Original Article

Concentrated Bone Marrow Aspirate-Coated Hydroxyapatite for Reconstruction of Small-to-Moderate-Sized Mandibular Defects Caused by the Removal of Benign Pathologies

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Abstract

Purpose: The aim of this study was to evaluate the bone regeneration potential of concentrated bone marrow aspirate (BMA)-coated hydroxyapatite (HA) for reconstruction of mandibular defects caused by the removal of benign pathologies. **Patients and Methods:** This prospective clinical study included ten patients with histopathologically proven benign pathologies of the mandible measuring <5 cm anteroposteriorly, who were treated with enucleation or marginal resection, followed by autologous concentrated BMA-coated synthetic biphasic HA (HA and beta-tricalcium phosphate) graft placement. Clinical and radiological evaluations of grafted sites of the mandible were done at 1 week, 1, 3, and 6 months postoperatively using Irwin's radiologic staging and grayscale histogram. **Results:** All patients (10/10, 100%) had proper incorporation of the graft with the normal adjacent bone. Grayscale histogram revealed the initial stages of graft resorption, followed by formation of new bone-grafted sites. No complications such as infection and total graft loss were encountered except for one patient who had partial wound dehiscence that responded well to local wound care and resuturing. **Conclusion:** Concentrated BMA-coated synthetic HA effectively promotes bone regeneration in small-to-moderate-sized defects of the mandible.

Keywords: *Bone graft substitute, bone marrow aspirate, bone marrow stem cells, bone regeneration, calcium phosphate ceramic, hydroxyapatite, mandible, mesenchymal stem cells, osteoprogenitors, tissue engineering*

Introduction

A plethora of pathologies occur in the mandible that is treated by ablative surgical procedures resulting in functional and cosmetic morbidity to the patients. A myriad of options exist to reconstruct such bony defects ranging from autogenous bone grafts, allografts/xenografts, to the recently evolving tissue-engineering approaches based on the cellular therapy. The use of autogenous bone grafts is a time-tested and "golden standard" approach that has osteogenic, osteoinductive, and osteoconductive properties.[1] However, the drawbacks of this approach are donor-site morbidity, increased operating, recuperating time, and financial burden on the patients. Reported problems with allogeneic, xenogeneic, and synthetic bone grafts are risk of disease transmission, incompatibility reactions, and chronic granulomatous inflammation.[2]

In view of these problems, there has been an increasing interest on the use of cell-based tissue engineering therapies to promote bone regeneration in the recent years. The application of the whole or unfractionated bone marrow aspirate (BMA) that contains mesenchymal stromal cells (MSCs) to enhance and expedite bone healing had been used extensively in orthopedics with successful results.[3]

These MSCs have a great potential to divide into osteoblastic, chondroblastic, cells of muscle, and nerve lineages. Since the number of these MSCs is very low in adult marrow, centrifugal concentration of BMA or *in vitro* culture and expansion had been practiced to achieve higher cell counts for efficient bone regenerative applications.[4,5] BMA concentrate (BMAC) had been used successfully for treating avascular necrosis of femoral head, osteoarthrosis of the knee, nonunions/malunions of the tibia, the shaft of humerus, femur, etc.[6]

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Many previous preclinical and clinical studies have demonstrated and proven the importance of number, and the concentration of osteoprogenitors present in the BMA has a direct effect on the repair and regeneration of bone.[7] BMAC had been used in combination with various types of biological scaffolds such as hydroxyapatite (HA), polylactic acid, and collagen for regeneration of the bone, cartilage, and tendons with good results.[8]

The use of BMAC with biological scaffolds for bone regeneration in the maxillofacial region had been limited compared to their uses in orthopedics for long-bone defects. BMAC had been used to reconstruct resorbed alveolar ridges before the placement of dental implants, maxillary sinus lifts, nonunion of fracture of the atrophic mandible, etc.[9,10] Gali *et al*. have described the use of unfractionated BMA with hydroxyapatite scaffold for reconstruction of maxillomandibular osseous defects.[11] In light of these observations, using BMAC with HA scaffolds for reconstruction of postenucleation/marginal mandibulectomy defects appears very promising. However, published literature on this concept is scarce. Hence, we conducted a study to evaluate the osteogenic potential of synthetic HA and beta-tricalcium phosphate (β-TCP) coated with autogenous concentrated BMA when placed in osseous defects that were created by the removal of benign pathologies of the mandible.

Patients and Methods

Ten adult patients with histopathologically proven benign pathologies of the mandible are measuring not >5 cm anteroposteriorly on preoperative orthopantomogram (OPG) and requiring treatment by enucleation/marginal resection of the mandible be included in the study. Patients with malignant osteolytic lesions, patients with inadequate overlying mucosa to achieve primary closure, and patients receiving immunosuppressive drugs were excluded from the study. The study proposal was approved by the Institutional Ethics Committee, and written informed consent was obtained from all the participants before the start of the study.

Methodology

Preoperatively, all patients underwent detailed clinical examination, OPG, and incisional biopsy [Figure 1]. Under general anesthesia through nasoendotracheal intubation, patients underwent enucleation/marginal mandibulectomy, followed by reconstruction with autogenous BMAC-coated HA.

Bone marrow aspiration

After standard preparation and draping, autogenous bone marrow aspiration was performed from the posterior superior iliac spine using Jamshidi bone marrow aspiration needle. About 60 ml of bone marrow was aspirated from each patient using three 20 ml syringes [Figure 2]. The aspirate was then mixed with 0.1 mL of heparin anticoagulant and was taken for processing. Hemostasis was achieved by pressure dressing on the donor area.

Preparation of bone marrow aspirate concentrate

Processing and concentration of BMA were done simultaneously during the primary mandibular surgery by a research scientist/biotechnologist within the operating room itself, thereby reducing the duration of anesthesia and surgery. The aspirated blood with anticoagulant was placed in centrifugation tubes which were 5–6 in number each tube containing about 10 ml of BMA, then the Histopaque solution was added to these tubes. Centrifugation process was done for 20 min by increasing slowly till 2000 rpm, then gradually decreased. After centrifugation, four layers were formed. The second layer (buffy coat layer), which contains the maximum number of MSCs, was then separated from all the centrifuge tubes and collected in a single centrifuge tube [Figure 3].

Surgery for primary mandibular pathology

After harvesting the BMA, the patient was shifted to a supine position and removal of the benign mandibular pathology was done either by enucleation/marginal mandibulectomy depending on the extent/histopathological type of lesion. The resultant bony defect was reconstructed using synthetic HA-coated with BMAC [Figure 4a].

Graft placement in mandibular defects

G-Bone (Surgiwear, India) Synthetic HA blocks (synthetic multiphasic calcium HA in low crystalline form, tricalcium phosphate, and other forms of calcium such as calcium carbonate and bicalcium phosphate) were crushed into small crystals and were soaked in BMAC [Figure 4b].

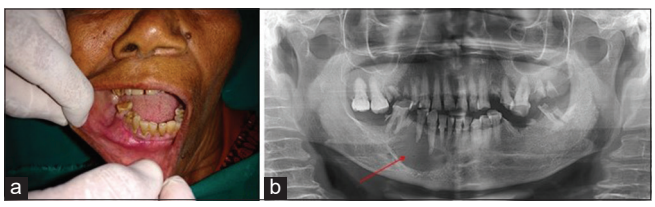

Figure 1: (a) Preoperative clinical picture showing expansile bony swelling obliterating the buccal vestibule on the right side of the mandible. (b) Preoperative orthopantomogram showing unilocular radiolucent lesion in relation to periapical region of rootstump - 45, grossly attrited 44 in the right parasymphysis region of the mandible

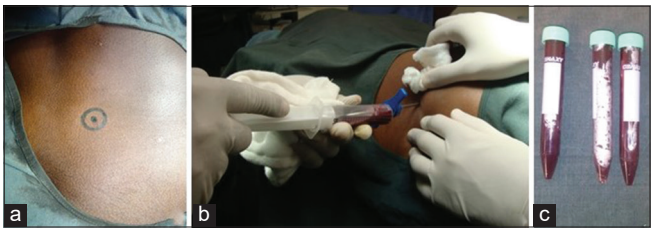

Figure 2: (a) Skin marking at the posterior superior iliac spine for bone marrow aspiration. (b) Aspiration of iliac bone marrow using Jamshidi needle. (c) Bone marrow collected in the Falcon conical tubes for centrifugation

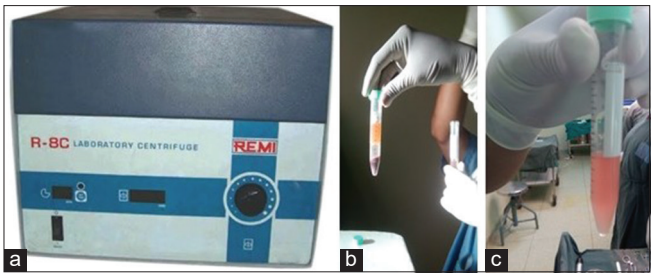

Figure 3: (a) Centrifuge used for intraoperative concentration of autologous bone marrow. (b) Centrifuged bone marrow aspirate showing the buffy coat layer rich in progenitor cells that needs to be extracted. (c) Bone marrow aspirate concentrate obtained after collecting the buffy coat layer from all centrifugation tubes

This mixture with semisolid consistency was placed in the mandibular osseous defect. The watertight closure was done with 3–0 vicryl [Figure 4c and d]. Patients were kept on nothing by mouth for 6-h postsurgery, followed by clear oral fluids and soft solid diet. Patients were monitored for vital signs, intake and output, vomiting, bleeding, or respiratory distress; appropriate antibiotics and anti-inflammatory drugs were given by parenteral route. Patients were asked to start soft and semisolid diet, the very next day and to maintain oral hygiene. Intraoral sites were irrigated with 0.2% chlorhexidine solution. Donor site pressure dressing was removed on the 2nd postoperative day. Postoperative instructions were given and all the patients were discharged on the 2nd postoperative day.

Postoperative follow-up and evaluation

All the ten patients were evaluated for a minimum period of 6-month postoperatively at intervals of 1 week, 1, 3, and 6 months. During the postoperative follow-up, clinical and radiological evaluations were done at the site of mandibular reconstruction. Clinical parameters included assessment of healing of the overlying mucosa at grafted site, and postoperative complications such as wound dehiscence over recipient site, leaching of graft, pain, and infection at recipient sites.

All the preoperative and postoperative radiographs were taken with equal exposure and magnification using PLANMECA DIAMAXIS PRO 4.4 digital software (Asentajankatu 6 FIN-00880 Helsinki, Finland). Irwin's radiological staging was done to assess incorporation of the graft on sequential postoperative radiographs taken at 1-, 3-, and 6- month intervals. Radiological assessment of preoperative and postoperative digital orthopantomographs using grayscale histogram was done [Figure 5]. Digital panoramic radiograph was processed with the Adobe Photoshop Elements 7.0 by selecting osseous defect area. As a measure of control, the radiodensity of tooth on the uninvloved side of mandible was used. The control region (tooth) and the regions of interest (cyst cavities) were defined through a gray scale of 255 tonalities using gray-level histograms. The control regions from radiographs taken at different times were matched, and the mean

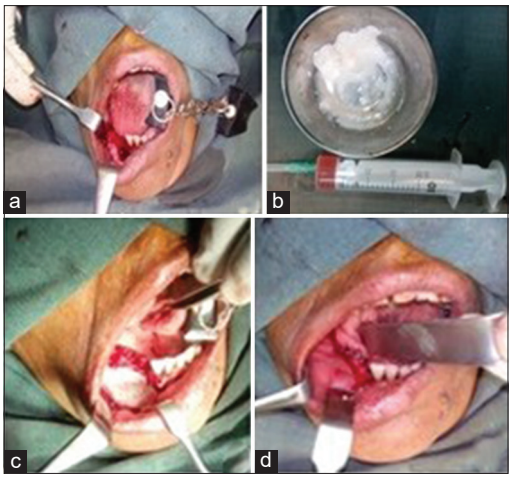

Figure 4: (a) Postenucleation mandibular defect after removal of the radicular cyst. (b) Bone marrow aspirate concentrate with saline-soaked and -crushed synthetic hydroxyapatite blocks, ready to be mixed. (c) Grafting the mandibular defect with bone marrow aspirate concentrate-coated synthetic hydroxyapatite. (d) Water-tight closure of mandibular defect

gray-level values of the regions of interests were calculated and then compared with each other; the mean and average values of density in histogram were noted preoperatively and at every follow-up intervals of 1, 3, and 6 months.

Statistical analysis

Data were tabulated in Microsoft Excel Spreadsheet 2016 and were analyzed with the help of GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego, California, USA. Data were presented as mean ± standard deviation actual numbers. One-way repeated-measures ANOVA followed by "*post-hoc* Tukey's" test was used for group-wise comparisons. $P<0.05$ was considered as statistically significant.

Sample size was calculated assuming a standard deviation of measurements on grayscale histogram with 80% power and two-sided alpha error of 0.05. A total of nine patients were sufficient to detect 20 points on the histogram.[11]

Results

Clinical assessment

Grafted site

All the ten patients had good healing of overlying mucosa at 6-month follow-up. Only one patient (seventh case) had minor area of wound dehiscence and partial leaching of graft on the 7th postoperative day, and it responded well to local wound care, short course of antibiotic therapy for 5 days, and resuturing the wound. No other major complications were encountered [Table 1].

Donor site

No donor-site complications such as swelling, hematoma formation, and infection were encountered.

Table 1: Patient characteristics

Age/sex	Diagnosis	Mandibular site of involvement	Size of detfect (cm)	Radiological appearance of lesion	Treatment done	Clinical outcome	Irwin's radiological staging
16/male	Odontome	Right posterior region - 48	3×3	Sclerotic	Excision + BMAC + HA	Good	Stage III
43/female	Periapical cyst	Left posterior region - 37, 38	2×2	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
15/male	Dentigerous cyst	Right posterior region - 44	3×2	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
70/female	Periapical cyst	Right premolar-molar region 43, 44, 45, 46	4×2	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
30/female	Periapical cyst	Left posterior region - 37	2×1	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
25/female	Odontogenic keratocyst (orthokeratinized)	Right posterior region - 47, 48	2×1	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
43/female	Periapical cyst	Left posterior region - 36	3×1	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
25/male	Odontogenic keratocyst (orthokeratinized)	Left posterior region - 44, 45	3×2	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
32/male	Dentigerous cyst	Right posterior region - 48	3×1	Osteolytic	Enucleation + BMAC + HA	Good	Stage III
38/male	Dentigerous cyst	Left posterior region - 38	4×2	Osteolytic	Enucleation + BMAC + HA	Good	Stage III

BMAC: Bone marrow aspirate concentrate; HA: Hydroxyapatite

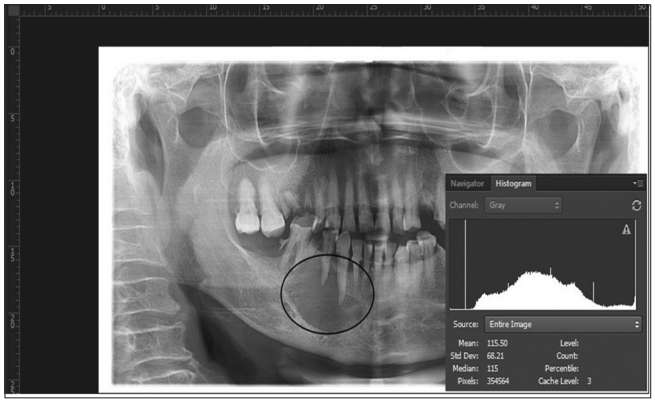

Figure 5: Assessment of bone density at the mandibular defect using grayscale histogram processed using Adobe Photoshop 7.0 Elements on a digitized orthopantomogram

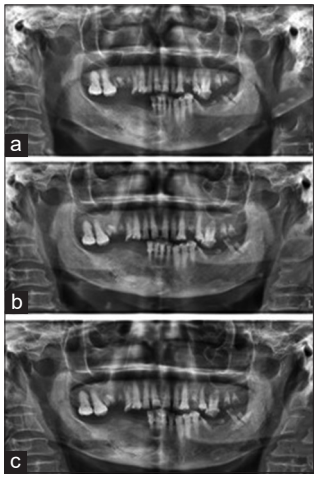

Figure 6: (a) Immediate postoperative radiograph radioopacity at grafted mandibular defect. (b) 3 months postoperative radiograph showing mild decrease in radiodensity due to graft resorption. (c) 6 months postoperative radiograph showing unremarkable and near-normal bone density comparable to that of adjacent healthy bone, suggestive new bone formation

Radiological assessment

Sequential changes of bone density at the grafted site were measured using grayscale-level histogram which was processed in Adobe Photoshop 7.0 elements (345 Park Avenue San Jose, CA 95110-2704, USA) [Figure 6].

Initial mean values were lower in preoperative period owing to the osteolytic lesions presenting as radiolucencies in the mandible, (except in patient number 1, who had compound odontoma presenting as radio-opaque mass). Immediate- and 1-month postoperative histograms showed increased values because of the radio-opaque nature of the HA graft. In 3rdmonth postoperative period, decreased mean gray-level values were observed indicating graft resorption. This was followed by an increased 6-month postoperative mean value suggestive of increased new bone formation when compared to 3rd-month postoperative histogram values in mandibular osseous defects [Tables 2 and 3].

Discussion

Ablative procedures of mandible performed for removal of pathologies result in osseous defects that cause functional and cosmetic problems leading to poor quality of life of the patients.

Table 2: Demographic and grayscale histogram (pixel intensity) findings of patients

Parameters	Female patients (*n*=5)	Male patients (*n*=5)	All patients (*n*=10)
Age (years)	42.20±17.46	25.20±9.98	33.70±16.12
Greyscale histograms			
Preoperative (a)	75.92±10.46	92.42±19.84	84.17±17.30 (a)
1 week after grafting	111.18±5.48	123.61±12.78	117.40±11.35 (b)
1 month after grafting	111.18±5.48	123.61±12.78	117.40±11.35 (c)
3 months after grafting	101.84±5.63	115.36±9.93	108.60±10.43 (d)
6 months after grafting	115.25±4.85	122.88±5.92	119.07±6.49 (e)

$P<0.05$ is between groups a versus b, a versus c, a versus d

Table 3: Multiple comparisons between pre and postoperative sequential histograms

Tukeys multiple comparisons test	Significant or not
Baseline versus 1 week after grafting	Yes
Preoperative versus 1 month after grafting	Yes
Preoperative versus 3 months after grafting	Yes
Preoperative versus 6 months after grafting	Yes
1-week postoperative versus 1-month postoperative	No
1-week postoperative versus 3-month postoperative	Yes
1-week postoperative versus 6-month postoperative	No
1-month postoperative versus 3-month postoperative	Yes
1-month postoperative versus 6-month postoperative	No
3-month postoperative versus 6-month postoperative	Yes

Spontaneous bone regeneration of postenucleation defects of mandible had been reported, but the natural healing process can take up to a year for 43% of osseous filling to occur with a 48% increase in bone density.[12] Various treatment strategies have been tried and tested to expedite and enhance the bone regenerative capacity such as autogenous bone grafts, vascularized flaps, osteoconductive bone scaffolds of allogenic or xenogenic origin, tissue engineering, and cell-based regenerative therapies. The success of autogenous bone grafts is attributed to the three critical elements: (a) certain proteins and growth signaling factors present in cancellous portion that cause osteoinduction, (b) cells present in the marrow that perform osteogenesis, and (c) the cortical portion that acts as a scaffold leading to osteoconduction.

Despite these advantages, the demerits of autografts are the need for another donor site and its added morbidity, the need for specialized equipment, training, increased operating, recuperating time, and cost factor. This has led to a search for better alternative to autografts. The use of allografts/alloplastic scaffolds only provides osteoconduction. In this context, tissue engineering approaches based on the cellular therapy had been widely tested and used in routine clinical practice. Bone marrow is a rich source of osteoprogenitor cells and growth factors that have a great regenerative potential.[13] A very low concentration of osteoprogenitor cells are present in adult marrow to the proportion of 0.005% of total nucleated cells. Other factors such as technique of aspiration, site, and volume also affect the number of MSCs extracted in aspirate.[14] Connolly *et al*. had demonstrated that achieving higher numbers of MSCs by concentrating the marrow enhances the regenerative potential of bone.[7]

Marcus Jager had reported a comparative study on the use of unfractionated (BMA) versus BMAC along with collagen and HA scaffolds, respectively, in promoting healing of critical-sized defects of long bones.[15] This study demonstrated that BMAC, when used with HA, is superior to BMA with collagen sponge in long-bone defects. Flow cytometry studies showed earlier and larger colony-forming units fibroblasts with BMAC than BMA.

Based on these observations, our study was also included the use of BMAC with synthetic HA scaffolds for reconstruction of small-to-moderate mandibular defects. Our clinical and radiological results are similar to this study as there was clinical and radiological evidence of bone regeneration and healing by 6-month postoperatively.

In maxillofacial surgery, the use of BMAC with osteoconductive scaffolds had been reported in maxillary sinus floor augmentation, nonunion of atrophic mandibular fracture.[9,10]

However, reconstruction of mandibular defects, postablative or posttemporomandibular joint ankylosis release, had been reported with unfractionated marrow/BMA with HA scaffolds.[11,16]

The use of BMAC with HA scaffolds for reconstruction of postenucleation mandibular defects had not been reported to the best of our knowledge. The advantages of this approach as evidenced by this study are as follows: (a) intraoperative enrichment of BMA is achievable by concentrating it using a benchtop centrifuge within the operating room itself, thereby producing a high MSC cellular yield that has a direct effect on bone regeneration, (b) in contrast to the FICOLL method, which requires *in vitro* culture and expansion of MSCs, the BMAC approach does not require extensive and expensive laboratory equipment as per the GMP standards, approvals of stem cell regulatory bodies, (c) reduced chances of infection, and (d) the use of synthetic biphasic HA scaffold (low crystalline HA and β-TCP) renders it the balance of rigidity and resorbability, gradually to be replaced by the new bone.

This approach provides all the three critical elements required for bone regeneration – BMAC-containing growth factors and other proteins promoting osteoinduction, osteoprogenitors leading to osteogenesis, and HA scaffold-promoting osteoconduction.

Limitations of this study are the smaller sample size and absence of histopathological confirmation of resorption and replacement of HA scaffolds by new bone formation.

Conclusion

Concentrated BMA-coated synthetic HA effectively promotes bone regeneration in small-to–moderate-sized defects of the mandible. The advantages of this approach are (a) no additional donor-site morbidity such as the conventional bone graft harvest approach, (b) concentrating the bone marrow permits enrichment with increase in the available MSCs that accelerate osteogenesis at the grafted site, and (c) this procedure can be done at the point of care, that is, within the operating room itself in a sterile environment, simultaneously during the removal of primary mandibular pathology, thereby reducing operating time, cost, and chances of contamination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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