Maxillofacial Defects and the Use of Growth Factors

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KEYWORDS

• Maxillofacial defects • Regenerative medicine • Grafts • Growth factors • BMP

KEY POINTS

- Growth factors can be used in addition to or as an alternative to conventional reconstruction techniques for maxillofacial defects.
- Recombinant human bone morphogenic protein-2 has been shown to be the most promising among the growth factors, showing good results when applied in clinical studies.
- The clinical applications of growth factors may represent a solution or alternative to the need for donor sites and improve qualitative and quantitative bone healing.
- The lack of information concerning doses, indications, and/or adverse reactions and complications still limits the use of growth factors as routine treatment.

INTRODUCTION

Despite recent advances in regenerative medicine, reconstruction of maxillofacial defects remains a challenge. These challenges stem from the complex set of criteria that needs to be met for a successful substitute to restore, maintain, and improve tissue function. There are many causes of tissue loss, including trauma, pathologic processes, and congenital anomalies. The resulting characteristics such as the size, geometry, and vascularity of the defects dictate the surgical options available for treatment. Grafting of the defective site can be performed with different biomaterial options. Autologous bone grafts and free vascularized fibular grafts are considered to be the gold standard for treating these defects.[1]

Autogenous bone grafts have the advantage of stimulating bone regeneration through osteoinduction while avoiding an immunologic reaction. For large continuity defects, harvested iliac crest bone is used in conjunction with reconstruction plates. Continuity defects involving the removal of a malignancy will often result in both a hard and soft tissue defect that may best be treated with free tissue microvascular flaps.[2] These flaps can be suitable options for patients who are undergoing radiotherapy. Although holding a high success rate for reconstructing bone defects, the limitations surrounding the use of autogenous flaps arise from donor site morbidity and the variable quantity and quality of tissue harvested. The chosen donor site may not provide adequate bone graft material for the defect, depending on the size. Other adverse events include damage to adjacent structures, infection, and prolonged pain at the donor site. Bone grafting can have unpredictable resorption and difficulties in maintaining closure of the soft tissue over the graft.[3,4] Although they provide the most biocompatible option, the disadvantages of autogenous grafts have driven the search for alternatives.

Allogeneic bone grafts provide an attractive alternative option to regenerate bone defects. These types of bone grafts provide an osteoconductive scaffold for bone ingrowth without the

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associated morbidity of an autograft. A primary disadvantage of allograft bone as a graft option is the loss of the majority of its associated growth factors during the sterilization process.[5] The significant changes to its architecture allows for bone ingrowth from the perimeter of the defect rather than new bone formation de novo. To accomplish the regeneration of a bone defect, the bone margins must exceed the rate of fibrogenesis growing in from the surrounding soft tissue.[6] Because of the limitations of this type of graft, allografts may be successful in small defects but are rather limited for larger defects.

The surgeon must weigh the risks specific to autograft harvest versus the limited ability of bone regeneration associated with allograft materials when planning the reconstruction of maxillofacial defects. The addition of growth factors combined with various types of graft materials and techniques have shown to be a promising effort in the improvement of bone regeneration.

GROWTH FACTORS

Growth factors are defined as a group of proteins capable of stimulating cellular growth, migration, proliferation, and differentiation. These signaling molecules can generate different kinds of effects by upregulating or downregulating the synthesis of proteins and receptors.[7–9] The importance of the role of these molecules is well-recognized, even if all the mechanisms involved are not completely known. Growth factors are involved in tissue formation beginning in the embryologic phases. Mutations in the genes that code for these proteins can cause various craniofacial skeletal anomalies resulting in certain syndromes (ie, Apert syndrome, Crouzon syndrome, and the achondroplasia syndromes).[10]

With the advances in recombinant technology, growth factors and biologics have become available as an alternative to traditional grafting procedures. Growth factors have been used to augment bone formation with various grafting techniques. Several of these signaling molecules have been studied for their inductive regenerative potential such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), platelet-derived growth factor (PDGF), platelet rich Plasma (PRP), and bone morphogenic proteins (BMPs).[11,12]

VASCULAR ENDOTHELIAL GROWTH FACTOR

For proper healing to take place, the defect must have appropriate vascularization. Much of the formation and maintenance of angiogenesis is orchestrated by VEGF. It has been well-documented that VEGF, as a part of the cascade, controls bone development during the promotion of vascular structures, particularly in the process of bone healing, by acting on osteoblasts.[13–15] Just as blood vessel formation does not occur at 1 specific time, the deposition of 1 particular type of VEGF at a high concentration within a defect is not likely to produce a vasculature system. The release of VEGF over time and other confounding factors create a unique challenge in creating a vasculature that could support a regenerative tissue construct. A temporal formulation of VEGF, applied locally at the site of bone damage, may prove to be an effective therapy to promote human bone repair.[14,16] Zhang and colleagues[17] investigated the effects of VEGF alone and in association to BMP-2. They observed how the application of a single angiogenic agent was not sufficient for bone generation. However, the effect of VEGF simultaneously applied with BMP-2 enhanced the bone formation, in terms of both density and volume. Furthermore, VEGF was significantly effective in increasing the resorption speed of the carrier used in the study.

FIBROBLAST GROWTH FACTOR

The role of FGFs and their receptors in fracture healing has been widely analyzed and discussed. In small and large rodents and nonhuman primates, FGF2 has been found to stimulate the proliferation of periosteal cells, osteoprogenitors, and chondrogenitors, enhancing callus formation.[18] FGF application, with FGF2 above all, has been studied for promoting fracture healing. However, some studies showed that FGF2 treatment was not effective in increasing bone mineral density or mechanical strength of the callus.[19] This can be explained by suggesting that the effect of FGF on bone formation is biphasic, with inhibitory effects at high doses.[18] Kawaguchi and colleagues[20] showed instead how topical application of recombinant human FGF2 shortens the healing time of tibial shaft fracture, with a higher percentage of radiographic bone union. These papers suggest that FGFs' usefulness is not clearly demonstrated, however, a precise, time-controlled regulation of FGF signaling during bone healing may be helpful in bone-regenerative procedures, including those of the oral cavity.

PLATELET-DERIVED GROWTH FACTOR

PDGF has an active role in the wound healing processes of various tissues, including bone. The most important specific activities of PDGF include