Efficacy of cerament in large defects created by giant cell tumor

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Abstract

Background: Giant cell tumors are an aggressive and potentially malignant lesion that is commonly treated by surgery involving bone grafts or synthetic bone void fillers. Although synthetic bone grafts may provide early mechanical support while minimizing the risk of donor-site morbidity and disease transmission, difficult manipulation and less than optimal transformation to bone have limited their use.

Materials and Methods: In a prospective series, 14 patients of giant cell tumour with a mean age of 25 years (20–30 years range) were treated by extended curettage followed by the use of a biphasic (composed of two components 60% weight synthetic calcium sulfate and 40% weight hydroxyapatite powder) and injectable ceramic bone substitute (CERAMENT™ BONE VOID FILLER, BoneSupport, Sweden). The most common location was proximal tibia (n = 6), followed by distal end of femur (n = 5), distal end humerus (n = 2), and distal end of radius (n = 1). Patients were followed clinically and radiologically for 6 months. Serial X-rays were performed thereafter to look for recurrence and bone remodeling of the bone substitute. All lower limb patients were allowed partial weight bearing immediately after surgery. All upper limb patients were allowed the active gentle range of movement exercises after surgery.

Results: Lesion started bone remodeling by 2–3 months. After 6 months, the defects completely demonstrated full resolution. A serous discharge, probably response to cerament, was noted in all patients postoperatively that resolved within 2–3 weeks spontaneously. No lesions required revision surgery during the observation period. No post-operative fracture or infection was recorded.

Conclusions: Extended curettage followed by high-speed cutting bur and cavity lavage with appropriate irrigants primary to the use of biphasic and injectable ceramic bone substitute might offer an alternative to regular bone grafting due to convenient handling properties and rapid bone remodeling.

Key words: Cerament , giant cell tumor, large defects.

Introduction

The World Health Organization has classified giant cell tumor (GCT) as "an aggressive, potentially malignant lesion," which means that its evolution based on its histological features is unpredictable [1]. Statistically, 80% of GCTs have a benign course, with a local rate of recurrence of 20–50%. About 10% undergo malignant transformation at recurrence and 1–4% give pulmonary metastases even in cases of benign histology [2]. Nearly 50% of cases occur in the region of the knee, but other frequent sites are the distal part of the radius, proximal humerus, fibula, and pelvic bones [2]. The treatment of choice in most GCTs is curettage and bone grafting. The use of PMMA cement has advantages in that it is cheap, and immediate weight-bearing is allowed. Furthermore, a local recurrence is easily recognized around the cement both by radiographic and MRI investigations [3, 4, 5]. Extended curettage and application of bone cement are, therefore, the most accepted methods in the treatment of GCT [2]. CERAMENT™|bone void filler is an injectable synthetic bone graft substitute combining two natural materials - hydroxyapatite (HA) and calcium sulfatewith a radiopacity enhancing agent iohexol [6]. Synthetic bone graft substitutes have been gaining popularity as viable alternatives for void and defect filling eliminating the concerns with autograft and allograft. These synthetic bone substitutes have invariably been based on calcium phosphate and/or calcium sulfate (CaS) materials which are osteoconductive and facilitate bone remodeling, although either side effects such as drainage and wound complications, slow remodeling to bone, or negligible bone generation has limited their use [6]. Relatively high cost of cerament has also curtailed its use.

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Materials and Methods

Materials

A biphasic ceramic bone substitute (CERAMENT™

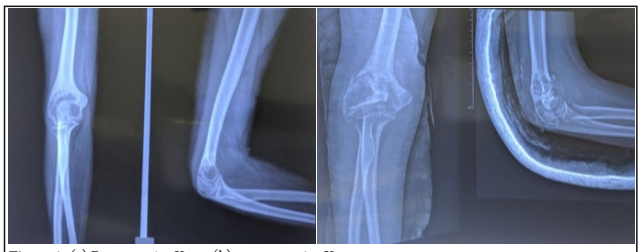

Figure 1: (a) Pre-operative X-ray, (b) post-operative X-ray

bone void filler, Bone Support AB, Lund, Sweden) composed of 60% weight synthetic CaS and 40% weight hydroxyapatite (HA) powder was mixed with a water-soluble radio-contrast agent iohexol (180 mg/ml) to make the material radiopaque.

Patient handling

In a prospective series, 14 patients of giant cell tumour with a mean age of 25 years (20–30 range) and male-to-female ratio of 3:4 (male: 6 and females: 8) were treated by extended curettage followed by the use of a biphasic and injectable ceramic bone substitute (CERAMENT™ bone void filler, BoneSupport, Sweden). The most common location was proximal tibia (n = 6), followed by distal end of femur (n = 5), distal end of humerus (n = 2), and distal end of radius (n = 1) (Table 1). Patients were followed clinically and radiologically for 6 months. Serial X-rays were performed thereafter to look for bone remodeling of the bone substitute. All patients were allowed partial weight bearing immediately after surgery. All procedures were performed under regional anesthesia. Standard approach with good soft tissue coverage was used. A bone window big enough to allow extended curettage was prepared. To enable bone remodeling of the subsequently injected bone substitute, proper contact with cancellous bone was ensured by curettage followed by high-speed bur until bleeding was demonstrated. The cavity was lavaged by normal saline, hydrogen peroxide, and phenol. The bone substitute paste was then prepared by mixing the liquid component containing iohexol with the powder for 30 s. At the time of 4 min from the start of mixing, the paste was sufficiently viscous to withstand dissolution by the rinse fluid and injection was started with a backfill technique starting at the distal part of the void and injected as withdrawn proximally. Bone flap was replaced on hardened cement. X-ray was used in a qualitative way to demonstrate bone bridging of the defects and absence of remaining bone substitute, as an indirect sign of bone remodeling. All patients received standard post-operative treatment with paracetamol 1 g 4 times daily.

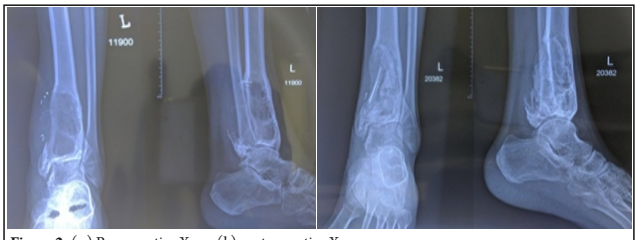

Figure 2: (a) Pre-operative X-ray, (b) post-operative X-ray

Results

Lesion started bone remodeling by 2–3 months. After 6 months, the defects completely demonstrated full resolution. A serous white-colored discharge, probably response to cerament, was noted in all patients postoperatively that resolved within 2–3 weeks spontaneously which did not jeopardized the success of surgery. No lesions required revision surgery during the observation period. No post-operative fracture or infection was recorded.

Discussion

The presented prospective patient series shows a new bone remodeling technique that relies on the properties ascribed to the ceramic bone substitute composite used. The immediate pain relief, partial weight bearing recovery, bone consolidation, and incorporation as well as the structural bone integrity and durability demonstrated in the study indicate that the material can provide a safe and effective long-term solution for the treatment of benign bone tumors. Another observation was that, in spite of incomplete filling, complete or almost complete healing was attained, which indicates that the material or the procedure triggers a bone healing process beyond that

Table 1: ???

Patient No.	Age	Sex	Site of tumor	Resolution of bony defect (months)
1	21	M	Proximal tibia	5
2	25	M	Distal end femur	6
3	24	F	Distal end humerus	6
4	27	F	Proximal tibia	6
5	30	M	Distal end femur	5
6	21	F	Distal end humerus	6
7	24	M	Proximal tibia	5
8	26	F	Proximal tibia	6
9	28	F	Distal end femur	5.5
10	21	F	Distal end radius	6
11	22	M	Distal end femur	5
12	30	F	Proximal tibia	5.5
13	29	M	Distal end femur	6
14	25	F	Proximal tibia	6

facilitated by the material itself. The key to ensure an adequate curettage with complete removal of tumor is obtaining adequate exposure of the lesion. This is achieved by making a large cortical window to access the tumor so as to avoid having to curette under overhanging shelves or ridges of bone. A high power burr to break the bony ridges helps extend the curettage and is recommended. A pulsatile jet lavage system used at the end of the curettage helps to bare raw cancellous bone and physically wash out tumor cells. Adjuvants such as phenol used in a percentage varying from 5% to 80% after completion of curettage may be of additional benefit in helping to decrease recurrence rates after curettage [7]. In vitro studies have also demonstrated the efficacy of using hydrogen peroxide as adjuvant therapy after extended local curettage for benign giant cell tumors of bone [8]. Reconstructing the defect after curettage can be quite challenging. In case the gap left behind after the curettage is small and does not jeopardize the structural integrity of the bone, it can be left alone and the cavities fill up with blood clot which then gets ossified to form bone.. For larger defects, the traditional methods of reconstruction have been cementation or use of bone graft with each method having its advantages and disadvantages [9]. Cementation using methyl methacrylate has shown encouraging results [5]. It is postulated that the exothermic reaction of methyl methacrylate generates local hyperthermia which induces necrosis of any remaining neoplastic tissue, yet it does not extend to the normal tissues to result in local complications [10]. In theory, the possibility that the polymerization of methyl methacrylate may produce a local chemical cytotoxic effect cannot be excluded. Cytotoxic agents such as methotrexate and adriamycin have been incorporated in bone cement and other drug delivery systems in an attempt to reduce recurrence [11, 12]. Even pathological fractures through a giant cell tumor are not a contraindication to treatment by curettage and cementation [13, 14]. Cryosurgery using liquid nitrogen first propagated by Marcove, though used in some centers, is associated with a high incidence of local wound and bone complications [15, 16]. In a study by Nathan et al., two of 24 patients reported local tumor recurrences. All patients underwent intralesional curettage followed by reconstruction with PRODENSE (Wright Medical Technology, Arlington, Tennessee). It is a fully synthetic bone substitute comprising a composite CaS–calcium phosphate (CaSO4/CaPO4) matrix mixed with beta-tricalcium phosphate granules [17]. In a study by Jacek et al., patients with benign bone tumors were treated by minimal invasive intervention with a biphasic and injectable ceramic bone substitute (CERAMENT™ BONE VOID FILLER, BoneSupport, Sweden). No lesions required recurrent surgery during the observation period of 12 months [6]. Further research is needed to warrant any cytotoxic effect of cerament that might prevent the recurrence rate of tumors. In a study by Abramo et al., gap created by osteotomy of distal radius malunion was treated by fragment specific fixation system, TriMed and cerament. With follow-up of 1 year, grip strength increased from 61 of contralateral hand to 85 (58–109)%, $P < 0.001$. DASH scores decreased from 37 to 24 [18]. The combination of cerament produces an easily injectable paste that sets within 15 min and fully hardens after 60 min and shows a wet compressive strength exceeding that of healthy cancellous bone. The CaS component undergoes gradual reabsorption during the 1st month being replaced by in-growing bone that remodels to form trabecular bone, whereas the HA component has a slower [19]. The biphasic ceramic bone substitute is designed to remodel in tune with the natural bone remodeling process. Due to the microporosity of the cured CaS component, an immediate flow of tissue fluids with nutrients and growth factors is allowed so to penetrate the bone. That in turn promotes osteoclasts and macrophages to enter the material and create macropores resulting in a widespread ingrowth of early bone. The end result seems to be full transformation and remodeling into mature bone in 6 months. In a previous study on a composite bone graft substitute similarly consisting of CaS and HA (Schindler et al.), the graft material was still present after 2 years, whereas in the current study, a X-ray confirmed that complete bone remodeling was demonstrated in 6 months in all patients [20]. One explanation for the faster remodeling in the present study might be a more favorable proportion of CaS to HA (CaS/HA = 60–40%) compared to that used in the study by Schindler et al. where the graft material consisted of somewhat inverted proportion of 35–65%. Reasonably fast remodeling has also been described with composite calcium phosphate-based products. It has been reported that products consisting of pure CaS have a tendency to quickly dissolve which, together with a low pH, leads to a high frequency of long-term drainage and subsequent wound complications [6]. Furthermore, products mainly based on calcium phosphate cements have been reported to cause adverse and sometimes painful soft tissue reactions. The product used in the study presents with a neutral pH, and once implanted, a passive precipitation of endogenous HA takes places on the bone surface which seems to extend the gradual resorption of the CaS component over months allowing the cement to resist immediate dissolution and be actively degraded and replaced by ingrowing bone that eventually remodels to form trabeculae. These two product differences (pH and composition) might partly explain: (1) The absence of

prolonged postoperative drainage and/or late wound complications and (2) the rapid and reliable remodeling to bone [6]. Although the actual prospective study presents with favorable results, it must be emphasized that it is a rather small and non-controlled study which requires repeated and larger trials to confirm the findings.

Conclusion

Extended curettage followed by high-speed cutting bur and cavity lavage with appropriate irrigants primary to the use of biphasic and injectable ceramic bone substitute might offer an alternative to regular bone grafting due to convenient handling properties and rapid bone remodeling.

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