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Review Article

Reconstruction of maxillofacial bone defects: Contemporary methods and future techniques

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Abstract

Reconstruction of maxillofacial continuity defects has always been a challenging tasks for the scientist and surgeons over the years. The main goal of the reconstruction of the maxillofacial region is to restore facial form, function, full rehabilitation of occlusion and articulation. A refinement in surgical technique and methods of reconstruction has improved patient's quality of life. This manuscript reviewed exciting methods of bone reconstruction and confirms that the ideal system for reconstruction of critical size continuity defect of the jaw bones has yet to be found. Shortcoming and limitation of each method has been discussed. The author highlight recent advances on how tissue engineering which could offer biological substitute to restore, maintain, or improve oro-facial function**.**

Keywords: Mandible Reconstruction, graft, bone regeneration, Bone engineering.

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Introduction

Maxillofacial bone defects are caused by cancer resections, followed by trauma, clefts, burns, and infection. Reconstruction of maxillofacial bone defects has been observed throughout recorded history. Human beings have found the need to reconstruct missing or defective maxillofacial parts — such as eyes, ears, noses, maxilla, mandible and teeth — with artificial substitutes . Reconstruction to reconstruct large bony defects in the maxillofacial region remains a major surgical challenge. The size of the defect and the effect of radiation therapy (in case of cancer treatment) on the blood supply of the surrounding tissues are the main limiting factors of successful reconstruction. 1]. Sykoff performed the first surgical attempt for maxillofacial reconstruction, most of the published data were based on an expert opinion, and the studies provided only limited objective guidelines for successful treatment [2]. The surgical techniques for facial reconstruction were regional, historical, and individual bases for use rather than evolving and evidence based. In addition, researchers did not agree on clear outcome measures for comparative studies [2]. Assessment of function, aesthetic and quality life assessments of reconstruction techniques are needed to be standardized to allow reconstruction of maxillofacial bone defects rational and robust. This paper reviews current techniques available for reconstruction of continuity defect in maxillofacial region based on human trials and highlights the advantages and disadvantages of each method

Free bone grafts

The autogenous bone graft has been a satisfactory technique for osteoconduction, osteoinduction and osteogenesis. Osteoconduction occurs when the bone graft material serves as a scaffold for new bone growth that is perpetuated by the native bone. Osteoinduction involves the stimulation of osteoprogenitor cells to differentiate into osteoblasts that then begin new bone formation. The most widely studied type of osteoinductive cell mediators are bone morphogenic protein (BMPs). Osteogenesis occurs when vital osteoblasts originating from the bone graft material contribute to new bone growth along with bone formation generated via the other two mechanisms (osteoconduction and osteoinduction). At present, many surgeons choose a cortico-cancellous block graft taken from the anterior or posterior iliac crest for jaw reconstruction. The success of these grafts is probably much dependent on the way the bone is fixed because the survival depends of the graft largely on revascularization from the recipient site [3]. This revascularization is of paramount importance for the process of resorption and deposition of new bone that is known as creeping substitution. However, there are two major limitation of using an autogenous bone graft: poor osteointegration and excessive resorption when the defect is larger than 6 to 9 cm. Insufficient blood supply for the surrounding tissues secondary to irradiation, scarring, and infection is major detrimental factor. Moreover, donor site morbidity limits the use of autogenous bone graft [4].

Particulate cancellous bone marrow graft (PBCM)

Since 1944, reconstruction of long bone has been demonstrated using PBCM. This method of grafting has been proved to attain superior osteogenic potential and lower rate of surgical complication compared to cortical graft[5] . Due to the inherent lack of cohesion, the PBCM graft was placed in a frame or crib to maintain its physical dimensions, and to provide a mechanical stability. Titanium, vitallium, tantalum, chrome cobalt and stainless steel metal cribs were frequently used to deliver the PBCM [6-9]. These metal trays had clean disadvantage, especially for the patients who would be subjected to radiotherapy later. In addition, it has higher modulus of elasticity compared to bone resulting in tray

absorbing much of the functional stress (stress shielding effect) which causes resorption to the supporting bone [3]. To overcome the drawback of metal trays, dacron- coated poly- urethene trays are beeing used for reconstruction of human mandible [9, 10]. Complication are reported even with the use of metal or dacron tray like wound dehiscence, and postoperative infection. Thus introduction of resorbable alloplastic trays to the world of maxillofacial reconstruction has attracted attention of many researcher to test it is feasibility before the clinical application [11, 12]. Apart from alloplastic cribs, a freeze dried allogenic mandibular tray filled with PBCM has been used in clinical trials and the tested trays have showed success in restoring form, shape and function in more than 80% of the cases [13, 14]. Major limitation of this technique was the lack of availability. The use the patient`s own mandible after scrubbing the diseased part from bone was also used as a crib to hold PBCM for reconstruction. The bone crib was autoclaved or freeze dryad before being filled with PBCM. These atttemps have showed variable rate of success in animal and human trials [15, 16].

Furthermore, the use of plasma rich protein and PBCM has been tested for the reconstruction of continuity defect of the mandible in animal model and in clinical trials [17-20]. The reported advantages of PBCM grafts are the potential to create an anatomic mandibular reconstruction of adequate height, symmetrical arch form and width, and the ability to adequately support dental implants. Moreover, this type of graft has proved its ability to bridge large mandibular defect of any length [16,3]. Paradoxically, the main reported disadvantage included the resorption, and wound dehiscence which may lead to loss of the graft [16]. The later was the main reason why PBCM grafts are not recommended in patients with malignant tumours where scar fibrosis and lack of vascularity which affect the covering soft tissues [3].

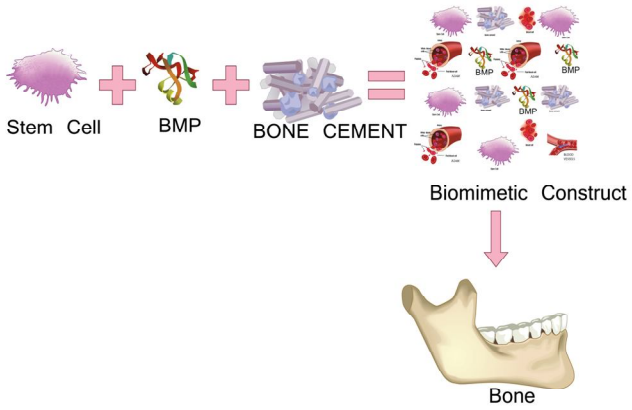

Figure-1: Illustration demonstrate the objective of bone bioengineering is to develop a biomimetic construct which consists of osteognic cells (Stem cells), growth factor (BMP) and scaffolding (bone cement), all will lead to chemoattaraction and angiogenesis when implanted in vivo which ultimately lead to complete bone regeneration

Pedicled composite grafts

It is a graft that composed of bone, muscle or skin, and with their feeding blood vessels (vein and artery). To overcome the problem of vascularity of free bone graft, the use of pedicle bone and composite graft become more popular in the field maxillofacial reconstruction. The most commonly used

is the pedicle scapula flap for maxillofacial reconstruction. Many techniques have been advocated and their feasibility has been investigated. Surgeon reported successful results in clinical trial [21-23] where this technique is used. Nevertheless, some obvious drawbacks of using different flaps were reported. Pedicle composite flap based on sternocleidomastoid muscle may not be always possible. Moreover, the aesthetic results of pedicle bone graft were not always acceptable [3]. Furthermore, these techniques are also associated with donor site morbidity [24].

Microvascular free flap transfer

At present mandibular reconstruction using microvascular free flaps is the gold standard, as it provides, in most cases, a satisfactory functional reconstruction [25]. In a prospective study, irradiated mandible was reconstructed using free vascular bone graft, cases were followed up for 10 year and a 90% success rate was reported [26]. However, shaping of microvascular bone graft to restore complex 3-dimensional orbitomaxillary defects is requires greter expertise [25]. Furthermore, iliac crest free vascular flap, which is the most common microvascular flap has a short vascular pedicle and the lack of segmental perforating vessels limits its use [27]. In contrary, fibula flap has reported widest application, it can provide up to 30 cm of bone with adequate length and diameter of the feeder vessels [26, 28]. However, pre-existing peripheral vascular disease will preclude use of this flap. Another limitation for fibula flap was inadequate height in relation to the jaw bone to be restored [29]. A similar limitation has been also reported with the use of radius forearm microvascular flap for maxillofacial reconstruction [30].

Tissue engineering and regenerative medicine

Tissue engineering was initially introduced to describe the technology producing biological tissue in vitro [31]. Recently, the term regenerative medicine has been used to describe the development of technology and surgical procedures for the regeneration of tissue in vivo [31]. The working goal of tissue engineering is the implementation of existing knowledge for the creation of a product (tissue) that can resemble autogenous tissue and able to act as a substitute for any lost tissue at any point in time. The objectives of tissue engineering and regenerative medicine are to promote healing and ideally to simulate true regeneration of a tissue structure and function more predictably, and to be less invasive than previous grafting techniques. Advances in research have shown that the tissue engineering and design of the scaffold matrices, and the mechanical signals that regulate engineered tissues, have an important role for successful tissue bioengineering, the use of three-dimensional biomaterial scaffolds to support regeneration and to substitute autograft is essential. Numerous scaffolds matrices, including allogenic, xenogenic, and synthetic graft materials have been available on the market for use in oral surgical procedures and orthopedics surgery. The exact mechanism of the action of these matrices is to provide foundation for cells to migrate from the wound edges, eventually leading to the repair of the defect. The principle disadvantage of using scaffold without cells or cytokinas is lack of osteoinductive properties and osteogenesis. In addition the rate of resoption of some types of allograft scaffolding mismatched the rate of the new bone formation leading to failure of integrating the bioengineered tissue with the surrounding bone. A review by Neovius E and Engstrand T, (2009) compared the commonly used biomaterial and bone graft or combination in non-load-bearing areas for craniofacial reconstruction for 11 years from 83 studies. The study concluded that, significant difference in outcome were mainly related to size and location of defects rather than bio-material used [32].

The major turn point in the arena of bone reconstruction is the introduction of Bone Morphogenic Proteins (BMP). BMP's are

cytokines which are produced by variety of cells and can be produced biologically in large quantities and are available commercially. They stimulate osteoinuction, thus inducing osteoprogentor cell to produce bone, and resulting in a chemo-attraction for the mesenchymal stem cells to the defect area [33]. At the level of preclinical animal research, the use of BMP reported promising results [34-36]. Few cases were published on successful reconstruction of the maxillofacial region in clinical trials [37-40]. Two prospective longitudinal control clinical trials were carried out using BMP and scaffolds [38-33]. Herford et al 2007 tested the feasibility of bone morphogenic protein in repairing a premaxillary cleft. Twelve patients were selected in this study [39]. The planned procedure was to repair the oral-nasal fistula and to graft the alveolar cleft with BMP-2 delivered into type-1 bovine collagen sponge carrier. The surgery was performed by a surgeon, two patients were grafted using particulate marrow cancellous bone and were considered as control. The cases were evaluated pre-surgery and 4 month postoperatively by computed tomography (CT). A special imaging protocol (computer-assisted software IMPAX) was followed to measure the volume of the defect and measurement of bone filling after grafting. Result showed that the mean bone volume ratio preoperative to postoperative was 71.7% in the BMP-2cases whereas, preoperative to postoperative mean volume ratio was 78.1% for the control group. The author concluded that BMP-2 is an effective alternative to conventional grafting technique.

On the same vein, (Ferretti et al, 2002) tested bone regeneration in mandibular critical continuity defect of human with naturally derived BMPs, and this was compared with autologous bone grafts [39]. The BMP was delivered on a scaffolding of human cortical bone chips. Data from the morphometric analysis for the successful BMP graft had highly active osteogenesis compared with autogenous bone graft group. Despite the failure to induce bone in four of the constructs, the author concluded the study was a successful introduction of this novel approach to repair critical mandibular defect through extraction of BMPs from the natural milieu of bovine bone matrix that preclude the need to harvest autologous bone. Although there is definitely a future for engineered graft using BMP, the long term effect of this material on various tissue cells and its oncogenic effect not yet determined. Another factor related is the costs involved in using the commercially available BMP which preclude their use on large scale [3]. In systematic review by Herford et al, (2011) for the use of BMP in reconstruction of the jaw, it was concluded that with the reported failure rate for the used growth factors in clinical trial was 13.9%, therefore, it is not possible to conclude that BMP can replace the need for autognous bone grafts [41].

Another dimension of bone tissue engineering is the use of prefabricated bioengineered bone flaps. Kokemueller et al, 2010 conducted a study to determine the effectiveness of the implantation procedure and the role of the vascular axial perfusion for a large bioartificial scaffold on bone formation [42]. Twenty-four cylindrical tri-calcium phosphate (β-TCP) scaffolds (25 mm long) were intraoperatively filled with bone marrow harvest prepared in special way to maximise their osteogenic potential and implanted into back muscle in an animal trial. The successful results of this pre-clinicl animal trial on sheep has encouraged the researchers for clinical application by preparation of construct with the same technique, then implanted into a continuity jaw defect. Similarly, Warnke et al (2004) reported a novel method of repairing a human mandible by in vivo tissue engineering. Bone morphogenic protein-7 (rhBMP-7) and bone marrow-derived mesenchymal stem cells were added to a bioresorbable polylactite scaffold, which was loaded in a titanium mesh tray as an external scaffold [43]. The patient served as his own bioreactor, as the titanium

mesh was grown inside the patient's latissimus dorsi muscle. After seven weeks the formed bone with titanium mesh was transplanted to the patient's mandible. The results showed greater osteoblastic activity and marked bone formation were detected in all parts of the mandible during the 38th week. The authors concluded that transplantation could have been performed at a later stage, as osteoblast activity and bone remodelling remained highly active during the first 8 months.

Another successful reconstruction of the mandible was recorded by Warnke and his coworkers (2006) [44]. They reported a patient who underwent a secondary reconstruction after tumor resection. The engineered graft was allowed to heal in the trapezius muscle and subsequently transplanted to the recipient side in mandible. The graft was anastmosed to the recipient side and the outcome of this study were encouraging.

An important human trial aiming to maintain sustainable blood supply to the graft was conducted by using perfabricated tissue engineeried graft which was transfered in a pedicaled flaps. Heliotis et al, (2006), demonstrated the preparation of vascularised bone flap extra-skeletally, with combination of osteogenic protein-1 (OP-1) and hydroxyapatite HA flap used for reconstruction of large mandibular defect in human [45]. A 60 year old patient presented with hemimandible as a result of previous surgical resection of malignant tumor. The patient underwent radiotherapy postoperatively and no reconstruction of the jaw was performed. Three blocks of HA were adjusted to the shape of the mandibular body and ramus, OP-1 was smeared over the blocks and then implanted within the pectoralis major muscle for 15 weeks. Skeletal scintigraphy was performed to assess bone formation on the graft material. The implanted composite was raised with attached muscle leaving it pedicaled to thoracoacromial artery for mandibular reconstruction. Then it was fixed externally to left side of the mandible, after certain preparation for soft tissue bed on the mandible, the pedicle was covered by free skin graft. An external fixation device was used to secure the graft in place and to prevent unwanted movement. Radiographs were taken which reported a reasonable anatomical position of the graft. Despite the initial success of the technique after, 5 months patient developed MRSA infection at the graft site. Subsequently, the bone graft was immediately removed. In spite of the reported success of use of BMP, yet it`s uses need further improvement and studies for the reconstruction of large complex defect in cranio-maxillofacial region [32].

Bone Mesenchymal Stem Cells (BMSCs)

Bone mesenchymal stem cells (BMSCs) were introduced in the repair of large bony defects during the last decade. Several studies investigated the use of expanded BMSCs which were seeded on various scaffolds in animal models. Variable degree of success was reported [46-50]. The basic principle of tissue engineering involves a "triad" wherein a combination of cells in a suitably engineered material scaffold with appropriate biochemical signals is used to provide viable therapeutic options for clinical applications. Advances in research have shown that the engineering and design of the scaffold matrices, and the mechanical signals that regulate engineered tissues, have an important role [51] (Figure-1). The rationale behind the use of Mesenchymal stem cell into scaffolds with/or without PRP or BMP is to achieve osteogenesis, osteoconductivity, osteopromotion and osteoinductivity. The advantage of using stem cell for reconstruction is that they have inherent multipotetial properties i.e. they can differentiate into different cell lineages, if these cells have been induced to follow the osteogenic lineague using BMP, would stimulate vascular in growth from the recipient bed. Furthermore it has been proved that bone formed using this technique is more likely to respond appropriately to secondary surgical intervention e.g. distruction osteogenesis. In contrary bone graft from ribs or fibula

respond poorly to second surgery manipulation [52]. To date, one clinical trial by Lee et al, (2010) reported a successful reconstruction of 15 cm segmental mandibular defect using bone marrow stem cells [16]. Following a segmental mandibulectomy jaw bone were fixed using reconstruction plates. The resected jaw was freeze - dried for 48 hours and was perforated using surgical burs. At the same time, autogenous bone marrow stem cells were aspirated, isolated and cultured in vitro before load onto the bone segment immediately prior to the surgical implantation. One year postoperatively, the mandible showed excellent clinical and radiographic evidence of bone regeneration. Another idea introduced to maxillofacial reconstruction is the In Situ Osteogenesis (ISO) which is based on creation of periosteum chamber and implantation of BMP into the chamber [40]. The use of osteoprogentor cells in combination with alloplast/or allograft and gowth factors were studied extensively in literature and reported different success rate. The problem with cell seeding and its survival depend on vascularity of the construct. Most of research have used osteoprogintor cells and reported less promising result claimed that lack of vascularty could be the cause [53, 54, 50]. Therefore the idea of using autognous pedical muscle flap could overcome the point of lack of vascularty as the muscle will act as bioreactor for the introduced biomimitic bone cement and the rMSCs. Similar concept was reported a promicing result when muscle used to reconstruct cranial defect in rats (Liu et al, 2011) [53].

Molecular therapy

The popularity of using molecular therapy in regenerative medicine, has led to emergence of intricate research in cranio-facial region. The idea of having sustained release of growth factors which was the fundamental premise of using molecular therapy and genetic engineering is of great interest [55, 56]. Moreover, providing a dual action of transfected MSCs and and vascular induce factor with BMP-2 gene was introduced and justified by He X, (2013) [57]. Another use of molecular therapy is to enhance endogenous cell mechanism recruitment to regenerate injured bone by local targeting and activation of Sphingosing-1-phosphate (S1P) receptors [58]. Molecular therapy urges the scientist to evaluate the ability of genetically modified, autologous muscle to heal large cranial defects in rats [53]. The effect of hypoxia induced factor-1α (HIF- 1α) gene on osteogenesis of BMSCs using point mutant technique was explored by Zou et al, 2011[59]. Furthermore, the term antibody-mediated osseous regeneration (AMOR) was recently introduced to tissue engineering research. Ansari S et al, (2013) have assessed the efficacy of newly generated chimeric anti-BMP-2 monoclonal antibodies (mAb) in mediating AMOR as well as evaluating the suitability of different biomaterials as scaffolds to participate in AMOR [60].

Conclusion

Surgeons are tirelessly working to reconstruct continuity defect in maxillofacial region for more than a century. Enormous progress has made especially over the last 40 years .Technique such as microvascular autogenous graft procedures have proved better options for reconstructing large and complex defects, but morbidity associated with harvesting bone graft is a major disadvantage. Alternatively, use of tissue engineering showed exciting promising results at pre-clinical level and in the limited clinical trial. Yet refinement of the technique and identification of the ideal scaffolding are necessary before wider clinical application. Further studies are required to produce an evidence based practice in tissue bioengineering clinically. This could have significant impact on the reconstruction of maxillofacial defects due to bone loss following trauma or cancer resection.

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