ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at: www.ijdsir.com

Volume – 2, Issue – 5, September – October - 2019, Page No. : 215 - 227

Recent Advancements in the Reconstruction of Jaw Defects: A Review

[1]Dr. Himani Dadwal,M.D.S, Reader, Dept. of Oral & Maxillofacial Surgery, Himachal Institute Of Dental Sciences, Paonta Sahib.

[2]Dr. Priyanka Sharma,M.D.S,Dept. of Oral & Maxillofacial Surgery,Himachal Institute Of Dental Sciences, Paonta Sahib.

[3]Dr. S. Shanmugasundaram,M.D.S, Professor,Dept. of Oral & Maxillofacial Surgery,S.R.M Dental College, Chennai.

[4]Dr. Tripti Mukherjee,P.G Student, 3rd M.D.S,Dept. of Oral & Maxillofacial Surgery, Himachal Institute Of Dental Sciences, Paonta Sahib.

[5]Dr. Senthil Murugan,M.D.S, Reader,Dept. of Oral & Maxillofacial Surgery,Saveetha Dental College, Chennai.

[6]Dr. Ritika Kataria,P.G Student, 2nd M.D.S,Dept. of Oral & Maxillofacial Surgery,Himachal Institute Of Dental Sciences, Paonta Sahib.

Corresponding Author: Dr. Ritika Kataria, P.G Student, 2nd M.D.S, Dept. of Oral & Maxillofacial Surgery, Himachal Institute Of Dental Sciences, Paonta Sahib.

Type of Publication: Review Paper

Conflicts of Interest: Nil

Abstract

Reconstruction of maxillofacial defect has always been a challenging task. Challenges can further increase by anatomical complexities or already seated complications like scarring, infection or rejection of the already placed graft at the site of the defect. Although many reconstructive methods has been invented and adopted till date which improved the functional and aesthetic outcomes of the procedure, there are still advancements going on to improve the quality of the treatment received by the patient and to make the procedure comfortable both to surgeon and the patient.

Keywords: Recent Advancements, Maxillofacial Defects, Bone Morphogenetic Proteins, Plasma Rich Proteins, Tissue Engineering, Hyperbaric Oxygen, Face Transplantation, Modular Endoprosthesis.

Introduction

Due to highly complex nature of the facial skeleton, presence of vital structures and most importantly aesthetics and the functions associated with the face, reconstruction of the defects in this revealed site has increased the challenges faced by the surgeons many times. Composite defects of the jaws that require bone, muscles and skin limit the donor site availability and thus results in compromised aesthetic and functional outcomes[1]. Various new modalities are developed and utilized now a day to overcome these types of situations. This article gives the overview of the present recent advancements in the field of oral and maxillofacial reconstruction.

1) Bone Morphogenic Proteins

Bone matrix is a treasury of regenerative and differentiation factors that help in bone induction, regeneration and maturation. Bone morphogenic proteins are a group of signalling molecules that belong to the TGF-β superfamily[2]. There are 20 members in this family of osteoinductive proteins known till now[3]. Out of all these members BMP-7 in particular, may be

considered as an alternative reconstructive method for bony defects in maxillofacial skeleton apart from the "gold standard", autogenous bone grafting[4].

On the basis of their function at cellular level, it is known that BMPs acts on both osteogenic and chondrogenic linage[5]. Within 5-7 days of application of BMP, these cells are stimulated to differentiate into chondrocytes. Thereafter due to capillary invasion, the chondrocytes become calcified and hypertrophied, and ultimately replaced by new formed bone within 9-12 days. Finally it takes 14-21 days for the mineralised bone to undergo the remodelling process[6].

Preparation: Each unit of rhBMP-7 consists of 3.5 mg[7-11] of the recombinant human protein mixed with 1 g of collagen type-I. The powder has to be mixed with 3–5 ml of sterile saline. The implantation of 2 units of BMP-7 is the acceptable maximum quantity.

In 2007, the FDA approved rhBMP-2 for only intraoral applications like sinus augmentation and for localized alveolar ridge augmentation. Because it is produced in a recombinant form, an unlimited amount of rhBMP-2 can be produced, making it extremely pure and safe, as well as a commercially available product[12]. Moghadam et al in 2001 used rhBMP-2 for the first time in human mandible for 6cm of segmental defect[13]. Presently, treatment of mandibular continuity defects with rhBMP-2 is considered an "off-label" [12].

Advantages

1. Lower morbidity rate as compared to autogenous bone grafts.[14]
2. Can be used with allografts.
3. Patients return to normal activities much sooner.
4. Hospital stay is reduced
5. Promotes vascularisation[15]
6. Can be used in cases for the treatment of poorly vascular mandibular conditions like osteoradionecrosis and biphosphonate osteonecrosis[16,17]

Disadvantages

1. Cases of extensive facial edema has been reported[18]
2. BMPs have shown the potential to cause toxicity, immune reactivity and uncontrolled bone formation.
3. High cost

2) Platelet-Rich Proteins (PRP):

Platelets are one of the first cells to retort at an injury site as it is one of the important elements during wound healing. For the formation of bone and its regeneration, a complex cascade of events regulated by growth factors (GF) takes place. Apart from having procoagulant effects, platelets acts as a wealthy source of significant growth factors like, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), tansforming growth factor-b (TGF-b) which serves in coagulation cascade and help in hard or soft tissue wound healing[19-21].

It was in 1998 when Marx et al[22] for the first time delineated the fact that the addition of PRP to an autologous bone graft results in faster bone regeneration and maturation rate in an alveolar defects by delivering a high concentration of growth factors at the injured site when activated with thrombin and calcium chloride.

In the field of oral & maxillofacial surgery, PRP is predominantly used in synchronicity with bone grafting in alveolar ridge augmentation[23], sinus floor augmentation[24], dental implantology[25] etc. More recently its use has been advocated in the management of biphosphonate-related osteonecrosis of the jaw (BRONJ) or avascular necrosis (osteoradionecrosis)[26].

Preparation of PRP Gel[27]

- Prior to surgery, 40ml of autologous venous blood is withdrawn in four 10ml test tubes containing 0.5ml of sodium citrate solution (anticoagulant).

- Centrifugation of the tubes is done at 1,500 rpm for 10-15 min to obtain 3 components.
- The middle layer of PRP (platelet-rich plasma) is separated from the PPP (platelet poor plasma) and RBCs (red blood corpuscles).
- The separated PRP is again centrifused at 1,500 rpm for 10-15 min and the middle layer is collected in a beaker along with 10% calcium chloride.
- 5,000 units of topical bovine thrombin (activator) is then added and kept in water bath for 30-40 min to obtain the PRP in gel form.

Platelet concentration of at least 1,000,000/L in a 5ml volume of plasma is found in PRP, whereas normal platelet count found in the blood range is from 1,50,000/L to 3,50,000/L[28].

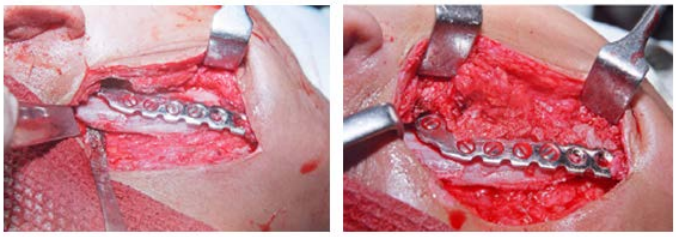

Fig. 1 Autogenous Bone Graft Fixed To Reconstruction Plate With Prp Packed In And Around The Defect *Magesh DPU, Kumaravelu C, Maheshwari GU. Efficacy of PRP in the reconstruction of mandibular segmental defects using iliac bone grafts. J Maxillofac. Oral Surg. 2013;12(2):160-167.*

Advantages

1. When combined with bone grafts, it results in controlled release of growth and differentiation factors from the site[29]
2. No foreign body reaction or morbidity.
3. When combined with BMPs it helps in inhibition of osteoclastic activation by increasing the concentration of TGF-β_2[30,31]
4. PDGF in PRP stimulate chemotaxis, mitogenesis and the reduplication of stem cells at the site of a wound to the site of tissue injury[32]
5. Hastens soft tissue healing due to neo-vascularization[32]
6. Amplification of osseointegration by the use of PRP coated implant surface preliminary to insertion[33]
7. Use of PRP intensifies wound healing and reduces bone exposure in cases of BRONJ patients[34]

Disadvantages

1. High concentrations of PRP bring out counter effects such as suppression of proliferation of osteoblasts[35,36]
2. Some studies showed that the combining xenograft and PRP did not have any effect on implant stabalization[37]
3. After tooth extraction it influences only the initial phases of wound healing.

3) Tissue Engineering

Tissue engineering was previously defined by the attendees of the first NSF (National Science Foundation) sponsored meeting in 1988 as “application of the principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationship in normal and pathological mammalian tissues and the development of biological substitutes for the repair or regeneration of tissue or organ function.”[38]

It was later in 1993, when Langer and Vacanti[39] after recapitulating the early evolution in this field, defined tissue engineering as “an indisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain or improve tissue or organ function.”

Principles of Tissue Engineering

Regeneration of new tissues requires a specific environment and 3 basic prerequisites: the stem cells, a

scaffold or extracellular matrix and the signaling molecules. This in turn forms the "classic" tissue engineering triad [40]. FIG.2

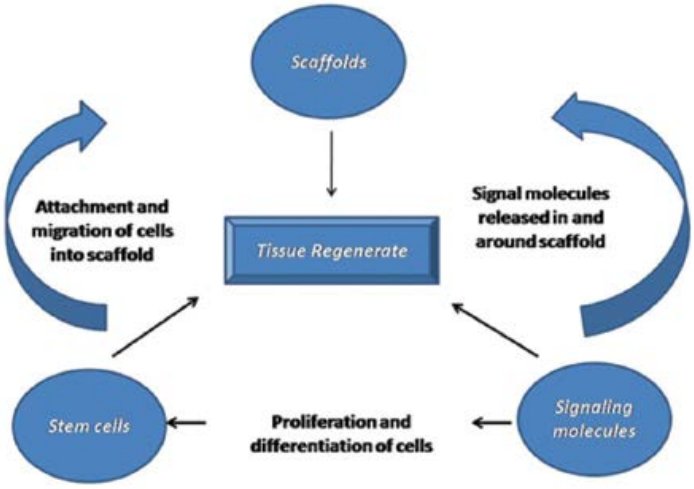

Fig.2: Triad Of Tissue Engineering *Rai R et al. Tissue Engineering: Step ahead in maxillofacial reconstruction. Journal of International Oral Health. 2015;7(9):138-142.*

A) Stem Cells: Depending upon their potential to differentiate into other cell types, stem cells can be classified as totipotent, pluripotent or multipotent[41]. Presently MSCs (multipotent stem cells) are commonly used in dentistry based tissue engineering owing to some ethical and technical issues concerned to iPSC (pluripotent stem cells) and embryonic cells. MSCs can be isolated from variable sources; such as bone marrow, peripheral blood, umbilical cord blood, adult connective tissues etc. They can also be extracted from the oral cavity e.g. dental pulp stem cells (DPSCs), dental follicle progenitor stem cells (DFPCs), stem cells from apical papilla (SCAP)[42].

B) Scaffold: a scaffold can be regarded as a "support" either temporary or a permanent, natural or synthetic 3 dimentional porous and permeable biomaterial that is biocompatible and allow cell adhesion and induce cell proliferation and differentiation without the side effects of tissue rejection or inflammatory response[40,43]. A scaffold must have osteoconduction, osteoinduction and osteogenic potential. To allow a bone graft to be used for its osteogenic potential, it is advised to use the graft as expeditiously as possible, so that the cells remain vital to carry out its function[44]. Another feature of scaffold is, it should have easy penetrability. As per few reports, the biomaterial should be 90% porous. They can be microporous (<10μm) or macroporous (>50-60μm)[45]. Other properties that a scaffold should manifests are bioinert, biocompatible, biodegradable with suitable mechanical properties[44].

Scaffolds can be divided into organic and inorganic materials:[45]

Organic: Natural: Collagen, Chitosan, Silk Etc.

Synthetic: Polyglycolic Acid, Polylactic Acid Etc.

Inorganic: Metals, Alloys Or Mineral Compositions Like Calcium, Potassium, Silicate, Magnesium Etc.

C) Cell Signaling: Biological signals and morphogenic signals plays a pivotal role in tissue engineering. Biological signals takes part in casing the injured site by stuffing the defect with increasing cell population, simultaneously morphogenic signals helps in forming a specialized tissue by inducing the tissue specific differentiation[39]. Various growth factors and cytokines are mixed to extracellular matrix (ECM) to carry out their specific functions. An intracellular signaling is initiated when a growth factor binds to its receptor to carry out different functions like proliferation, migration and cell differentiation.

For the tissue regeneration mainly 3 approaches are followed: First is recombinant protein therapy that depends on stimulating specific cell type in the target site by the growth factors. Second approach is cell based therapy that modifies the genotype of the cells to behave as a medium for differentiation into various tissue types. The third approach is the gene therapy, where the genetic information is delivered to the cells to guide them to directly secrete a specific protein product[39].

Another aspects of tissue engineering that cannot be overlooked, is the angiogenesis and the vascularisation of the graft. The two main etiologies of large graft failure in major bony defects are the inability of the integration of graft with that of the host tissue and the graft necrosis due to compromised vascular beds. Considering this, repair of the vascularity and integration with the host tissue especially, must be attained in multiple levels[47].

4) Hyperbaric Oxygen Therapy (HBO):

One of the major disappointments we face today in the field of reconstruction is failure of graft because of necrosis due to compromised or inadequate vascularity. Surgeons who deals with craniomaxillofacial defects, knows how difficult it is to maintain the viability inside the bone grafted tissue and ensure the restoration of the defect. One of the techniques for supplying the graft is with its own blood supply. But, it results in significant donor site morbidity. This results in hypoxic wounds and thus necrosis of the site. Hyperbaric oxygen therapy has been currently used with clinical success in treating hypoxic wounds and in anoxic conditions.

Biochemical And Cellular Effects

Local hypoxia make wounds vulnerable to infection, because of the decrease in neutrophil- mediated bacterial killing by free radicals[48]. Hyperbaric oxygen reinstate this shielding against infection and increases the killing by phagocytosis. Adequate angiogenesis is essential for the formation of collagen matrix, for which proper oxygen tension is the first and the foremost requirement[49]. That is why, in irradiated tissues, hyperbaric oxygen is more effective than normobaric oxygen to promote angiogenesis and collagen matrix formation.

It is known that reperfusion injuries can deteriorate crush injuries and cause skin flaps and reconstructive procedures to fail. Neutrophils adhere to the walls of ischemic vessels, release proteases and free radicals which in turn leads to pathologic vasoconstriction and extensive tissue destruction[50]. Hyperbaric oxygen therapy counters it by inhibiting neutrophilic adherence and thus post ischemic vasoconstriction as seen in the rat tissue[51].

Therapeutic Uses

Therapeutic uses of hyperbaric oxygen[52]

- Decompression sickness
- Arterial gas embolism
- Severe carbon monoxide poisoning and smoke inhalation
- Prevention and treatment of osteoradionecrosis
- Improved skin graft and flap healing
- Clostridial myonecrosis
- Refractory osteomyelitis
- Radiation induced injury
- Acute traumatic ischaemic injury
- Prolonged failure of wound healing
- Exceptional anaemia from blood loss

Administration

It involves intermittent inhalation of 100% oxygen under a pressure greater than 1atm. To be effective, hyperbaric oxygen must be inhaled in the atmosphere or through an endotracheal tube in a monoplace chamber (FIG.3), or through masks, tight-fitting hoods, or endotracheal tubes in a larger, multi-occupant chamber also known as multiplace chamber. For carbon monoxide poisoning, the duration of single treatments varies from 45 minutes whereas it can take almost 5 hours for some severe decompression disorders. For wounds that do not respond to debridement or antibiotics, most protocols average 90 minutes for each of 20 to 30 treatments [53,54]. Mechanical ventilation and critical care monitoring, should be readily available.

Fig. 3 Monoplace Hyperbaric Oxygen Chamber *Tibbles PM, Edelsberg JS. Hyperbaric Oxygen therapy. The New England Journal of Medicine. 1996;334(25);1612-1618.*

Complications:[55]

Barotrauma

- Ear or sinus trauma
- Tympanic membrane rupture
- Pneumothorax
- Air embolism

Oxygen toxicity

- Central nervous system toxic reactions
- Pulmonary toxic reactions

Other

- Fire
- Reversible visual changes
- Claustrophobia

5) Transport Distraction Osteogenesis

Since Codivilla[56] first introduced the technique of distraction osteogenesis for femoral extension in 1905, and in 1988 when Ilizarov[57] for the first time gave the biological basis behind this technique, it was not until 1973 when Snyder et al[58] perfomed this technique for the first time in craniofacial skeleton of the canine. But it was in 1992 when McCarthy et al[59] performed this technique for the first time in 4 human mandibles suffering from Nagar's syndrome and mandibular hypoplasia.

5 steps are involved in this technique, starting from phase of osteotomy, latency period (1-2 days: children, 5-7 days: adults)that allows the formation of soft callus in the osteotomized site, distraction phase (Children – 1.5-2mm/day, Adults – 1mm/day) where the osteotomized fragments are moved apart with the help of traction applied across the fragments. Next is the consolidation phase and last is the phase of remodelling.

Transport disc distraction osteogenesis (TDDO) (FIG.4) is used in mandibular defect and was introduced by Costantino and co-workers[60] in 1995 to restore the continuity of mandibular defect formed as a result of cancer resection following radiation therapy. After resection of the lesion, bone is cut adjacent to the defect and moved across the other side of the defect with the help of a mechanical device. The piece of the bone that is moved across is the transport disc. Earlier extraoral devices were used of the transport of the bony disc, but they caused facial scarring. Recently, an advanced type of intraoral distractor (A plate-guided distraction device) (FIG.4), is introduced for mandibular segmental defects, that not only adapt to the mandibular curvature but also allows for 3 dimensional vector control[61].

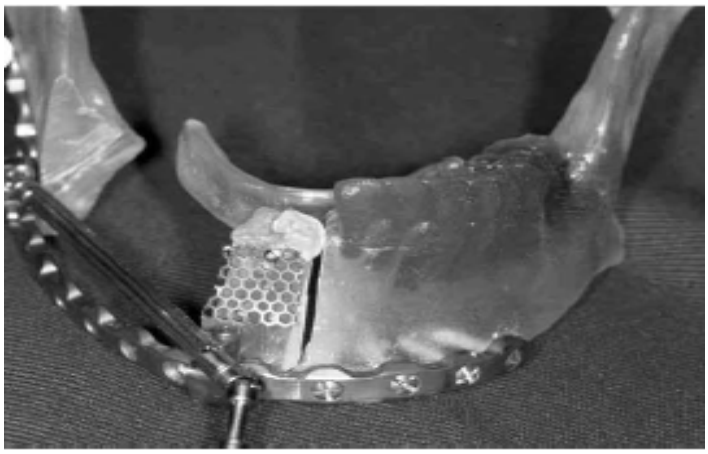

Fig.4: Plate guided distractor secured to the plate and transport segment on acrylic model. *Herford AS. Use of a Plate-Guided Distraction Device for Transport*

Distraction Osteogenesis of the Mandible. J Oral Maxillofac Surg 62:412-420, 2004

Advantages

- It avoids any other surgical site morbidity for harvesting the graft.
- It not only grows the bone but also the surrounding soft tissues locally and later on allows the placement of the implants in a newly formed bone.

Disadvantages

- Difficult to be used to recreate curvatures in the bone.
- It not only needs costly equipment but also compliance of patients.

6) Facial Transplantation

Facial transplantation is one of the recent advancements in the field of maxillofacial reconstruction. Although it has opened new gates for the restoration of the damaged facial parts, it is a complex procedure involving unavoidable outcomes with long term or short term risk for the patients.

The first facial transplantation was performed in France on Nov 27(2005) and led to a new era with further exploration of new possibilities in this field[62]. On one hand, where it was considered as a hope for the patients to get over their social or psychological stigma associated with the trauma, it also raised some ethical and psychological issues not predicted before. Facial transplantation is used as the last resort where other conventional techniques have failed to restore function. One of the important aspects of this method is that, it is never carried out for aesthetics alone.

Goals : To regain the movements and functions of the underlying tissues and to restore the normal appearance of the face[63]. To achieve these goals, every step is important; from patient selection, recognizing the patients psychological aspect, medical condition, the extent of trauma etc. along with having a realistic approach towards the procedure and be ready for the complications associated with the surgery.

Preoperative **candidate selection** is an important characteristic separating it from the solid organ counterparts. Unlike concealed solid organ transplant, composite transplants (face and hand transplants) is revealing and one of the major factors in affecting the social interaction and self esteem in these vulnerable group of patients. Decisive attitude towards social encounters is the key to patient selection. Physical and speech therapies carried out as a part of physical rehabilitation is mandatory and the patients who are not inspired enough for this may not be able to regain adequate facial mobility. To know the psychological response of the patient towards the procedure Coffman and Siemionow (2013) developed 3 scales (the perception of teasing-FACES, Facial Anxiety Scale-State, and the Cleveland Clinic FACES score) for the purpose of prioritizing patients for a face transplant registry[63]. A classification system is recently proposed for composite tissue transplantation (CTA) which assigns face and hand allotransplants, based on their unmatched level of relative surgical complexity and accompanying psychologic/rehabilitative challenges[64].

An increased emphasis is given on **informed consent** from both the candidate/family members of donor and recipient for this more or less experimental procedure that is not considered to be specifically life saving but could be life improving. It is very important for the patient and the recipient family to know about the possible complications associated with the procedure and should be educated and aware about the potential risks like the tissue rejection, infection, long hospital stay, long standing tracheostomy care and possible lifelong immunosuppression[63]. For some patients, scars from grafts may be painful and esthetically unpleasant. Antiviral resistant CMV due to

transplants is one of the frequent problems today after transplantation.

Tissue rejection In contrast to solid transplant, timing of rejection is later in facial transplant, mentioned to be occurring usually between 18-120 days. To overcome this incidence of tissue rejection, **immunosuppression** is carried out. A general approach was mentioned in one of the research reports by Coffman and Siemionow (2013) for immunosuppression. It involves the use of tacrolimus (immune suppressive drug) for the first 3 months with a target level of 12-15ng/ml, following 10-12ng/ml thereafter. It was given in a combination with mycophenolate mefetil (MMF) and prednisone for immunosuppression. Any incident of rejection is monitored by taking biopsy of the skin and oral mucosa weekly for 1 month, followed by monthly for next four months and then every 6 months[63].

Face transplantation is a complex, technique sensitive and relatively new technique that requires further research in this field. Although it comes with various risks, it can decrease depression, improves the quality of life to an extent and societal reintegration. Though is it the last resort when other conventional techniques for reconstruction fails to restore function, it may evolve to become the “gold standard” in future.

7) Modular Endoprosthesis

For more than a century, endoprosthesis have been used by orthopaedic surgeons to reconstruct the gap after the tumor resection of long bones or total hip or knee arthoplasties. This innovative technique for reconstruction of mandibular condyle and ascending ramus has been recently reported. Endoprosthesis is metallic device that replaces the gap formed after the resection of bone and fixed with bone cement within the medullary space of the remaining mandibular stump without the need for screw fixation[65]. It is made according to the patient’s specifications with the help of CT scans. A modular system consists of different components of different dimensions that when assembled fit in the defect. (FIG.5)

Currently available alloplastic replacements for temporomandibular joints depend on bicortical screw fixation for stabalization[66]. According to the study done by Dechow and Hylander, the difference in stress and strain during function results in tortional forces in the screws that engage both the buccal and the lingual cortices that may result in screw loosening overtime. It is mentioned that using this principle, an endoprosthesis undergoes less unfavourable forces and more stable reconstruction, when placed within the contour of mandible[67].

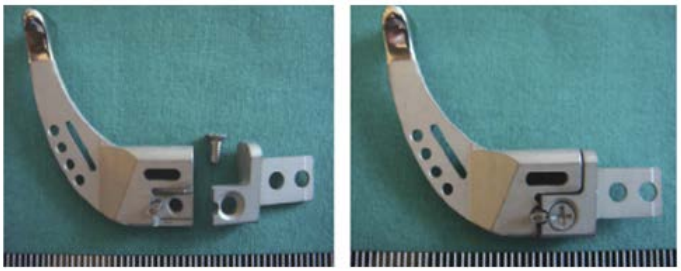

Fig.5 Modular Endoprosthesis consisting of 2 separate modules. *Goh et al. Replacement of the Condyle and Ascending Ramus by a Modular Endoprosthesis. J Oral Maxillofac Surg 2009*.

After inserting the cemented endoprosthesis, a region of necrosis is seen immediately adjacent to the implant and a blood clot is formed at the interface. Within first 48hrs, this blood clot starts to organise followed by gradual revascularization and bone healing. This is confirmed in the study done by Goh, Lee and Stoelinga (2009) where an increase in bone volume percentage is seen from 3-6 months. Resolution of any signs and symptoms of inflammation overtime supports the fact that these prosthesis are biocompatible[66].

Another factor that is important in the placement of endoprosthesis is the stability. It is important to determine

the long term success of the prosthesis. Although bone cements have proven to provide long term stability with improved function in long bones[68], periprosthetic osteolysis (a well known complication of the cemented endoprosthesis) cannot be overlooked. However there are 2 schools of thoughts associated with this event. According to one thought, osteolysis occurs before the prosthesis movement[69,70]. Another school of thought says that movement of the prosthesis is the primary event that causes pressure variations around the prosthesis followed by osteolysis[71]. Whatever the reason is, any type of unwanted movements in the prosthesis is a negative stimulus for bone formation but a positive response for fibrous tissue formation. Here cemented prosthesis has an additional advantage as due to the penetration of cement in the interface results in interlocking and reduction of the micromotion of the prosthesis. But, with the experience of some orthopaedic surgeons, the presence of this fibrous membrane not always results in loosening of the prosthesis however long term studies are necessary to draw any conclusion.

Conclusion

Like the universe, science is always expanding. And the curiosity to further explore the horizons is the prime reason for the advancements taking place in the field of science. Reconstruction of the defects of jaw and face is an age old technology to restore the aesthetics and the functions of the jaws and the face per se. But it's the inquisitiveness of the surgeon that leads to further improve the methods of reconstruction in order to help both the patient and the surgeon to come to a realistic and acceptable conclusion. The methods mentioned in this article are being used today to make it feasible as well as to improve the outcome of the surgical procedures. Still further researches are necessary to conclude it in a better way.

Compliance with Ethical Standards

Conflict of interest All the authors involved in this article have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Yadav P. Recent advances in head and neck cancer reconstruction. Indian Journal of Plastic Surgery. 2014;47(2):185-190.
2. Chenard KE, Teven CM, He TC, Reid RR. Bone morphogenetic proteins in craniofacial surgery: current techniques, clinical experiences, and the future of personalized stem cell therapy. Journal of Biomedicine and Biotechnology. 2012;https://doi.org/10.1155/2012/601549.
3. Cook SD, Baffles GC, Wolfe MW, Sampath TK, Rueger DC, Whitecloud TS. The effect of recombinant human bone morphogenetic protein-7 induces healing in a canine long bone segmental bone defect model. Clin Orthop. 1994;301:302-312.
4. Sen MK, Miclau T. Autogenous iliac crest bone graft: should it still be the gold standard for treating non-unions: A 4-year multicenter experience. Injury. 2007;38(Suppl 1):S75-80.
5. Nohe A, Keating E, Knaus P, Petersen NO. Signal transduction of bone morphogenetic protein receptors. Cell Signal 2004; 16(3):291-299.
6. Cecchi S, Bennet SJ, Arora M. Bone morphogenetic protein-7: Review of signalling and efficacy in fracture healing. Journal of Orthopaedic Translation. 2016; 4:28-34.
7. Dimitriou R, Dahabreh Z, Katsoulis E, Matthews SJ, Branfoot T, Giannoudis PV. Application of recombinant BMP-7 on persistent upper and lower

limb non unions. Injury. 2005 36(4,Supplement):S51-59.

8. Calori GM, Tagliabue L, Gala L, d'Imporzano M, Peretti G, Albisetti W . Application of rhBMP-7 and platelet rich plasma in the treatment of long bone non-unions: A prospective randomised clinical study on 120 patients. Injury. 2008;39(12):1391-402.
9. Friedlaender GE, Perry CR, Dean Cole J, Cook SD, Cierny G, Muschler GF, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial non unions. J Bone Joint Surg Am. 2001;83-A(Suppl 1(Pt 2)):S151-8.
10. Desmyter S, Goubau Y, Benahmed N, de Wever A, Verdonk R. The role of bone osteogenic protein-7 in the treatment of tibial fracture non-unions. An overview of the use in Belgium. Acta Orthop Belg. 2008;74(4);534-7.
11. Kanakaris NK, Lasanianos N, Calori GM, Verdonk R, Blokhuis TJ, Cherubino P, et al. Applications of bone morphogenetic proteins to femoral non- unions: A 4-year multicenter experience. Injury. 2009;40(Supplement 3):S54-61.
12. Carter TG, Brar PS, Tolas A, Beirne OR. Off label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for reconstruction of mandibular bone defects in humans. Journal of Oral and Maxillofacial Surgery.2008;66(7):1417-1425.
13. Moghadam HG, Urist MR, Sandor GKB, Clokie CML. Successful mandibular reconstruction using a BMP bioimplant. Journal of Craniofacial Surgery. 2007;12(2):119-127.
14. Goulet JA, Senunas LE, DeSilva GL, Greenfield ML. Autogenous iliac crest bone graft. Complications and functional assessment. Clin Orthop. 1997;(339):76-81.
15. Raida M, Heymann AC, Gunther C, Niederwieser D. Role of bone morphogenetic protein 2 in the crosstalk between endothelial progenitor cells and mesenchymal stem cells. Int J Mol Med. 2006;18(4);735-9.
16. Mont MA, Jones LC, Einhorn TA, Hungerford DS, Reddi AH. Osteoradionecrosis of the femoral head. Potential treatment with growth and differentiation factors. Clin Orthop.1998;355(Suppl):S314-35.
17. Kwon TK, Song JM, Kim IR, Park BS, Kim CH, Cheong IK, et al. Effect of recombinant human bone morphogenetic protein-2 on bisphosphonate-treated osteoblasts. J Korean Assoc Oral Maxillofac Surg. 2014;40:291-296.
18. Shah MM, Smyth MD, Woo AS. Adverse facial edema associated with off-label use of recombinant human bone morphogenetic protein-2 in cranial construction for craniosynostosis: case report. Journal of Neurosurgery.2008;1(3):255-257.
19. Nikolidakis D, Jansen JA. The biology of platelet-rich plasma and its application in oral surgery. literature review. Tissue Engineering: Part B. 2008;14:249-258.
20. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat M, Van Dyke TE. Platelet rich plasma: growth factors and pro- and anti-inflammatory properties. J Periodontol. 2007, 78:661–669.
21. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as source of proteins for healing and tissue regeneration. Thromb Haemost. 2004, 91:4–15.
22. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma. Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85:638-46.
23. Masago H, Shibuya Y, Munemoto S, Takeuchi J, Umeda M, Komori T, et al. Alveolar ridge augmentation using various bone substitutes-a web

form of titanium fibers promotes rapid bone development. Kobe J Med Sci. 2007;53:257-63.

24. Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernandez G, et al. Effect of platelet- rich plasma on sinus lifting. A randomised-controlled trial. J Clin Periodontol. 2009;36:677-87.
25. Tozum TF, Keceli HG. Treatment of peri-implant defect with modified sandwich bone augmentation. Case report and follow up. NY State Dent J. 2008;74:52-7.
26. Coviello V, Peluso F, Dehkhargani SZ, Verdugo F, Raffaelli L, Manicone PF, D' Addona A. Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients. J Biol Regul Homeost Agents. 2012;26:151–155.
27. Magesh DPU, Kumaravelu C, Maheshwari GU. Efficacy of PRP in the reconstruction of mandibular segmental defects using iliac bone grafts. J Maxillofac. Oral Surg. 2013;12(2):160-167.
28. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma(PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immunity & Ageing. 2013;10:23.
29. Bertoldi C, Pinti M, Zaffe D, Cossarizza A, Consolo U, Ceccherelli GB. Morphologic, histochemical, and functional analysis of platelet-rich plasma activity on skeletal cultured cells. Transfusion. 2009.[Medline:19413738]
30. Cochran DL, Wozney JM. Biological mediators for periodontal regeneration. Periodontology. 2000;19:40-58.
31. Rose LF, Rosenberg E. Bone grafts and growth and differentiation factors for regenerative therapy: a review. Pract Proced Aesthet Dent. 2001;13:725-734.
32. Yang D, Cheng J, Jing Z, Jin D. Platelet-derived growth factor (PDGF)-AA: a self-imposed cytokine in the proliferation of human fetal osteoblasts. Cytokine.2000; 12:1271–1274.
33. Anitua EA. Enhancement of osseointegration by generating a dynamic implant surface. J Oral Implantol. 2006, 32:72–76.
34. Curi MM, Cossolin GS, Koga DH, Araújo SR, Feher O, dos Santos MO, Zardetto C. Treatment of avascular osteonecrosis of the jaw in cancer patients with a history of bisphosphonate therapy by combining bone resection and autologous platelet-rich plasma: report of 3 cases. J Oral Maxillofac Surg 2007, 65:349–355.
35. Choi BH, Zhu SJ, Kim BY, Huh JY, Lee SH, Jung JH. Effect of platelet-rich plasma(PRP) concentration on the viability and proliferation of alveolar bone cells: an in vitro study. Int J Oral Maxillofac Surg. 2005;34(4):420-4.
36. Nagata MJ, Messora M, Pola N, Campos N, Vieira R, Esper LA, et al. Influence of the ratio of particulate autogenous bone graft/platelet-rich plasma on bone healing in critical-size defects:a histologic and histomeric study in rat-calvaria. J Orthop Res. 2010;28(4):468-73.
37. Cabbar F, Güler N, Kürkcü M, Işeri U, Sençift K. The effect of bovine bone graft with or without platelet-rich plasma on maxillary sinus floor augmentation. J Oral Maxillofac Surg. 2011, 69:2537–2547.
38. Melek LN. Tissue engineering in oral and maxillofacial reconstruction. Tanta Dental Journal. 2015:1-13.
39. Langer R, Vacanti JP. Science 1993;260:920e6.
40. Rai R, Raval R, Khandeparker RVS, Chidrawar SK, Khan AA, Ganpat MS. Tissue Engineering: Step ahead in maxillofacial reconstruction. Journal of International Oral Health. 2015;7(9):138-142.

41. Zhao H, Chai Y. Stem cells in teeth and craniofacial bones. Journal of Dental Research. 2015;94(11):1495-1501.
42. Hughes D, Song B. Dental and non dental stem cells based regeneration of the craniofacial region: a tissue based approach. Stem Cells International. 2016, Article ID 8307195.
43. Evans ND, Gentleman E, Polak JM. Scaffolds for stem cells. Material Today. 2006; 9(12):26-33.
44. Corrales PL, Esteves ML, Vick JE. Scaffold design for bone regeneration. Journal of Nanoscience and Nanotechnology.2014;14(1):15-56.
45. Burg KJ, Porter S, Kellam JF. Biomaterials developments for bone tissue engineering. Biomaterials. 2000;21(23):2347-59.
46. Salgado AJ, Coutinho OP, Reis RL. Bone tissue engineering: state of the art and future trends. Macromol Biosci 2004;4:743e65.
47. Mercado-Pagan AE, Stahl AM, Shanjani Y, Yang Yunzhi. Vascularization in bone tissue engineering constructs. Ann Biomed Eng. 2015;43(3):718-729.
48. Hunt TK. The physiology of wound healing. Ann Emerg Med 1988;17:1265-73.
49. Marx RE, Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg 1990;160:519-24.
50. Weiss SJ. Tissue destruction by neutrophils. N Engl J Med 1989;320:365-76.
51. Zamboni WA, Roth AC, Russel RC, Nemiroff PM, Casas L, Smoot EC. Effect of acute hyperbaric oxygen therapy on axial pattern skin flap survival when administered during and after total ischemia. J Reconstr Microsurg.1989;5:343-7.
52. Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. BMJ 1998;317.
53. Tibbles PM, Edelsberg JS. Hyperbaric Oxygen therapy. The New England Journal of Medicine. 1996;334(25);1612-1618.
54. Marx RE. Ames JR. The use of hyperbaric oxygen therapy in bony reconstruction of the irradiated and tissue-deficient patient. J Oral Maxillofac Surg 1982;40:412–20.
55. Grim PS, Gottlieb LJ, Boddie Allyn, Batson Eric. Hyperbaric Oxygen Therapy. JAMA.1990;263(16):2216-2220.
56. Codivilla A. On The Means Of Lengthening, In The Lower Limbs, The Muscles And Tissues Which Are Shortened Through Deformity. Am J Orthop Surg. 1905;2:353.
57. Ilizarov GA. The principles of the Ilizarov method. BullHosp Joint Dis Orthop Inst.1988;48: 1-11.
58. Snyder CC, Levine GA, Swanson HM, Browne EZ. Mandibular lengthening by gradual distraction: Preliminary report. Plast. Reconstr. Surg. 1973;51:506.
59. Mc Carthy JG, Schreiber J, Karp N, Thorne CH, Grayson BH. Lenghtening the human mandible by gradual distraction. Plast. Reconst. Surg. 1992;89(1):1-8.
60. Costantino PD, Johnson CS, Friedman CD,Sisson GA. Bone regeneration within a human segmental mandible defect: A preliminary report. American Journal of Otolaryngology. 1995;16(1):56-65.
61. Herford AS. Use of a Plate-Guided Distraction Device for Transport Distraction Osteogenesis of the Mandible. J Oral Maxillofac Surg. 2004;62:412-420.
62. Dubernard JM, Lengele B, Morelon E, Testelin S, Badet L, Moure C, et al. Outcomes 18 months after the first human partial face transplantation. N Engl J Med. 2007;357(24):2451-2560.

63. Coffman KL, Siemionow MZ. Face Transplantation: Psychological outcomes at three-year follow up. Psychosomatics. 2013;54:372-378.
64. Gordon CR, Siemionow M, Zins J. Composite tissue allotransplantation: a proposed classification system based on relative complexity. Transplant Proc.2009;41:481-484.
65. Charnley J. The bonding of prosthesis to bone by cement. J Bone Joint Surg. 1961;46-B:518.
66. Goh BT, Lee S, Tideman H, Stoelinga PJW. Replacement of the Condyle and Ascending Ramus by a Modular Endoprosthesis in Macaca fascicularis. Part 1. J Oral Maxillofac Surg 2009.
67. Henshaw R, Malawer M. Musculoskeletal cancer surgery treatment of sarcomas and allied diseases. Review of endoprosthetic reconstruction in limb-sparing surgery. Kluwer Academic Publishers. 2001;381-401.
68. Riede U, Luem M, Ilchmann T, et al. The M.E Müller straight stem prosthesis: 15-year follow-up. Survivorship and clinical results. Arch Orthop Trauma Surg. 2007;127:587.
69. Jasty MJ, Floyd WE III, Schiller AL, et al. Localised osteolysis in stable, non-septic total hip replacement. J Bone Joint Surg Am. 1986;68:912.
70. Massin P, Chappard D, Flautre B, et al. Migration of polyethylene particles around nonloosened cemented femoral components from a total hip arthroplasty—An autopsy study. J Biomed Mater Res B Appl Biomater. 2004;69:205.
71. Mohler CG, Callaghan JJ, Collis DK, et al. Early loosening of the femoral component at the cement-prosthesis interface after total hip replacement. J Bone Joint Surg Am.1995;77:1315.