up period. Clinical limb-length discrepancy was noted in 3 cases with upper limb lesions (mean 1.8 cm, range : 1 to 2.5 cm) and 2 cases with lower limb lesions (mean 2 cm, range : 1 to 3 cm). Two of the three upper limb lesions were simple bone cysts and the other was an aneurysmal bone cyst. The two cases with simple bone cyst had previously been treated with methylprednisolone injection plus intramedullary fixation, owing to pathological fractures. The two lower limb lesions resulting in limb-length discrepancy were osteomyelitis in one patient and simple bone cyst of the distal femur in the other one.

Radiological results

All defects resulting from the lesion itself or from surgical curettage and debridement healed with gradual replacement or disappearance of the composite graft during the follow-up period.

In cystic lesions, healing followed a centripetal pattern, in which the peripherally placed composite graft material was resorbed or replaced first and the more centrally placed material was the last to disappear.

The average time to healing was 19.9 weeks with a range between 13 to 28 weeks. The rate of healing



Fig. 3. — 44-year-old female patient with simple bone cyst of the right proximal ulna. A. Preoperative AP view of the elbow and proximal forearm showing the cystic lesion ; B. Post-operative follow-up AP view showing the lesion packed with composite graft.

was directly related to the size of the bone defect after curettage and this was clear when comparing times to healing in relation to the size of the lesion and the amount of composite graft used, which is directly related to the size of the cyst. This relationship was found to be statistically significant using Pearson's correlation (p value of 0.795 for the size of the lesion, and 0.788 for the amount of composite graft).

The expansile lesions were seen to decrease gradually with thickening of the cortex manifest on follow-up radiographs.

The five patients with upper or lower limb length discrepancy were found to have premature closure of the nearby epiphysis, three of them before starting treatment and the other two during the follow-up period.

Using a modified Neer *et al* grading system (5,6,7) for radiological bone healing of cystic bone lesions described originally for simple and aneurysmal bone cyst, it was found that 24 patients (70.6%) demonstrated substantial healing (Neer grade I),

9 patients (26.5%) showed partial healing (Neer grade II), and one patient (2.9%) showed local recurrence (Neer grade III).

ANOVA test showed a significant relationship between the size of the lesion and the amount of bone graft on the one hand and the final radiological outcome in the Neer grading system on the other hand (p value of 0.01 for the size of the lesion, and 0.001 for the amount of composite graft).

No significant correlation was found between patients' age, gender, post-operative diagnosis, location of the lesion and the final radiological outcome, using Pearson chi-square test.

DISCUSSION

Autogenous bone graft remains the gold standard in the treatment of osseous defects associated with benign bone lesions. However because of donor site morbidity, variation in quality, and limited amount of bone available, the possibility to use artificial bone substitutes has been investigated. A standard treatment that would reproducibly achieve healing of cystic bone lesions has not yet been established, although Virchow first recognized bone cysts a century ago (22). All reported methods of treatment have been fraught with significant recurrence rates (9,16,22).

Many benign lesions may result in cavitory structural or non structural bone defects. Non ossifying fibroma is one of the most common benign bone lesions. Unicameral bone cyst represents 3% of all bone lesions in children before skeletal maturity and aneurysmal bone cyst represents 1% of primary bone tumours.

Other pathological conditions such as osteomyelitis, eosinophilic granuloma, fibrous dysplasia, benign fibrous histiocytoma, intra osseous ganglion or lipoma, giant cell reparative granuloma, and enchondroma may require bone grafting (1,16,24).

The success rate of intra-lesional curettage and grafting with allograft, autograft or synthetic bone substitute for treatment of simple bone cyst has ranged from 40 to 88% (2,11,29) with recurrence rates of 12 to 48%. Methylprednisolone injection reportedly gave 40-95% success rate with 10-15% recurrence rate ; 50 to 76% of patients had required

Table IV. — Treatment results from published series for simple bone cyst together with our results

Method of treatment	Follow up period	Neer's Radiological grading								Total No of cases	Author (s)
		D		C		B		A			
		%	No	%	No	%	No	%	No		
Curettage + Composite Graft	12-24 m	—	—	—	—	7.2	1	92.8	13	14	El Adl <i>et al</i>
Curettage + Calcium Sulphate	12-24 m	—	—	—	—	—	—	100	13	13	Mirzayan <i>et al</i> (19)
Curettage + Hydroxyapatite	15-39 m	—	—	13.0	3	8.7	2	78.3	18	23	Inove <i>et al</i> (14)
Curettage + Hydroxyapatite	8.5 y	—	—	47.6	10	28.6	6	23.8	5	21	Mylle <i>et al</i> (21)
Curettage + Demineralized bone matrix	24 m	—	—	—	—	18.2	2	81.8	9	11	Killian <i>et al</i> (17)
Curettage + Cancellous allograft	7-156 m	—	—	36.2	64	9.0	16	54.8	97	177	Spence <i>et al</i> (28)
Curettage + crushed cortical allograft	12-48 m	—	—	25.0	36	6.9	10	68.1	98	144	Spence <i>et al</i> (27)
Curettage + allo-autograft	6 m-12y	—	—	36.4	12	3.0	1	62.6	20	33	Oppenheim & Galleno (24)
Percutaneous Steroid injection	5.6 y	—	—	46.7	7	20.	3	33.3	5	15	Bovill & Skinner (4)
Percutaneous Steroid injection	1-35 y	9.2	13	19.9	21	25.6	36	50.3	71	141	Campanacci <i>et al</i> (5)
Curettage + Zinc Chloride or Phenol Cauterisation	> 24 m	—	—	24.8	33	15.0	20	60.2	80	133	Neer <i>et al</i> (22)
Curettage + Cryosurgery	13-64 m	12	5	—	—	38	16	50	21	42	Schreuder <i>et al</i> (26)
Percutaneous Bone Marrow Injection	9-57 m	16.7	2	—	—	16.7	2	66.6	8	12	Yandow <i>et al</i> (30)
Percutaneous Bone Marrow Injection	12-48	—	—	—	—	—	—	100	10	10	Lokiec <i>et al</i> (18)
Percutaneous Flexible Intramedullary Pinning	25-105 m	—	—	6	2	50.0	16	44	14	32	Reposch <i>et al</i> (25)

repeated injections, and 5-15% of patients reported limb-length discrepancy. Bone marrow injection for simple bone cyst reportedly gave 83-100% success rate (18,20,27,30).

The standard treatment for aneurysmal bone cyst has been for a long time curettage followed by bone grafting, with recurrence rates close to 50% after less than 2 years (1,3,7). During the last decade autogenous bone marrow injection after saucerisation or arterial embolisation has resulted in 100% success rate with 0% recurrence (13,14).

Mirzayan *et al* reported their experience with calcium sulphate as a synthetic bone substitute in the treatment of various benign bone lesions and concluded that medical grade calcium sulphate may be an effective alternative to autogenous bone graft in the treatment of non structural bone defects, with a success rate of 100%, with healing achieved in an average period of 13.4 weeks (range 5 to 24 weeks) (19).

This study showed that the composite graft had a highly successful clinical outcome as 31 patients

had no pain or limitation in their ADLs. There were no significant soft tissue or bony complications, and no secondary infection, nor even exacerbation of infection in cases with osteomyelitis.

The composite ceramic bone substitute used in this study resulted in a high rate of radiological bone healing (97.1%) in an average period of 19.9 weeks, without any pathological fracture during the follow-up period. It was also successful in cases not responding to or recurring after methylprednisolone injection, as 7 out of those 8 cases went on to full radiological healing and the remaining case showed partial healing without recurrence.

All reported complications in this study were minor and unrelated to the composite graft itself. Table IV summarises the reported radiological outcome of cases with simple bone cyst treated with different methods.

CONCLUSION

The biphasic macroporous ceramic soaked with autogenous bone marrow aspirate which was used in this study appears as a safe and effective bone graft substitute in the treatment of benign bone defects resulting from various benign bone lesions. Compared with data reported in literature for other treatment methods, healing of bone defects was achieved with similar or higher success rate, while avoiding any donor site morbidity.

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