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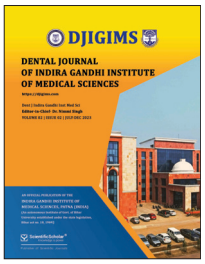

Review Article

The Impact of INFUSE A Novel Biomaterial in Periodontal Regeneration—A Review of Literature

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ABSTRACT

Bone morphogenetic proteins (BMPs) are critical bone regeneration and repair regulators, offering promising alternatives to traditional autogenous bone grafts. Recombinant bone morphogenetic protein-2 (rhBMP-2) derived from human origin has emerged as a significant osteoinductive agent capable of inducing the mesenchymal stem cells to convert into osteoblasts, thus promoting the formation of bone. The FDAapproved rhBMP-2/ACS (absorbable collagen sponge) combination demonstrates efficacy in spinal fusion, sinus augmentation, and alveolar ridge augmentation. Mechanistically, BMP-2 induces endochondral and intramembranous bone formation through specific receptor-mediated signalling pathways, activating Smad proteins and subsequent gene regulation. In dental applications, rhBMP-2 enhances the success of implants, supports periodontal regeneration, and optimizes bone regeneration outcomes. Despite its benefits, challenges include high costs, technique sensitivity, and risks of ectopic bone formation and inflammation. Clinical trials and studies continue to validate its efficacy across various orthopedic and maxillofacial applications, emphasizing its role in optimizing bone healing while reducing the need for additional surgical interventions. This review explores the mechanisms, benefits, limitations, and clinical applications of rhBMP-2 in bone regeneration, highlighting its impact on advancing dental and orthopedic therapeutic strategies.

Keywords: Bone morphogenic protein, INFUSE, Periodontal regeneration, Recombinant human bone morphogenetic protein-2.

INTRODUCTION

Bone is an intricate biological tissue with an elaborate hierarchical nanocomposite architecture. Significant physiological and pathological bone defects can considerably disrupt the natural microenvironment of the bone tissue.[1] These defects are frequently addressed through complex surgical procedures involving the use of autografts or allografts.[1] Surgeons have been exploring alternatives to autogenous bone grafts due to the complications associated with harvesting the patient's bone.[2,3] Autogenous bone grafts have long been considered the 'gold standard' and most effective material in bone regeneration procedures. Nevertheless, the limitations of this augmentation technique, such as donor site morbidity, unpredictable resorption, limited available quantities, and the necessity for additional surgical sites, encourage surgeons to seek alternatives.[4] Due to the potential morbidity linked with autogenous bone grafting, researchers sought various alternatives, with recombinant human bone morphogenetic protein-2 (rhBMP-2) being one notable option.

Human bone morphogenetic protein (rhBMP), developed through genetic engineering, was first isolated by Urist in 1965. It is recognized as a substance that can induce the differentiation of

mesenchymal stem cells into osteoblasts, the cells responsible for the synthesizing bone matrix.[5] Urist's experiment involved implanting muscle tissue into the demineralized bone matrix of a rabbit's leg, which led to the formation of ectopic bone within 3 weeks. This group comprises 12 distinct inducing molecules, each with a specific function, though they can act synergistically. They are categorized as BMP 1, 2, and 3 (osteogenin), 4 to 7 (Osteogenic Protein-1), 8 (osteogenic protein-2 ca) 9–12 in the isolated group.[5] Bone morphogenetic protein-2 (BMP-2) stands as the sole osteoinductive growth factor sanctioned by the Food and Drug Administration (FDA) for use as a bone graft substitute.[6]

rhBMP-2 is a disulfide-linked dimeric protein consisting of two major subunit species, one with 114 amino acids and the other with 131 amino acids.[7] The Absorbable Collagen Sponge (ACS) is a soft, pliable, white, absorbent implant matrix designed for rhBMP-2. ACS serves as both a carrier for the rhBMP-2 and a scaffold for new bone growth.[6] Each kit includes all the necessary components to prepare the INFUSE Bone Graft: rhBMP-2 (which must be reconstituted), sterile water, absorbable collagen sponges, syringes with needles, and instructions for preparation.[6] The rhBMP-2 is supplied as a lyophilized powder in vials containing 12 mg of protein.[6] Once reconstituted, the rhBMP-2 concentration is 1.5 mg/mL.[6] The INFUSE Bone Graft is prepared at the time of surgery and must be allowed to sit for at least 15 minutes before being placed at the augmentation site.[8,9]

In dentistry, BMPs, especially BMP-2, are extensively utilized in various procedures, including alveolar bone regeneration, sinus augmentation dental implants, as well as periodontal and dental regeneration.[10] This review article examines the significance of rhBMP-2 and its diverse clinical applications in dentistry.

Mechanism cascade of BMP

BMP induces endochondral and intramembranous bone formation from mesenchymal cells. BMPs are both mitogenic and morphogenic, i.e., they cause the multiplication of the connective cells and the transformation of connective tissue cells, respectively.[10] The bipotential osteo-chondro progenitor cells get induced by BMP and produce osteoblast and chondroblast. Inductive outcome depends on the dose, concentration, and time of action of the BMP. [9,10]

BMPs are produced inside a cell in its precursor form, where it is conjugated to its mature form. A proteolytic activity occurs, followed by the separation of the precursor form from its mature form. The separated mature form dimerizes with other BMPs. Depending on the dimerization with other BMPs, it can be either homodimers or heterodimers.[11]

BMP receptors

BMPs bind to the cell surface through two receptors, Type I, and Type II serine/threonine kinase receptors. There are three types of type II receptors: BMP type II receptor, Activin type II receptor, and Activin type II B receptor. BMP type II receptor is specific for BMP. It has long and short forms. The long form is expressed in most cells, while the short form is expressed in specific cells. The type I receptors for BMP are ALK-3, ALK-6, ALK-2 and ALK-1.[12] The primary binding site is the type II receptor. Over its activation, phosphorylation of the Type I receptor occurs. BMP-2 binds to ALK-3 and ALK-6.

The activated type I receptors phosphorylate the Smad-1, Smad-5, and Smad-8 proteins, which in turn form complexes with Smad-4. Hence the formed complex together moves into the nucleus and binds to the target genes to regulate the transcriptional responses for cell differentiation. In addition, a number of negative regulators of BMP action exist within the nucleus. Together, these regulatory mechanisms tightly control and limit the bone-induction process.[13]

Implantation of the BMP-2 induces cartilage by day 7 and bone by day 14. At high doses, it can induce bone even on the day of 5.

Beneficial aspects of rhBMP in dentistry

1. Improved success rate in dental implants
   rhBMP-2/ACS is effective in inducing bone following a maxillary sinus floor augmentation procedure, which can support the placement and long-term functional loading of dental implants in approximately 75% to 80% of the patients treated.[9]
2. Periodontal regeneration
   Animal studies show that a single dose of rhBMP-2 increases the rate of normal intramembranous bone formation and enhances cementum formation during periodontal wound healing.[14]
   The anabolic effect of BMPs on periodontal tissues is through stimulation of osteoblastic differentiation in human PDL cells and by stimulation of alkaline phosphatase activity in periosteal cells, thus enhancing the regeneration of new connective tissue attachment and bone in both root-submerged and non-submerged environment. Thus concluding that BMPs offer promise as an attractive candidate for treating severe periodontal lesions with significant potential for stimulating periodontal regeneration.[15]
3. Enhanced bone regeneration:
   BMP-2 also induces osteoblast differentiation and regulates angiogenesis and new bone formation.[1]

4. Optimizing outcomes:
   The circumstantial use of BMP-2 has the capability to decrease the prevalence of repeated surgical re-entry, trauma, complications, and additional medical costs.[16]

Disadvantages

1. Unpredictable outcomes
   Application of rhBMP-2 might have a limited function because the patients in this study are very old, and their healing capacity is, therefore, more impaired than that in younger people. Moreover, rhBMP-2 has a relatively short life at the operation site.[17]
2. Technique sensitive
   When working with rhBMP, caution should be taken because it is a very sensitive material regarding technique; any error in handling can lead to unsatisfactory results.[5]
3. High cost
   When rhBMPs are compared to PRPs (platelet-rich plasma), the main disadvantages of the morphogenetic proteins are the high cost and the need to use a carrier agent.[5]
   The degradation rate of the carrier matrix should be in sync with the rate of bone regeneration. If the matrix degrades too slowly, it will inhibit bone growth and retard the remodeling process.[11]
4. Ectopic bone formation
   The most recognized adverse event related to BMP-2 use is ectopic bone formation associated with BMP-2 leakage outside the implant site.[7]
5. Inflammation and swellings
   A significant host of side effects is associated with the induction of local inflammation secondary to BMP-2 implantation. These range from benign seroma formations to life-threatening effects, such as cervical spine swelling.[7]

CLINICAL APPLICATION

Calcium phosphate (CaP) bioceramics are mostly used as bone substitutes in clinical practice and low doses of recombinant human bone morphogenetic protein-2 (rhBMP-2) (approved by the FDA).[18] In 2002, INFUSE® Bone Graft was approved by the US Food and Drug Administration (FDA) as a replacement for autogenous bone graft in anterior lumbar interbody fusion (ALIF), used in combination with the LT-CAGE® Lumbar Tapered Fusion Device (Medtronic Spinal and Biologics, Memphis, TN).[19] Spine surgeons began to develop surgical techniques for conducting interbody fusion procedures through posterior lumbar interbody fusion (PLIF) and, later, transforaminal lumbar interbody fusion (TLIF) procedures.[20] The approval of INFUSE® Bone Graft for use in open tibia fractures in 2004 was the culmination of over a decade of preclinical and clinical development.[21] In March 2007, INFUSE® Bone Graft was approved by the FDA as an alternative to autogenous bone graft for sinus augmentations and for localized alveolar ridge augmentations for defects associated with extraction sockets.[22,23] The efficacy of bone-derived BMPs (BMP 2, osteogenin, osteoprotein 1) for regeneration in surgically created large furcation defects in the mandibular first and second molar was investigated in adult male baboons (Papio ursinus).[24] BMP 7 gene transfer not only enhanced alveolar bone repair but also stimulated cementogenesis and PDL fiber formation.[25] BMPs have been approved for clinical use in vertebral arthrodesis, nonunions, and open fractures of long bones after their definite osteoinductive ability was confirmed by several preclinical and clinical studies.[26-28] Recombinanthumanbonemorphogeneticprotein-2 (rhBMP 2) is an activation factor for bone repair.[29] Teriparatide has recently been approved for osteoporosis management and has shown accelerated healing of vertebral and long bone fractures.[30]

CONCLUSION

Multiple studies have shown that rhBMP-2/ACS at a concentration of 1.5mg/cc is comparable to that of gold standard autogenous bone graft. BMPs play a crucial role in bone induction and maintenance. In dentistry, BMPs, particularly BMP-2, are widely employed in regenerative procedures such as extraction socket healing, maxillary sinus augmentation, bone regeneration in osteonecrosis of the jaw, and periodontal regeneration. Despite advancements, further research is still needed to develop innovative biomaterials for BMP delivery, particularly for periodontal and craniofacial applications, as well as dentin regeneration in teeth.

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