RSBO Revista Sul-Brasileira de Odontologia
ISSN: 1806-7727
fbaratto@uol.com.br
Universidade da Região de Joinville
Brasil

Rocha Valadas Marques, Lídia Audrey; Alves da Costa Júnior, Edvan; Assef Leitão Lotif, Mara; Martins Rodrigues Neto, Edilson; Carvalho da Silva, Francisco Filipe; de Queiroz Martiniano, Carlos Ricardo
Application of BMP-2 for bone graft in Dentistry
RSBO Revista Sul-Brasileira de Odontologia, vol. 12, núm. 1, enero-marzo, 2015, pp. 88-93
Universidade da Região de Joinville
Joinville, Brasil

RSBO

ISSN:
Electronic version: 1984-5685
RSBO. 2015 Jan-Mar;12(1):88-93

Literature Review Article

Application of BMP-2 for bone graft in Dentistry

Lídia Audrey Rocha Valadas Marques[1]
Edvan Alves da Costa Júnior[1]
Mara Assef Leitão Lotif[1]
Edilson Martins Rodrigues Neto[2]
Francisco Filipe Carvalho da Silva[1]
Carlos Ricardo de Queiroz Martiniano[1]

Corresponding author:
Carlos Ricardo de Queiroz Martiniano
Rua Carolina Sucupira, n. 1.985, ap. 402 – Cocó
CEP 60140-120 – Fortaleza – CE – Brasil
E-mail: cricardo.martiniano@gmail.com

[1] Department of Dental Clinics, School of Pharmacy, Dentistry, and Nurse, Federal University of Ceará – Fortaleza – CE – Brazil.
[2] Department of Physiology and Pharmacology, School of Medicine, Federal University of Ceará – Fortaleza – CE – Brazil.

Received for publication: January 21, 2014. Accepted for publication: November 24, 2014.

Keywords: dental implants; maxillary sinus; biocompatible materials.

Abstract

Introduction: The global increase life expectancy and the resulting tooth loss has required searching for new rehabilitation alternatives in Dentistry. Biomaterials can be defined as any material that acts replacing a lost bone defect and its function. In Dentistry, many studies have aimed to improve bone regeneration through the use of BMPs for bone replacement. **Objective:** To review the literature on the use and clinical viability of human morphogenetic protein for the jaws reconstruction. **Material and methods:** The following databases were searched: Pubmed, Bireme, Lilacs, and Scielo and 30 articles published between 1965 and 2013 were found using the following descriptors: "dental implants", "maxillary sinus", and "biocompatible materials". **Results:** Several studies demonstrate the biological advantages of rhBMP-2 on bone regeneration of the jaws. In recent years, morphogenetic protein has presented a large clinical use. **Conclusion:** Despite being a high-cost biomaterial, rhBMP-2 is a viable and very effective alternative for reconstruction of defects of the face.

Introduction

The increased expectation of worldwide life and the consequent tooth loss have required more and more of Dentistry the search for viable alternatives to oral rehabilitation [20].

After the scientific evidence of osseointegration in the ending of the 1970s, which made viable Implantology, increased the interest of researchers in search by new natural or synthetic substances that could replace tissues bone lost [9]. In Dentistry autogenous bone is the most useful tissue used in pre-prosthetic surgery and rehabilitation treatment of bone defects, thereby contributing to the function and aesthetics [8].

Biomaterials can be defined as "any material, natural or synthetic, that acts in tissues/organs in order to replace the bone defect lost and s function" [13]. The biomaterials may be considered autogenous when the bone is taken from the individual to be treated; halogens, when the gathered from another individual of the same species, and heterogeneous, when taken from other species [6].

The human bone morphogenetic protein (rhBMP) developed by genetic engineering, was isolated by Urist, in 1965, and it is considered a substance capable of inducing differentiation of mesenchymal stem cells into osteoblasts, the cells that are responsible for the synthesis of bone matrix. Research given to BMPs the capacity of fracture repair, osteogenic, osteoinductive, and osteoconductive potential of the graft [22].

In Dentistry, many studies have aimed to improve bone regeneration through the use of BMPs for bone replacement. Because of the osteoinductive capacity, BMPs have various application possibilities in the Dentistry, raising great interests in various specialties, especially in the Implantology, assisting in osseointegration [30].

The aim of this study was to conduct a literature review on the use and clinical viability of human bone morphogenetic protein (rhBMP-2) for grafting bone in Dentistry.

Literature Review

Grafts in Implantology

The success of rehabilitation with dental implants is directly related to the amount of bone tissue of the patient. As the resorption is something common mainly in older patients, it is increasingly common the application of techniques for maxillary sinus augmentation by using grafts. In addition, tumors, congenital deformities, trauma, among others, may require the need for reconstruction of jaws [14, 25].

The autogenous graft type, considered the gold standard, is best used for the rehabilitation of the jaws, because of their osteogenic, osteoconductive, and osteoinductive properties. However, autogenous grafts require a second surgical site, and the bone is removed normally from the mandibular ramus, chin, skullcap, iliac, or tibia. The need for a second surgical site makes the surgical process more complex with side effects to the patient [27].

The homogenous and heterogeneous grafts lack of living cells, since pass through a process of purification, but may show osteoconductive or osteoinductive features. The great advantage of these two types of graft is that they do not need a second surgical site, which makes the reconstructive procedure faster, safer, and less complex [8].

The biomaterial for optimal bone grafting should be osteogenic, osteoinductive, osteoconductive, be biologically inert, and have fast revascularization activity [8].

History and classification of rhBMPs

Urist [28] conducted an innovative experiment and with very promising results, in which muscle tissue was implanted on rabbit leg in demineralized bone matrix. After 3 weeks, it was observed the formation of ectopic bone. Thus, it was concluded that the bone matrix contained some important factor capable of performing a self-induction. This factor was called bone morphogenetic protein (BMP). The initial advancement led to the study of several researchers seeking to isolate and clone the inductive entity. Actually it is known that it is not only one but several growth factors.

Currently, despite the knowledge of the capacity, by manipulation of the medium, of differentiating in osteoblasts, the mechanisms that govern these actions are not fully elucidated [21]. The molecular bases of bone morphogen protein, which mostly belong to the superfamily of transformation growth factor β (TGF-β) accounts for these mechanisms [15]. It is known that this set of proteins is made up of 12 different types of inducing molecules, each of which develops a specific function, and may also perform joint actions by interacting among each other. Thus, they are classified as: BMP 1, 2, and 3 (osteogenin); 4 to 7 (Osteogenic Protein-1); 8 (osteogenic protein-2 ca); 9-12 in isolated group [23].

Mechanisms of rhBMPs

The rhBMPs may be defined as signaling glycoproteins, and members of the superfamily of growth factor β (TGF-β), capable of recruiting osteoprogenitor cells to sites of bone formation, and are macromolecules of essential role in the repair process and bone growth. The osteoinductive action of autogenous and demineralized homogenous bone matrix graft may also be attributed to that protein. Nakashima [15] found that these proteins stimulated mitosis of mesenchymal stem cells because they have the ability to turn on specific receptors, as serine/threoninacinase and induce differentiation of precursor cells of osteodentin tissue, which are osteodentinocytes. The osteodentin, major component of dental matrix newly formed, seems to have a coadjutant role in the differentiation of osteoblasts, because in its absence, promising results were not obtained [15, 24].

Accordingly, the rhBMPs can be used in the reconstruction of bone tissue, having well-established benefit in Dentistry and Orthopedics, since they are able to induce migration, proliferation and differentiation of mesenchymal stem cells into secretory osteoblasts and form bone [7].

Brand and product

Bone morphogenetic proteins are obtained by genetic engineering techniques. They are produced by genetic recombination in *Escherichia coli* and sold as lyophilized powder in sterile vial, ready for use. This lyophilized powder associated with a vehicle benefits the bone-implant interface, accelerating osseointegration [12, 19].

The rhBMP commercially available and approved by FDA in the United States currently are: rhBMP-2 Infuse (Medtronic Sofamor Danek, Memphis, Tennessee) and OP1 (Stryker Biotech, Hopkinton, MA). Other BMP products are currently being evaluated for commercial use include BMP-X (Sulzer Biologics, Wheat Ridge, Colorado), BMP -9, and combinations of BMP animal and human [1].

Hu *et al.* [11] stated that BMP-9 is one of the most potent forms between 12 rhBMP types in the induction of osteogenic differentiation of mesenchymal progenitor cells, both *in vitro and in vivo,* through the regulation of several major targets during differentiation of the rhBMP-9 osteoblasts induced.

Application Form

A bone graft BMPs kit is used for the repair and bone growth, and after handling BMP is directly placed on the site. In addition, carrier agents are needed to make the diffusion agents among cells to facilitate osteoinduction [14].

The optimum carrier substrate should provide the following characteristics: relative insolubility under physiological conditions; to be biodegradable; to protect the tissue against proteolytic activities; to function as substrate for cell adhesion and proliferation; to be inert immunologically; to obtain the slow and controlled release of rhBMP through controlled biological degradation; and to have mechanic stability to unite bone defects [10].

Among the biomaterials tested as carriers, various extracellular matrix components may be used alone or in combination, for example: collagen, fibronectin, glycosaminoglycans, calcium hydroxide, and calcium phosphate [10].

The spongy bone graft has been considered an ideal carrier. It acts as a scaffold promoting early vascularization and osteoinduction, and provides osteogenic cells, is biocompatible, and has the ability to adapt to bone failures [14].

A rhBMP-2 Infuse® is marketed in package containing all the components needed to prepare the bone inducing component Infuse®: rhBMP-2 lyophilized powder to be reconstituted, sterile water, absorbable collagen sponge, syringe with needles, and preparation instructions. The number of each item may vary depending on the size to be used. The rhBMP-2 is provided as a lyophilized powder in vials with 4.2 mg or 12 mg of protein. After proper reconstitution, both sets result in the same formulation and concentration (1.5 mg/cc) of rhBMP-2 [5].

According to the manufacturer, the Infuse® bone graft should be prepared at surgery time, always 30 minutes before the application of the material in the surgical site. With the aid of syringe and needle, the sterile water must be removed from the bottle and inject in the vial containing rhBMP-2, then mix slowly without stirring and leave at least 15 minutes at rest for complete dissolution. The original packaging IS opened and puts the absorbable collagen sponge in sterile field. With the aid of the second syringe, the reconstituted bone graft is removed from ampule and is applied uniformly in the sponges. The moist sponges should rest for at least 15 minutes (time for incorporation of the protein to the sponge) and must be used within two hours (for avoiding the drying of the sponge) [5].

Advantages of rhBMP-2

The regenerative activity and bone induction of rhBMP-2 has been extensively studied by researchers

of Genetic Engineering, which its advancement allowed the characterization, cloning and large-scale commercial production. Studies evaluating the association of rhBMPs with biomaterials showed to be a viable and effective alternative to make bone regeneration ease [30].

Since the discovery of rhBMP, several studies have demonstrated the biological advantages of rhBMP-2 and significant rehabilitation on bone formation in studies both on rats and humans, which takes about six months [29].

A study evaluated the applicability of rhBMP-2 in a collagen sponge after it had been applied in bone defects. It was observed that after 12 weeks the mean neoformation and bone density in the group that received rhBMP-2 was nearly 4 times greater than that of the control group [18].

In recent years, the morphogenetic protein has been highly successful for the reconstruction of the jaw defects and large defects of the face. The great advantage compared to autogenous bone is that it eliminates the need for a second surgical site, which considerably increased the surgery time, and bone removal from another area as the iliac, tibial or skullcap [2, 14].

Clinical trials that studied the effect of BMP-2 in collagen sponges regarding to bone deposition detected a significant growth and bone formation in the surgery of maxillary sinus lifting. In addition, other studies show that rhBMP-2 has been successful in complex treatments of the face, as congenital jaw defects in alveolar atrophy, and maxillary fissures [18].

The association of rhBMP-2 with homogenous graft also showed favorable clinical outcomes in peri-implant bone resorption [18].

Disadvantages of rhBMP-2

The morphogenetic proteins are readily diffusible and soluble in water, so they must be applied with a carrier so that an effective inducing effect is established [10].

The carrier systems for rhBMPs still require research to optimize their formulations. The use of collagen isolated or associated with carrier systems, although widely used, has some disadvantages that must be observed, such as poor mechanical stability, immune response and potential for transmission of viral antigens [10].

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 [12].

Although the studies show good results in the process of the osteoinduction, they do not quantify the value of the speed increase of the process when using rhBMPs [12].

When working with rhBMP, caution should be taken, because it is a very sensitive material regarding to technique, any error in handling can lead to unsatisfactory results. The effectiveness of this material may be affected by factors such as amount, qualitative composition, possible presence of inhibitors, processing and storage. And, for the inductive result, the dose, concentration, and time of action of rhBMPs are influencing factors [26].

The multiple rhBMPs forms already identified demand new studies, which may happen slowly, due to the high costs involved in research with morphogenetic proteins. Such researches are needed to determine the choice for the most appropriate factor for each therapy and also enable the direction of new techniques [10].

The literature presents many advantages in the use of various forms of morphogenetic proteins, but the studies are still few compared to various therapeutic applications of rhBMP, beyond the specialties of Dentistry. This may occur because of the high costs needed to develop research with this material.

Discussion

Undoubtedly, the advances in Genetic Engineering have brought new viable and effective alternatives for Dentistry. These included, biomaterials stand out, and researches associated with the use of rhBMPs emerge as another option for new bone formation. Among the group consisting of the rhBMP proteins, rhBMP-2 showed higher expression in human bone in scientific research [13].

Yonezawa *et al.* [29] and Padovan *et al.* [18], in studies with the use of morphogenetic proteins, demonstrated positive results in terms of bone formation and density, implying a significant rehabilitation for critical defects and alveolar bone grafting.

In another study, in which the bone formation was investigated in the maxillary sinus of goats using rhBMP-2 in an absorbable collagen sponge, the osteoinductive capacity of the protein was proven without side effects [13]. The authors also claim that rhBMP-2 really is an alternative for maxillary sinus lifting in humans.

A clinical trial with 160 patients, in which the effectiveness of rhBMP-2 was compared to

autogenous bone in maxillary sinus lifting and installation of dental implants, concluded that bone formation in height was the same in both groups [16].

The study of Cruz *et al*. [4] found that progenitor cells derived from human adipose tissue expressed rhBMP-4, endogenous rhBMP-7. On the other hand, the supplementation of progenitor cells derived from adipose tissue with rhBMP-2 did not increase the level of osteogenic markers at the initial phase (activity of alkaline phosphatase), at the intermediate phase (osteonectin and osteocalcin), or final phases (calcium deposition), suggesting that the exogenous addition of rhBMP-2 did not improve the process of osteogenesis *in vitro* of progenitor cells derived from adipose tissue human.

Oliveira *et al*. [17] evaluated the healing of tibial defect induced in dogs. Eighteen adult dogs were divided into three groups of six dogs each. The defects were filled with bone collagen sponge. In group 1 (G1), a sponge added with 0.9% saline solution was used; in G2, a sponge added with processed autologous mononuclear bone marrow cells was used; and in G3, a sponge added with processed autologous mononuclear bone marrow cells and rhBMP-2 was used. Although G2 presented a better result than G1, bone growth in G3 (supplemented with rhBMP-2) showed the best results in the analyses of 15 and 30 days after the start of the experiment. Forty-five days later, 50% of this group of dogs already had complete healing of the bone defect [17].

Despite the excellent results obtained in various researches and clinics using rhBMP-2, little is reported in the literature on the adverse effects and complications that can occur when using this graft material. Carragee *et al*. [3] criticized the industry to report that it is a product that has no risk, even when several studies suggest the opposite. The same study did a survey on adverse effects using rhBMP-2 in human spinal surgeries and obtained as possible complications: infection, malignancy risk at high doses, morbidity (pain and functional impairment), ectopic bone formation, retrograde ejaculation and urogenital adverse effects.

Conclusion

The morphogenetic proteins have major clinical applications; however, research is still necessary to establish proper techniques for the use of rhBMP s for each specific case. In Implantology, rhBMPs emerged as the major substitute to autogenous bone grafting, especially for its osteoinductive characteristics and for dispensing the need of a second surgical site to the patient. Notwithstanding, the high costs of this biomaterial still prevent many individuals to benefit and that researches are developed.

References

1. Bagaria V, Prasad V. Bone morphogenic proteins: current state of the field and the road ahead. J Orthopaedics. 2005;2(4):30-3.

2. Balaji SM. Augmentation of residual alveolar bone height with tissue engineering for dental implant placement. Indian Journal of Dental Research. 2014;25(3):410.

3. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 2011;11(6):471-91.

4. Cruz ACC, Silva ML, Caon T, Simões CMO. Addition of bone morphogenetic protein type 2 to ascorbate and β-glycerophosphate supplementation did not enhance osteogenic differentiation of human adipose-derived stem cells. J Appl Oral Sci. 2012;20(6):628-35.

5. Dabasons. Infuse® rhBMP-2 indutor ósseo [cited 2013 Nov 11]. Available from: URL:http://www.bmp2.com.br/infuse.php.

6. Dalapicula SS, Vidigal Junior GM, Conz MB, Cardoso ES. Características físico-químicas dos biomateriais utilizados em enxertias ósseas: uma revisão crítica. Implant News. 2006;3(1):487-91.

7. Esposito M, Grusovin MG, Coulthard P, Worthington HV. The efficacy of various bone augmentation procedures for dental implants: a Cochrane systematic review of randomized controlled clinical trials. Int J Oral Maxillofac Implants. 2006;21(5):696-710.

8. Fardin AC, Jardim ECG, Pereira FC, Guskuma MH, Aranega AM, Garcia Junior IR. Bone graft in dentistry: review of literature. Innov Implant J Biomater Esthet. 2010;5(3):48-52.

9. Faverani LP, Ferreira GR, Jardim ECG, Okamoto R, Shinohara EH, Assunção WG et al. Implantes osseointegrados: evolução sucesso. Salusvita. 2011;30(1):47-58.

10. Gonçalves EAL, Guimarães SAC, Garcia RB. Proteínas morfogenéticas ósseas: terapêutica molecular no processo de reparo tecidual. Rev Odontol Univ. 1998;12(3):299-304.

11. Hu N, Jiang D, Huang E, Liu X, Li R, Liang X et al. BMP9-regulated angiogenic signaling plays an important role in the osteogenic differentiation of mesenchymal progenitor cells. J Cell Sci. 2013;126(2):532-41.

12. Loureiro CCS. PRP ou BMPs: qual a melhor opção para enxertia e aceleração de osseointegração nas reabilitações com implantes? Revisão de literatura. Innov Implant J. 2010;5(2):45-50.

13. Martins JV, Perussi MR, Rossi AC, Freire AR, Prado FB. Biomaterials used in maxillary sinus lifting surgery: clinical approach. Revista Odontológica de Araçatuba. 2010;31(2):22-30.

14. Misch CM. The use of recombinant human bone morphogenetic protein-2 for the repair of extraction socket defects: a technical modification and case series report. Int J Oral Maxillofac Implants. 2010;25(6):1246-52.

15. Nakashima M. Induction of dentine formation on canine amputed pulp by recombinant human bone morphogenetic proteins (BMP) -2 and -4. J Dent Res. 1994;73(9):1515-22.

16. Oliveira EMF, Vitorino NS, Freitas PHL, Wassal T, Napimoga MH. Uso de proteínas recombinantes na reconstrução de maxilares. Rev Gaúcha Odontol. 2011;59(3):491-6.

17. Oliveira GK, Raiser AG, Olsson D, Salbego FZ, Martins DB, Dezengrine R et al. Células-tronco mononucleares autólogas e proteína óssea morfogenética na cicatrização de defeitos tibiais experimentalmente induzidos em cães. Arq Bras Med Vet Zootec. 2010;62(1):72-9.

18. Padovan LEM, Luiz J, Claudino M. Aplicabilidade da rhBPM-2 em procedimentos de enxertia: relato de caso. J ILAPEO. 2013;7(2):20-7.

19. Ramazanoglu M, Lutz R, Ergun C, von Wilmowsky C, Nkenke E, Schlegel KA. The effect of combined delivery of recombinant human bone morphogenetic protein-2 and recombinant human vascular endothelial growth factor 165 from biomimetic calcium-phosphate-coated implants on osseointegration. Clin Oral Implants Res. 2011;22(12):1433-9.

20. Ribeiro DG, Silva MM, Nogueira SS, Arioli Filho JN. A saúde bucal na terceira idade. Salusvita. 2009;28(1):101-11.

21. Rutherford RB, Wahle J, Tucker M, Rueger D, Charette M. Induction of reparative dentine formation in monkey by recombinant human osteogenic protein-1. Archs Oral Biol. 1993;38(7):571-6.

22. Santos AA, Miranda CDO, Alves MTS, Faloppa F. The role of bone morphogenetic protein on bone tissue repair. Acta Ortop Bras. 2005;13(4):70-7.

23. Six N, Lasfargues JJ, Goldberg M. Differential repair responses in the coronal and radicular areas of the exposed rat molar pulp induced by recombinant human bone morphogenetic protein-7 (Osteogenc Protein-1). Arch Oral Biol. 2002;47(3):177-87.

24. Sommernan M, Hewitt AT, Varner HH, Schiffmann E, Termine J, Reddi AH. Identification of bone matrix-de-rived chemotatic factor. Calcif Tissue Int. 1983;35(1):481-5.

25. Spagnoli DB, Marx RE. Dental implants and the use of rhBMP-2. Dental Clinics of North America. 2011;55(4):883-907.

26. Sykaras N, Opperman LA. Bone morphogenetic proteins (BMPs): how do they function and what can they offer the clinician? J Oral Sci. 2003;45(2):57-73.

27. Toledo Filho JL, Marzola C, Sanchez MPR. Os enxertos ósseos e de biomateriais e os implantes osseointegrados. Rev Bras Cir Implant. 2001;8(30):126-43.

28. Urist MF. Bone: formation by autoinduction. Science. 1965;150(698):893-9.

29. Yonezawa H, Harada K, Ikebe T, Shinohara M, Enomoto S. Effect of recombinant human bone morphogenetic protein-2 (rhBMP-2) on bone consolidation on distraction osteogenesis: a preliminary study in rabbit mandibles. J Craniomaxillofac Surg. 2006;34(1):270-6.

30. Yoo D, Tovar N, Jimbo R, Marin C, Anchieta RB, Machado LS et al. Increased osseointegration effect of bone morphogenetic protein 2 on dental implants: An in vivo study. J Biomed Mater Res Part A. 2014;102A:1921-7.