Reconstruction of Craniofacial Bone Defects with Autologous Human Bone Marrow Stem Cells and Autogenous Bone Grafts: A Case Report with Review of Literature

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ABSTRACT

Reconstruction of craniofacial bony defects has always been a challenging task for the surgeons over the years. The science of reconstructing such defects is of utmost importance to craniofacial and plastic surgeons due to its relevance in facial aesthetics function as well as prerequisite procedure for continuing other surgical procedures. The main goal of the reconstruction of the craniofacial defects is to reduce the morbidity by restoring the facial form and aesthetics, as well as a good function of the facial structures by achieving a reasonable occlusion and articulation. Although significant improvements have occurred during the last few decades, challenges still exist as to what type of reconstruction to be carried out with regard to techniques and the type and quality of materials of choice to be used. As decades progressed, the advancement in surgical techniques and the variety of reconstruction methods have definitely improved the quality of life. This article reviews the method of bony reconstruction of craniofacial defects using autologous human bone marrow stem cells and autologous bone grafts and its modification, which includes much recent tissue engineering techniques and regenerative medicine, thereby replacing older techniques by biological substitutes, which can restore improve and maintain orofacial function and aesthetics.

KEYWORDS: Autologous bone grafts, bone regeneration, human bone marrow stem cells, reconstruction of craniofacial defects

INTRODUCTION

Stem cells are unique cells with remarkable potential to develop and differentiate into different types of cells. Growing popularity of stem cells has resulted it to be a strategic tool in regenerative medicine for the regeneration of damaged tissues. The reconstruction of large craniofacial bony defects remains a major surgical challenge due to the complex nature of the structures and the difficulty in reconstruction. The gold standard today for craniofacial bony defects...
caused by trauma, cancer resections, infections, burns, and other benign pathologies is vascularized autologous bone grafts (VABGs). Although the use of VABGs in general has good outcome in terms of osteogenesis, osteoinduction, osteoconduction, and osseointegration at the recipient site, the drawbacks of this approach are donor site morbidity, increased operating time, increased recuperating time, failure of flap due to vascular compromise, and financial burden to the patient.[1-3] Other myriad of options for bony reconstruction include

1. Free bone grafts
2. Particulate cancellous bone marrow grafts (PCBMs)
3. Pedicled composite grafts
4. Synthetic bone grafts
5. Allogenic/xenogenic bone grafts
6. Distraction Osteogenesis and
7. Guided bone regeneration, each one having its own advantages and disadvantages.[1]

The drawback with autologous free bone grafts is poor osseointegration and excessive resorption especially when the defect is large. Survival of the graft largely depends on the revascularization from the recipient site. Reported complications with allogenic/xenogenic and synthetic bone grafts are as follows:

1. Increased risk of disease transmitting diseases by the use of these materials
2. Incompatibility reactions, and
3. Chronic granulomatous conditions as a result of inflammation

PCBM grafts are not used in patients with malignant tumors due to lack of vascularity and scar fibrosis as a result of the secondary effects of the surgery or radiation, which can affect the uptake of the graft.[4]

The newer concepts in bone reconstruction of the craniofacial region include mainly the use of autologous human bone marrow stem cells and autologous bone grafts and its modifications. The newer techniques and modifications incorporated use the concepts of tissue engineering and regenerative medicine, which includes

1. Stem cell therapy
2. Protein therapy
3. Gene therapy/molecular therapy[1,5]

Stem cells can be obtained from bone marrow, adipose tissue, and even dental pulp. The sources of autologous bone grafts are various, but predominantly anterior and posterior iliac crest grafts are used commonly in surgical practice.

**Case Report**

An 18-year-old female patient reported to Department of Oral and Maxillofacial Surgery, Sree Anjaneya Institute of Dental Sciences with the chief complaint of pain and paraesthesia on the left side of the jaw, which was noticed since 1 month. It was initially mild in intensity, which gradually increased to the present state and radiating along the distribution of inferior alveolar nerve. There was no relevant medical history and the patient was moderately built, well nourished, and no signs of pallor, icterus, cyanosis, and clubbing. On clinical examination, there was missing 37 and partly erupted 38. A panoramic radiograph was taken, which shows impacted 37 and 38 [Figure 1]. Both 37 and 38 were surgically removed and iliac crest grafting was performed from anterior iliac crest on left side; grafting was done using both cortical bone and the cancellous bone from the marrow, following which surgical closure was performed using Vicryl 3-0 sutures. Satisfactory

![Figure 1: Preoperative orthopantomogram showing impacted 37 and 38](image-url)
healing of extracted socket was noticed after 1 week. A panoramic radiograph was taken after 2 months and satisfactory bone formation was noticed [Figure 2].

**DISCUSSION**

**Bone regeneration**

Bone regeneration is associated with the following properties:

*Osteogenesis:* it is the process of formation of new bone from osteoblast originating from the donor bone graft.

*Osteoinduction:* It is the differentiation of osteoprogenitor when stimulated to differentiate into osteoblasts usually under the influence of bone morphogenetic protein (BMP) released from the donor marrow cells.

*Osteoconduction:* It is the process by which graft provides an underlying skeleton for capillaries and precursor bone cells to develop, thus creating a scaffold into which more bone formation occurs. Bone regeneration followed by integration of the bone graft to the recipient site includes the following stages: inflammation, revascularization, osteoinduction, osteoconduction, and finally remodeling. Osseointegration is a concept applied when an implant is used. It is the stable anchorage of the implant achieved by direct bone to implant surface.[2,3]

**Tissue engineering**

Bone engineering techniques consist of three main components: cell, growth factor, and carrier. As osteogenic cells are responsible for the formation of new bone, cells lacking osteogenic potential can result in no new bone formation. The reconstruction of the craniofacial defect will not be achieved with cells lacking osteogenic potential. The proteins with osteoinductive potential known as growth factors are crucial for the reconstruction of large craniofacial bony defects. Growth factors represent a wide variety of molecules that can stimulate mesenchymal cells: its recruitment, proliferation, and differentiation. Bone marrow is rich in growth factors including BMP, platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and fibroblastic growth factor (FGF). BMP is considered the most important among the group, particularly BMP-2, -4, -6, and -7. Bone grafts possessing such molecules are characterized as osteoinductive.[1,3,5]

**Scaffolds**

The application of cultured cells or growth factors without any scaffold cannot produce a good outcome. Choosing the right scaffold is to recreate a three-dimensional mechanical structure that hosts and supports cells and extracellular matrix and growth factors as well as for delivery of cells by acting as mesh for new bone formation is a significant step in bone regeneration.[1,3-7] Scaffolds are important for the application of cultured cells and growth factors. The outcome of bone formation without a scaffold will be inadequate even if the defects are small. For larger defects, choosing a right scaffold with three-dimensional mechanical structure that can host and support cells as well as extracellular matrix and growth factors by acting as a mesh for bone regeneration is a crucial and significant step for the new bone formation. Scaffolds with pores of diameter between 200 and 400 nm are required so that osteoblasts are thought to perform better migration, adhesion, and proliferation.[3]

![Figure 2: Postoperative orthopantomogram showing substantial bone formation in impacted site](image)
Cancellous bone grafts, which do contain osteoblasts, osteocytes, and mesenchymal cells, stimulate osteogenesis. Stability is mainly provided by cortical grafts that are significantly deficient in osteogenic ability. A combination of cortical and cancellous grafts can ensure stability and osteogenesis.[3,8]

Autologous bone marrow stem cells in combination with autologous bone grafts in the reconstruction of craniofacial defects are a novel regenerative technique. Reducing the need of harvesting the bone from the donor site and thereby reducing morbidity and complications promises a better outcome for the patients. Bone marrow from anterior and posterior iliac crest aspirations is a common source of harvesting mesenchymal stem cells, other progenitor cells, and associated cytokines/growth factors. Other sources of stem cells include adipose tissues and dental pulp.[8,9]

But there are major concerns about the application of bone marrow stem cells in the reconstruction of bony defects—its effectiveness and delivery techniques. The harvesting and processing techniques of bone marrow cells giving rise to bone marrow aspirate concentrate (BMAC) is a crucial step to achieve satisfactory results. The BMAC obtained after density gradient centrifugation (DGC) is only a small population of the total cells (0.001%–0.01%). The DGC involves the removal of red blood cells, granulocytes, immature myeloidprecursors, and platelets—progenitor cells. There is high concentration of eye-derived growth factor, transforming growth factor-β, and BMP that have anabolic and anti-inflammatory properties. All these cardinal features of BMAC help it to be the ideal source in the bone marrow regenerative process. However, the autologous bone graft will act as an appropriate scaffold for the delivery of mesenchymal stem cells to gain the highest rate of new bone formation.[10]

Kakabaze et al.[9] used autologous bone and decellularized bovine bone grafts with freeze dried bone marrow stem cell paracrine factors. They called it a novel biologically active bone grafts (BAB). The aim of the study was to use it for large-sized defects of the mandible after tumor resection and to evaluate the bone regeneration potential.

Lendeckel et al.[9,10] used autologous stem cells from adipose tissues and fibrin glue, which were used to treat wide, spread traumatic calvarial defects in a 7-year-old girl after severe head injury with multifragment calvarial fractures.

Gali et al.[2] used concentrated bone marrow aspirate-coated hydroxyapatite for reconstruction of small-to-moderate-sized mandibular defects caused by the removal of benign pathologies. The aim was to evaluate the bone regeneration potential of the concentrate.

Liu et al.[6] used allogenic mandibular scaffolds and autologous mesenchymal cells for the reconstruction of beagle hemi-mandibular defects. Bone marrow density (BMD) and microarchitectural histologic parameters were studied.

Gjerde et al.[10] used bone marrow stem cells from posterior iliac crests and biphasic calcium phosphate granules as scaffold for the regeneration of severely atrophied mandibular bone in 11 subjects aged 52–79 years. The results induced significant new bone formation and the regenerative bone was adequate for dental implant placement.

All the above studies have concluded a positive outcome in the reconstruction of the complex craniofacial skeleton. More research and studies are required to create a better outcome in the reconstruction of bony defects with respect to function, aesthetics as well as minimizing the duration of the treatment.

**CONCLUSION**

Enormous progress has been made in the last 30 years with regard to reconstruction of bony defects not only in the craniofacial region but also with regard to other specialities. Techniques such as microvascular reconstruction using autogenous bone grafts have proved to be a superior and better outcome in reconstructing large and complex craniofacial defects when compared to the older techniques. Patient morbidity, complications, time, and cost associated with harvesting such grafts are enormous.[1] More intense elaborate and extensive researches are required to accomplish the ideal requirements in the field of bone regenerative medicine and tissue engineering to improve characteristics such as biocompatibility, mechanical strength, for future surgical procedures as well as molecular composition, and resemblance to natural bone. The success of the combined use of human bone marrow stem cell concentrate and autologous bone grafts in reconstruction of complex bony defects depends on the type of harvesting and processing techniques. Future of medicine and dentistry will be more and more dependent in the future on regenerative medicine and its progress, not only in the field of reconstruction but also in other areas.

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Conflicts of interest

There are no conflicts of interest.

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