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Original Research Article

Outcome of Hydroxyapatite Crystals as Bone graft Subistitute in Benign Lytic Lesions of Bone

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Abstract

Benign lytic lesions of bone are commonly treated by curettage and the resulting cavity filled by autogenous bone graft, the donor site morbidity is high in this method. In this study the resulting cavity had been filled by synthetic hydroxyapatite crystals which are used to overcome donor site morbidity of autogenous bone graft.

To assess the safety and efficiency of the hydroxyapatite crystals as an alternative for autogenous bone graft in the treatment of benign bone tumors and tumor-like lesions.

This is a prospective study included 30 patients (14 males and 16 females) with benign bone tumor who treated by intralesional curettage and the resulting cavity filled by hydroxyapatite crystals. The patient's ages ranged from 4.5 year to 39 year, patients selection according to the inclusion and exclusion criteria. The commonest diagnosis was aneurysmal bone cyst (10) followed by simple bone cyst (6), giant cell tumor (4), fibrous dysplasia (3), enchondroma (2), chondroablastoma(2), nonossifying fibroma (2), and chondromyxoid fibroma(1). Follow up period range from 12 to 24 months both clinically and radiologically according to Irwin's grading system.

Most of the study group had well postoperative recovery. The mean follow up period was 17 months (range 12 -24 months). In most patients operative wound healing proceeded well. For patients with lower limb pathology, the mean time of full weight bearing was 18 weeks (range 12 -22 weeks). Range of movements in near by joints was gradually increased and improved in patients were tumor approximated the joint. According to Irwin's classification, except 3 cases develop complication, all cases were Irwin's stage I incorporation at 6 months follow up. At 12 months follow up 1 case remain Irwin stage I, 14 cases were Irwin stage II and 12 cases were Irwin's stage III plus 3 cases develop complication. There was no rejection of implanted hydroxyapatite crystals and no abnormal hematological or biochemical findings in subsequent follow up.

Hydroxyapatite crystals are slowly absorbed by body. Bone ingrowth and bone formation around the hydroxyapatite crystals were well. Hydroxyapatite crystals have great biological safety, good biocompatibility and good bone conduction.

Key Words: Benign bone tumor, hydroxyapatite crystals, Irwin's grades.

نتيجة بلورات الهايدروكسيا باتتيت كبديل للتطعيم العظمي في علاج الاورام الحميدة للعظم

الخلاصة

الاورام الحميدة التالفة للعظم عادة تعالج بالقشط الجراحي والفراغ الناتج عنها يملأ بتطعيم عظمي يأخذ من المريض نفسه، مضاعفات موضع وهب العظم تكون كثيرة بهذه الطريقة. في هذه الدراسة نستخدم بلورات الهايدروكسي اباتيت المصنعة في ملء الفراغات العظمية بعد رفع الورم وذلك لتجنب المضاعفات الناتجة للمريض من موضع وهب العظم.

لتحديد سلامة وجدوى بلورات الهايدروكسي اباتيت في استعمالها كبديل للتطعيم العظمي الذاتي في علاج الاورام العظمية الحميدة.

شملت الدراسة ثلاثون مريضا" ،(١٤ رجل و١٦) امرأة، يعانون من اورام عظمية حميدة وخضعوا للعلاج الجراحي برفع الورم العظمي وملء الفراغ الناتج ببلورات الهايدروكسي اباتيت. كانت انواع الورم العظمي حسب الاكثر شيوعا هي كيسة عظمية امدمية الشكل (١٠)،كيسة عظمية مفردة الغرفة

(٦)، ورم ناقضات العظم(ورم الخلايا العملاقة) (٤) ،خلل التنسج الليفي (٣)، ورم غضروفي باطن (٢)،ورم اورمي غضروفي(٢)، ورم ليفي لا عظمي المنشأ(٢)، ورم ليفي مخاطي غضروفي (١) .

تراوحت فترة متابعة المريض ما بين ١٢ شهرا الى ٢٤ شهرا عن طريق المتابعة السريرية والاشعاعية حسب نظام تصنيف آروين.

معظم الثلاثون مريضا اجتازوا فترة النقاهة بدون مضاعفات. فترة المتابعة تراوحت من ١٢ الى ٢٤ شهرا. معظم الجروح التئمت بصورة جيدة. متوسط الرجوع الى العمل الطبيعي كان ١٨ اسبوعا (تراوحت من ١٢ الى٢٤). معدل حركات المفاصل القريبة للورم ازدادت تدريجيا وتحسنت خاصة في الحالات التي يكون فيها المرض قريب جدا للمفصل. جميع المرضى اكتسبوا التصنيف الاول (آروين) عند المتابعة في الشهر السادس ماعدا ثلاث حالات (عانوا من مضاعفات) وعند الشهر الثاني عشر احد المرضى كان تصنيف اول ،خمسة عشر (١٥) مريضا اكتسبوا التصنيف الثاني واثنا عشر(١٢) مريضا اكتسب التصنيف الثالث. لم نجد حالة رفض لبلورات الهايدروكسي اباتيت ، لا تأثير سمي ولا قراءات غير طبيعية للتحليلات الدموية والكيميائية في فترة المتابعة.

بلورات الهايدروكسي اباتيت تمتص بصورة بطيئة عن طريق الجسم. نمو العظم وتكوينه حول وخلال البلورات ممتاز. بلورات الهايدروكسي اباتيت تمتلك امان احيائي كبير، ملائمة احيائية جيدة وقدرة تواصل عظمي جيد.

الكلمات المفتاحية: ورم العظم الحميد، بلورات الهايدروكسي اباتيت وتصنيف آروين.

Introduction

The bone is a connective tissue and important organ of body, its vital for living with essential function of support , locomotion, protection, storage and haemopoeisis [1].

Bone defect are wide spectrum of disorder s and these might result of trauma, infection and bone tumor [1,2].

Many of benign lytic tumors of bone are symptomatic and may affect health state of patients regarding pain, swelling, patho-logical fractures and even malignant transformation [1-3].

The WHO classified benign bone tumors according to the types of originating tissues and matrix production [2].

The osteolytic tumor like lesion, are group with non-neoplasic disorders affecting bone with possible developmental, trauma and genetic etiology, and these included simple bone cyst, aneurysmal bone cyst , fibrous dysplasia and non-ossifying fibroma. The treatment of benign tumor and tumor like lesion are usually considered together because of similarity of principles of treatment [2,4-7].

The surgical principles were starting with diagnosis of benign bone lytic lesion and tumor like lesion after clinical and radiological followed up especially after progressive bone growth and development of symptomatology .after confirm of tumor with advance imaging (MRI and CT scan) and histopathological study, surgical treatment discussed with patients and their relatives and the surgery usually included intralesional curettage and defect reconstruction by grafting the defect with cancellous bone graft, and this represented the treatment of choice [5,8,9-12].

Bone graft from iliac crest represented the gold standard of autograft as this type of graft provide osteoinduction and osteo-conduction, in addition there were no immunological challenge of rejection or serious complication of infectious process transfer [13-17].

Allograft (taken bone graft from the another human being (same species) considered a good alternative method to fill large bone defect and this bone might be taken from living donor like head of femur after total hip arthroplasty or non-living donor and storage in bone bank after complicated process of denaturation and sterilization [18-24].

Xenograft (taken bone from another species) such as bovine source after demineralization and processing of organic material usually associated with great risk of immunological incompatability [23,25].

Xenograft(bovine type) firstly was introduced by Maatz and Bauermeister [25] .

Coral granules were harvested and used as bone substitute to treat bone defect in form of coral derived granules (CDG) [26-28].

The chemical formula of hydroxyapatite or hydroxylapetite is Ca5(PO4)3(OH) but

sometime is written as Ca10(PO4)6(OH)2 and this natural compound which can be used as bone substitute to fill bone defect.HA now regarded as a good choice for filling bone defect with desirable volume and not interrupting the physiology of surrounding tissues and eliminate the complication of second operation [29-34].

Many chemical modulation were tried to replace hydroxyl group of hydroxyapatite by fluoride or chloride to produce flouroapetite or chloroapetite [35-36].

Pure hydroxyapatite is white whereas the naturally occurring hydroxyapatite either brown or yellow color [35,37,38].

The bone mineral of human being (modified hydroxyapatite) represented about 7% of weight of human body and the compound of carbonated calcium deficient hydroxyapatite is main mineral of dental enamel and dentin .there was also calcification of Pineal gland or body which known as corpora arsencea or sometime called brain sands and this were composed of hydroxyapatite [36-39].

Hydroxyapatite crystal either found as coral base or formed by chemical techniques derived from synthetic ceramic. The synthetic type of hydroxyapatite crystals usually produced by process of precipitation of calcium nitrate and ammonium phosphate [35,39-41].

The more recent chemical used to promote bone formation in vitro are the bone morphogenic protein which thought to stimulate the pluripotent mesenchymal cells to have osteogenic and chondrogenic activities and this process would observed by increase alkaline phosphatase activity and histological evidence of angiogenesis [42,43].

The osteo-inductive potential for bone morphogenic protein were evaluated by clinical comparable studies with cancellous bone graft and the fusion rate was 80 -99% [42,44,45].

There were different types of BMP, mainly (BMP 2 &7), nowadays they were used with good fusion rate in spinal surgery and non-union of tibia. The cost effectiveness and variable dosage needed make it usage prohibited in most cases.

Platelet rich plasma might be used but still not proved of its clinical effectiveness and still controversy to be use as bone substitute.

The aim of this study was to assess the safety and efficiency of the hydroxyapatite crystals as an alternative for autogenous bone in the treatment of benign bone tumors and tumor-like lesions.

Materials and Methods

A prospective study included 30 patients with benign bone lytic lesion, from June 2013 to September 2014, were treated by intra-lesional curettage and the resulting defect were filled by hydroxyapatite granules. The patients presented for different complains, usually pain was commonest, swelling, deformity and some accidentally diagnosed at outpatient clinic of orthopedic in Al Sader medical city, teaching hospital in the Najaf Al-Ashraf governorate, Iraq.

Proper history was obtained from all the patients, clinical examination, radiological evaluation and the diagnoses were confirmed in some patients by aspiration cytology. The necessary preoperative haematological workups were done for all patients.

The patients with benign bone tumor or tumor like lesions selection according to inclusion and exclusion criteria:

Inclusion criteria:

Benign bone tumors confined to the normal anatomical limits of the bone

Exclusion criteria:

I) Pathological fracture.

II) Active contiguous infection.

III) Suspected or diagnosed malignant lesions.

IV) Recurrent tumor.

From all patients the consent was taken.

The hydroxyapatite granules used in this study were synthetic by Stryker Company, Granule size 2-3 ml and pore size 200 to 300 micrometer.

By using of radiolucent table and image intensification, standard surgical principles and approaches are used to exposed the pathology, in which The surgical sites were approached through the original biopsy tract, the periosteal layer was minimally dissect then cortical window was made which just enough to do good intralesional curettage with minimum disturbance to the tissue ,then through cleaning using 0.9% normal saline fluid. In cases of giant cell tumors and aneurysmal bone cyst was used hydrogen peroxide 3% to destroy the remaining tumor cell. Approximately, the tumor size was estimated intraoperatively by the volume of liquid injected; the volume was ranged from 4cc to 39 cc.

The hydroxyapatite granules were mixed with autologous blood from I V line, prior to application, after thorough drying of the resulting cavity; the bone graft substitute was put and firmly impacted.

After packing the defect, either the periosteam was meticulously re-apposed or in situations where periosteal flap coverage was inadequate, careful soft tissue coverage (mainly muscle) was done to prevent extravasations of the graft.

Plain radiograph were done intraoperative to confirm compact packing (complete packing of the cavity without keeping any voids unpacked. Postoperative immobilization and weight bearing was individualized according to the site and size of the lesion ,in children younger than 10 years and pathology in the femur spica cast immobilization and in the leg bones lesion long leg cast was done and upper limb pathology immobilization by cast, in older patients were instructed to not or partially weight bearing (sometimes by using cast) for 2 to 3 months (especially in lower limb tumor) in order to protect the grafted area and avoid fracture. Weight bearing was gradually increased depending on the size and site of lesion and degree of radiological consolidation.

The patient had follow up clinically and radiological follow up in 2 weeks, 6 months and 12 months and few patients at 18 month and 2 years, except patients with complication had more closer follow up and intervention.

CT or MRI scans were performed 12 months postoperative to rule out recurrence of bone tumors in patients with giant cell tumor, aneurismal bone cyst and chondroblastoma. Radiographic findings were described according to the classification system proposed by Irwin's radiological staging [48]. Table 1.

Table 1: Irwin's radiological staging of bone incorporation

The stage	Radiological appearance
Stage I	obvious margin
Stage II	Hazy margin
Stage III	obvious incorporation

The Results

There were 14 male 46.67% and 16 female 53.33% as shown in figure 1.

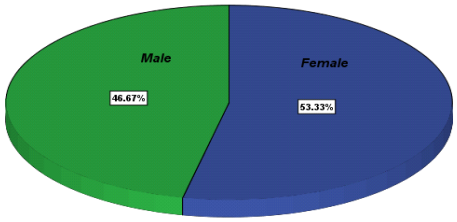

Figure 1 : Gender distribution of studied patients.

The main pathological osteolyticlesion were aneurysmal bone cyst followed by simple bone cyst as shown in table 2.

Table 2: Frequency and distribution of patients according to Diagnosis of patients

Number	Type of Osteolytic bone lesion	Frequency	%
1-	Aneurysmal Bone Cyst	10	33.3
2-	Chondromyxoid Fibroma	1	3.3
3-	Chondroblastoma	2	6.7
4-	enchondroma	2	6.7
5-	Fibrous Dysplasia	3	10.0
6-	Giant cell Tumor	4	13.3
7-	Non-Ossifying fibroma	2	6.7
8-	Simple bone Cyst	6	20.0
	Total	30	100.0

Regarding the location of osteolytic lesion the most commonly bone involved was proximal femur followed by proximal tibia as shown in table 3.

Table 3: Distribution of patients according to site of lesion

Number		Frequency	%
1-	3rd metatarsal	1	3.3
2-	calcanium	1	3.3
3-	Distal femur	3	10.0
4-	Distal radius	1	3.3
5-	hand	1	3.3
6-	Lower tibia	1	3.3
7-	Lower ulna	1	3.3
8-	Proximal femur	11	36.7
9-	Proximal humors	3	10.0
10-	Proximal tibia	5	16.7
11-	tibia	1	3.3
12-	Upper fibula	1	3.3
	Total	30	100.0

Most of the 30 patients had uneventful postoperative recovery .The average follow up period was 18 months (range 12 -24 months). In all patients operative wound healing proceeded uneventfully, except 2 patients. Subsequent follow-up, gradual weight-bearing was encouraged depend on age of patient, sit and size of bone defect and radiological finding.

The mean time of full weight-bearing was 18 weeks (range 12 -22 weeks). Ranges of movements in nearby joints were gradually increased and improved especially in cases where tumor approximated the joint.

The mean time to function well (patient return to full activity without pain or mild pain that may or may not need simple analgesia) was 4.7 months (range 2 -8 months), in which female lower limp lesions average 5.88 months (ranged 2 – 8) and male lower limp lesions average 5.22 months (ranged 3-6).

Table 4: Age, time of follow up and full function time of patients

	Minimum	**Maximum**	**Mean**	**Std. Dev.**
Age/years	4.50	39.00	18.3833	7.84954
Follow up/months	12.00	24.00	16.8000	4.56675
Full function time/ months	2.00	8.00	4.4333	2.09570

Radiological follow up done for the radiolucent zone around the hydroxyapatite crystals tended to decrease with time. Blocks and granule of hydroxyapatite crystals seem to become attached to each other with time. There was no disturbance of growth plate even if the hydroxyapatite crystals were implanted in very close proximity.

All the cases obtained Irwin's stage I incorporation at 6 months follow up, except 3 cases (developed complications). At 12 months follow up 1 case remain Irwin stage I, 14 cases were Irwin stage II and 12 cases were stage III, the remaining 3 cases developed complication (table3). The time of incorporation depend on size and age of patient. Although the young age patients show better incorporation than older patient still there was no clinical significance P value 0.155. (Table-5).

Table 5: Association between Irwings stage and age

		Age/years		**Total**	**P value**
		<=15	**>15**		
Irwins stage at 12 months	Major complication	2	1	3	0.155
		66.7%	33.3%	100.0%	
	I	0	1	1	
		0.0%	100.0%	100.0%	
	II	3	11	14	
		21.4%	78.6%	100.0%	
	III	7	5	12	
		58.3%	41.7%	100.0%	
Total		12	18	30	
		40.0%	60.0%	100.0%	

There was no rejection of implanted hydroxyapatite crystals and no abnormal hematological or biochemical finding in subsequent in short term follow –up. Hydroxyapatite crystals resorbtion and biodegradation was very slow process. In two years follow up (in 6 patients) very little hydroxyapatite crystals were resorbed.

There were 6 patients developed complications 2 patients had recurrence and treated by surgical excision and 2 patients had superficial infection as shown in table 6.

Table 6: Frequency and percentage of complications

Types of complications	Frequency	%
Superficial infection	2	6.7
Recurrence	1	3.3
Deep infection	1	3.3
Fracture at 3 months	1	3.3
Extravasation of granules	1	3.3
Nil	24	80.0
Total	30	100.0

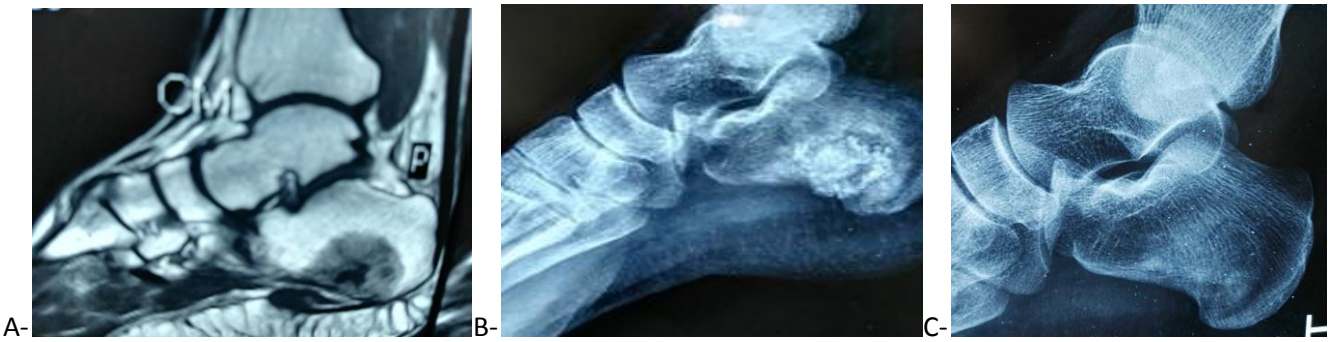

Figure 3: A-MRI of ABC of Calcaneum, B-X-ray Bone substitute 7 day postoperative C-X ray 18 months after surgery

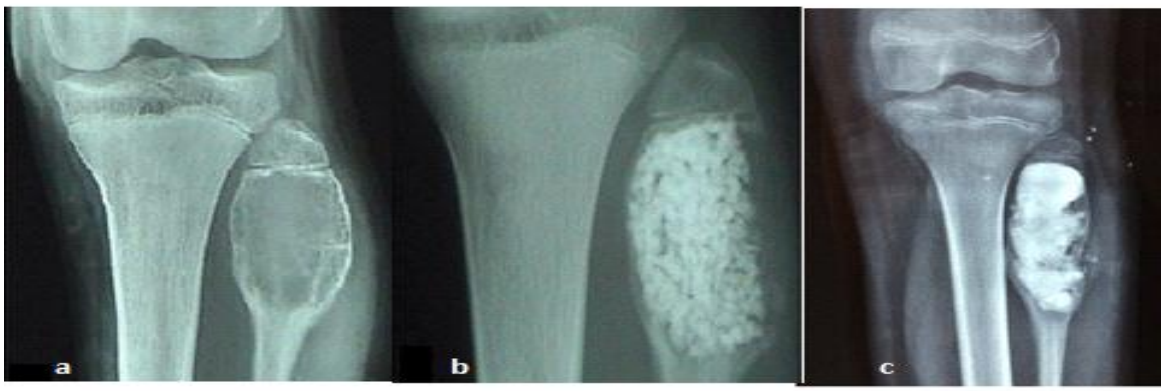

Figure 3 : Upper fibular aneurysmal bone cyst for 14 years patient (A), (B),7 days after intralesional curettage and hydroxyl apatite filling the defect.(C),12 months after surgery.

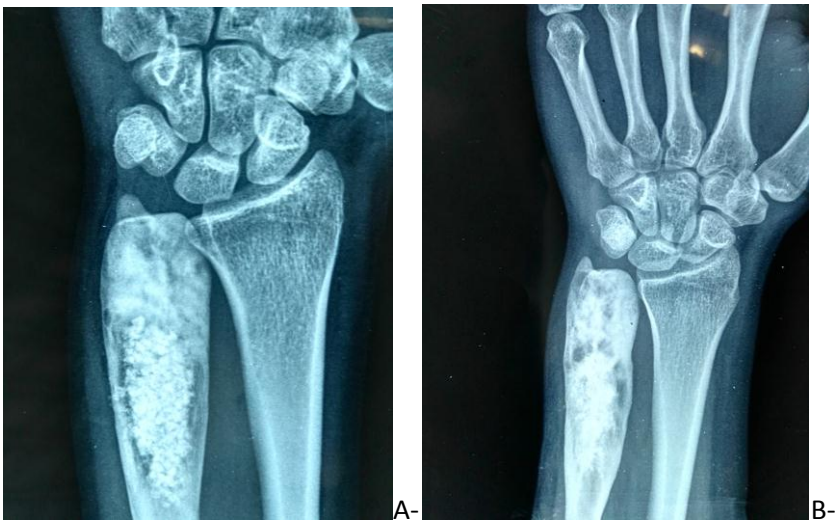

Figure 5 : A- X ray 14 days B-1 year postoperative of bone substitute in chondromyxoid fibroma

Discussion

Benign osteolytic bone lesions (tumor and tumor-like lesions) are wide range of disorders that may affect quality of life, functional state and challenge of surgical treatment including filling the bone defect [2,4].

The development of surgical treatment of benign lytic lesion of the bone in the recent years, were focusing on filling the bone defect efficiently with bone substitute that has no need for second operation in case of autograft taking the consideration of morbidity and also avoiding immunogenic incompatibility and risk of transmission of serious infections in case of allograft and xenograft [37,39,42].

In this study, the time taken to return patient to preoperative level of activity (taken the consideration of size of tumor, age of patient and associated surgical procedures in addition to filling the defect) was 4.2 months (patients < 15 years) and an average of 4.9 months (patients >15 years) and this results were disagreed with Irwi et al [48] as the average time of return to preoperative level was 7.6 weeks. Also Morett et al [49] who took young athletic patients was showed 3.3 months for return to preoperative level and the earlier return may be related to kind of patients who were young athletics.

The radiological evaluation of bone substitute and bone ingrowth incorporation reviewed by radiologist showed abundant bone formation around hydroxyapatite crystals at 12 months and these results were agreed with study done by Ranjan [37] in which showed abundant bone formation and bone growth with incorporation at 13 months. Saikia et al [39], were concluded that the calcium phosphate ceramic substitute remained not remodeled after long period of followed up.

In our study we observed that the clinical recovery was before the radiological recovery and this agreed with study done by Saikia [39].

Regarding the concept of complications , we had 2 (6.7%) minor complications (superficial wound infection) which treated by antibiotics for three weeks and 4 (13.4%) major complications including deep infection, recurrence and pathological fracture and these were treated accordingly. Irwin's study, they had 3 (12.5) major complications with no reported cases of recurrence and this may be due to fact that all their cases was small lesion with exclusion of large osteolytic lesion.

The extravasation was reported in two cases in the study done by Siakia and also in the Irwin et al [48], and these results were less than our result where we had only

one case of extravasation of granules and this may be related to techniques of application of bone substitute but we agreed with most of the studies that extravasation had no eventful symptoms.

Yamamoto et al [50], were reported bone ingrowth incorporation in most porous structures after histopathological studies ,however the histological examination is not obtained in our study as all of our patients refused consent .

Conclusion

1-Hydroxyapetite crystals achieved good bone conduction even with large defect with great biological safety and compatibility.

2-Hydroxyapetite crystal eliminates the side effect of donor site which add more morbidity by second operation.

3-Hydroxyapetite crystal absorbed slowly after filling the bone defect with good bone ingrowth around HA crystals.

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