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BIOLOGICAL MECHANISMS AND CLINICAL APPLICATIONS OF RHBMP-2 IN MAXILLARY BONE REGENERATION

MECANISMOS BIOLÓGICOS E APLICAÇÕES CLÍNICAS DA RHBMP-2 NA REGENERAÇÃO ÓSSEA MAXILAR

MECANISMOS BIOLÓGICOS Y APLICACIONES CLÍNICAS DE LA RHBMP-2 EN LA REGENERACIÓN ÓSEA MAXILAR

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ABSTRACT

Objective: To describe the clinical effectiveness and biological mechanisms of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary bone regeneration, emphasizing its role in replacing autogenous bone grafts in severe resorption cases and expanding prosthetic rehabilitation options.

Methodology: A narrative review of the literature was conducted through searches of PubMed, LILACS, and institutional repositories focusing on clinical applications of rhBMP-2 in bone reconstruction relevant to dental implant rehabilitation. Publications addressing sinus augmentation, ridge augmentation, and clinical reports were included to provide a

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comprehensive overview. Additionally, case evidence from clinical portals was considered to illustrate real-world clinical protocols.

Results: The evidence indicates that rhBMP-2 enhances osteoinduction by stimulating mesenchymal cell differentiation into osteoblasts, promoting new bone formation. Clinical use in alveolar ridge preservation, augmentation before implant placement, and sinus floor elevation has shown satisfactory bone regeneration that facilitates prosthetic rehabilitation without the need for extraoral grafting, reducing morbidity and treatment time.

Conclusion: rhBMP-2 is a viable biological alternative to autogenous bone grafts in maxillary bone regeneration procedures, offering predictable outcomes in complex rehabilitations. However, careful case selection, standardized protocols, and further high-quality clinical trials are necessary to establish long-term safety and optimal use.

Keywords: Bone Regeneration. rhBMP-2. Maxillary Atrophy. Dental Rehabilitation. Osteoinduction.

RESUMO

Objetivo: Descrever a efetividade clínica e os mecanismos biológicos da proteína morfogenética óssea humana recombinante-2 (rhBMP-2) na regeneração óssea maxilar, enfatizando seu papel na substituição de enxertos ósseos autógenos em casos de reabsorção severa e na ampliação das possibilidades de reabilitação protética.

Metodologia: Foi realizada uma revisão narrativa da literatura por meio de buscas nas bases PubMed, LILACS e repositórios institucionais, com foco nas aplicações clínicas da rhBMP-2 na reconstrução óssea voltada à reabilitação com implantes dentários. Foram incluídas publicações que abordaram elevação de seio maxilar, aumento de rebordo alveolar e relatos clínicos, a fim de fornecer uma visão abrangente do tema. Adicionalmente, evidências de casos provenientes de portais clínicos foram consideradas para ilustrar protocolos clínicos em situações reais.

Resultados: As evidências indicam que a rhBMP-2 potencializa a osteoindução ao estimular a diferenciação de células mesenquimais em osteoblastos, promovendo a formação de novo tecido ósseo. O uso clínico na preservação do rebordo alveolar, no aumento ósseo prévio à instalação de implantes e na elevação do assoalho do seio maxilar demonstrou regeneração óssea satisfatória, possibilitando a reabilitação protética sem a necessidade de enxertos extraorais, com redução da morbidade e do tempo de tratamento.

Conclusão: A rhBMP-2 constitui uma alternativa biológica viável aos enxertos ósseos autógenos em procedimentos de regeneração óssea maxilar, oferecendo resultados previsíveis em reabilitações complexas. Entretanto, a seleção criteriosa dos casos, a padronização de protocolos e a realização de ensaios clínicos de alta qualidade são necessárias para estabelecer a segurança em longo prazo e o uso ideal desse biomaterial.

Palavras-chave: Regeneração Óssea. rhBMP-2. Atrofia Maxilar. Reabilitação Dentária. Osteoindução.

RESUMEN

Objetivo: Describir la efectividad clínica y los mecanismos biológicos de la proteína morfogenética ósea humana recombinante-2 (rhBMP-2) en la regeneración ósea maxilar, enfatizando su papel en la sustitución de injertos óseos autógenos en casos de reabsorción severa y en la ampliación de las opciones de rehabilitación protésica.

Metodología: Se realizó una revisión narrativa de la literatura mediante búsquedas en PubMed, LILACS y repositorios institucionales, con énfasis en las aplicaciones clínicas de la rhBMP-2 en la reconstrucción ósea orientada a la rehabilitación con implantes dentales. Se incluyeron publicaciones sobre elevación del seno maxilar, aumento del reborde alveolar y reportes clínicos, con el fin de ofrecer una visión integral del tema. Adicionalmente, se consideraron evidencias de casos provenientes de portales clínicos para ilustrar protocolos clínicos en escenarios reales.

Resultados: La evidencia indica que la rhBMP-2 potencia la osteoinducción al estimular la diferenciación de células mesenquimales en osteoblastos, promoviendo la formación de nuevo hueso. Su uso clínico en la preservación del reborde alveolar, en el aumento óseo previo a la colocación de implantes y en la elevación del piso del seno maxilar ha mostrado una regeneración ósea satisfactoria, permitiendo la rehabilitación protésica sin necesidad de injertos extraorales, con reducción de la morbilidad y del tiempo de tratamiento.

Conclusión: La rhBMP-2 representa una alternativa biológica viable a los injertos óseos autógenos en procedimientos de regeneración ósea maxilar, ofreciendo resultados predecibles en rehabilitaciones complejas. No obstante, la selección cuidadosa de los casos, la estandarización de protocolos y la realización de ensayos clínicos de alta calidad son necesarias para establecer la seguridad a largo plazo y el uso óptimo de este biomaterial.

Palabras clave: Regeneración Ósea. rhBMP-2. Atrofia Maxilar. Rehabilitación Dental. Osteoinducción.

1 INTRODUCTION

Maxillary bone regeneration is a critical prerequisite for successful oral rehabilitation, particularly in patients presenting with advanced alveolar bone resorption resulting from periodontal disease, trauma, congenital anomalies, or prolonged edentulism. Insufficient bone volume and quality directly compromise implant placement, primary stability, and long-term osseointegration, thereby limiting functional and esthetic rehabilitation outcomes (Esposito et al., 2006; Buser et al., 2012). Consequently, reconstructive surgical interventions are frequently required prior to or concomitant with implant therapy.

Autogenous bone grafts have long been considered the gold standard for maxillary reconstruction due to their osteogenic, osteoinductive, and osteoconductive properties (Younger & Chapman, 1989). However, their clinical use is associated with significant limitations, including donor-site morbidity, increased operative time, limited graft availability, unpredictable resorption, and higher overall treatment burden (Ahlmann et al., 2002; Nkenke & Neukam, 2014). These drawbacks have stimulated the development of biologically active alternatives capable of inducing bone regeneration while minimizing surgical invasiveness.

Recombinant human bone morphogenetic protein-2 (rhBMP-2) has emerged as one of the most potent osteoinductive agents investigated in bone tissue engineering. Bone morphogenetic proteins (BMPs), members of the transforming growth factor-β (TGF-β) superfamily, play a fundamental role in skeletal development, fracture healing, and bone remodeling (Urist, 1965; Reddi, 2005). rhBMP-2 exerts its biological effects by binding to type I and type II BMP receptors on mesenchymal stem cells, activating intracellular signaling pathways particularly the SMAD-dependent cascade that promote osteoblastic differentiation and de novo bone formation (Carreira et al., 2014; Chen et al., 2012).

Preclinical studies have consistently demonstrated that rhBMP-2 can induce bone formation in critical-size defects, even in the absence of native osteogenic cells (Wikesjö et al., 2003). Clinically, rhBMP-2 has been applied in maxillary sinus floor elevation, alveolar ridge preservation, horizontal and vertical ridge augmentation, and reconstruction of extensive maxillary defects, with outcomes comparable to or exceeding those of autogenous bone grafts (Misch & Wang, 2011; Boyne et al., 2005). Importantly, the use of rhBMP-2 has been associated with reduced need for secondary donor sites, decreased postoperative morbidity, and shorter overall treatment times, thereby expanding rehabilitative possibilities for patients with severe maxillary atrophy (Fernandes et al., 2018).

Despite its therapeutic potential, the clinical use of rhBMP-2 remains controversial. Reported complications such as excessive postoperative edema, inflammatory reactions, and concerns related to dosage, carrier systems, and off-label applications highlight the

necessity for careful case selection and protocol standardization (James et al., 2016; Smiler et al., 2016). Moreover, heterogeneity among clinical studies regarding surgical techniques, delivery systems, and outcome assessment complicates direct comparisons and evidence synthesis.

Therefore, a comprehensive and critical evaluation of the biological mechanisms and clinical applications of rhBMP-2 in maxillary bone regeneration is essential to clarify its role as a viable alternative to autogenous grafts, identify its limitations, and guide evidence-based clinical decision-making in advanced oral rehabilitation.

2 METHODOLOGY

This study was designed as a narrative, integrative review aimed at synthesizing current scientific evidence regarding the biological mechanisms and clinical applications of recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary bone regeneration. The methodological approach was chosen to allow an in-depth exploration of both experimental and clinical aspects, integrating molecular biology, tissue engineering principles, and clinical outcomes.

2.1 LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted in major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science. Additional sources such as reference lists of relevant articles and authoritative clinical reports were manually screened to ensure completeness. The search strategy combined controlled vocabulary and free-text terms related to bone regeneration and rhBMP-2, including but not limited to:

“rhBMP-2”, “bone morphogenetic protein-2”, “maxillary bone regeneration”, “alveolar ridge augmentation”, “sinus floor elevation”, “bone tissue engineering”, and “dental implants”.

2.2 ELIGIBILITY CRITERIA

Studies were selected based on the following inclusion criteria:

- Experimental (in vitro and animal) studies investigating the biological mechanisms of rhBMP-2 in bone formation;
- Clinical studies, including randomized clinical trials, cohort studies, case series, and well-documented case reports addressing rhBMP-2 use in maxillary reconstruction;
- Publications in peer-reviewed journals written in English.

Exclusion criteria included studies unrelated to maxillary or oral applications, articles lacking methodological clarity, and publications focused exclusively on non-craniofacial skeletal sites without translational relevance.

2.3 DATA EXTRACTION AND SYNTHESIS

Relevant data were extracted qualitatively, focusing on:

- Molecular and cellular mechanisms of rhBMP-2-induced osteogenesis;
- Types of carrier systems and delivery methods;
- Clinical indications and surgical protocols;
- Outcomes related to bone volume, bone quality, implant feasibility, and complications.

Given the heterogeneity of study designs and outcome measures, a descriptive and thematic synthesis was performed rather than quantitative pooling. Findings were organized to establish a logical progression from biological principles to clinical application, enabling critical interpretation of current evidence and identification of knowledge gaps.

3 RESULTS

The analyzed evidence consistently demonstrated that recombinant human bone morphogenetic protein-2 (rhBMP-2) exhibits a strong and predictable osteoinductive effect in maxillary bone regeneration. Findings from experimental, translational, and clinical studies were synthesized to evaluate biological mechanisms, volumetric outcomes, bone quality, implant feasibility, and safety.

3.1 CELLULAR AND MOLECULAR OSTEOGENIC RESPONSE

Experimental studies confirmed that rhBMP-2 initiates osteogenesis by binding to BMP type I and II receptors on mesenchymal stem cells, activating SMAD-dependent intracellular signaling pathways. This cascade upregulated key osteogenic transcription factors, including Runx2, Osterix, and alkaline phosphatase, resulting in accelerated differentiation of osteoprogenitor cells into mature osteoblasts (Chen et al., 2012; Carreira et al., 2014).

Histological evaluations consistently demonstrated the formation of well-organized trabecular and lamellar bone, with evidence of active angiogenesis and marrow-like tissue development. Importantly, bone formation was observed even in critical-size defects lacking endogenous osteogenic capacity, confirming the intrinsic osteoinductive potential of rhBMP-2 (Wikesjö et al., 2003).

3.2 BONE VOLUME GAIN AND MORPHOLOGICAL OUTCOMES

Clinical studies assessing ridge augmentation and sinus floor elevation reported substantial increases in alveolar bone height and width following rhBMP-2 application. Radiographic analyses using cone-beam computed tomography demonstrated volumetric bone gains sufficient to allow placement of standard-diameter implants without additional grafting procedures (Boyne et al., 2005; Misch & Wang, 2011).

Histomorphometric analyses revealed that newly formed bone exhibited mineral density and trabecular organization comparable to native maxillary bone. Bone-to-implant contact ratios were consistently high, supporting favorable conditions for osseointegration and long-term implant stability (Fernandes et al., 2018).

3.3 CLINICAL PERFORMANCE AND IMPLANT OUTCOMES

Implant placement in rhBMP-2-regenerated sites was associated with high survival and success rates, typically exceeding 90% during short- and medium-term follow-up. Primary implant stability values were comparable to those achieved in autogenous bone graft sites, indicating adequate bone quality for functional loading (Boyne et al., 2005).

The elimination of donor-site morbidity emerged as a major clinical advantage. Patients undergoing rhBMP-2-based regeneration experienced reduced surgical time, decreased postoperative discomfort, and faster overall rehabilitation compared with autogenous graft protocols (Nkenke & Neukam, 2014).

3.4 DOSE DEPENDENCY AND CARRIER SYSTEMS

Dose-dependent effects were consistently reported. Lower to moderate rhBMP-2 concentrations achieved effective bone regeneration with minimal adverse effects, whereas higher doses were associated with increased postoperative edema and inflammatory responses. The absorbable collagen sponge, the most commonly used carrier, demonstrated limitations related to mechanical instability and uncontrolled protein release, potentially influencing both regenerative outcomes and complication rates (James et al., 2016; Smiler et al., 2016).

3.5 SAFETY PROFILE AND COMPLICATIONS

Adverse events were generally transient and localized, including swelling and discomfort. No consistent evidence of malignant transformation or long-term systemic effects was reported in maxillary applications; however, the heterogeneity of follow-up periods limits definitive safety conclusions. The off-label nature of many dental applications was highlighted

as a critical issue requiring ethical oversight and standardized protocols (Esposito et al., 2006).

The results support rhBMP-2 as a powerful and biologically effective osteoinductive agent capable of regenerating clinically functional maxillary bone. Nevertheless, outcomes are highly dependent on dose optimization, carrier selection, and defect characteristics, emphasizing the need for controlled clinical application.

4 DISCUSSION

The findings synthesized in the present review reinforce the relevance of recombinant human bone morphogenetic protein-2 (rhBMP-2) as a biologically active alternative for maxillary bone regeneration, particularly in cases of severe alveolar atrophy where conventional reconstructive approaches may be associated with increased morbidity. The osteoinductive capacity of rhBMP-2, extensively demonstrated in both experimental and clinical studies, supports its ability to promote de novo bone formation independent of preexisting osteogenic cells, a critical advantage in compromised maxillary sites (Urist, 1965; Reddi, 2005; Wikesjö et al., 2003).

When compared to autogenous bone grafts, rhBMP-2-based therapies offer distinct biological and clinical advantages. Autografts, although biologically superior due to their inherent osteogenic potential, are limited by donor-site morbidity, increased surgical complexity, and unpredictable resorption patterns (Younger & Chapman, 1989; Nkenke & Neukam, 2014). In contrast, rhBMP-2 eliminates the need for secondary surgical sites while maintaining satisfactory regenerative outcomes, particularly in sinus floor augmentation and alveolar ridge reconstruction procedures (Boyne et al., 2005; Misch & Wang, 2011). These attributes are especially relevant in patients with extensive maxillary defects, where treatment burden and morbidity must be minimized.

The biological mechanism underlying rhBMP-2-induced bone regeneration is well established. Upon delivery to the target site, rhBMP-2 binds to type I and II BMP receptors, triggering SMAD-dependent signaling pathways that regulate gene transcription associated with osteoblast differentiation and extracellular matrix mineralization (Chen et al., 2012; Carreira et al., 2014). This molecular cascade results in accelerated bone formation, which has been corroborated by histological and radiographic evidence demonstrating mature lamellar bone and adequate bone density for implant placement (Wikesjö et al., 2003; Fernandes et al., 2018).

Despite these favorable outcomes, the clinical application of rhBMP-2 remains subject to important limitations and controversies. One of the most critical issues related to dosage

and carrier systems. Excessive concentrations of rhBMP-2 have been associated with adverse events, including postoperative edema, inflammatory responses, and ectopic bone formation (James et al., 2016). Moreover, the absorbable collagen sponge (ACS), the most commonly used carrier, lacks mechanical stability and may influence protein release kinetics, potentially affecting regenerative outcomes (Smiler et al., 2016). These factors highlight the need for standardized delivery systems and optimized dosing protocols.

Another limitation concerns the heterogeneity of available clinical evidence. Variations in study design, defect morphology, surgical technique, and outcome assessment hinder direct comparison across studies and preclude definitive conclusions regarding long-term clinical superiority over autogenous grafts (Esposito et al., 2006; Fernandes et al., 2018). Furthermore, the off-label use of rhBMP-2 in oral and maxillofacial applications raises ethical and regulatory considerations that must be addressed through rigorous clinical trials and transparent reporting.

Overall, while rhBMP-2 represents a powerful tool in maxillary bone regeneration, its use should be guided by evidence-based protocols, careful patient selection, and a thorough understanding of its biological behavior. Future research should focus on controlled clinical trials, novel carrier systems, and long-term outcome evaluation to further define its role within contemporary regenerative dentistry.

5 CONCLUSION

Recombinant human bone morphogenetic protein-2 (rhBMP-2) represents a significant advancement in maxillary bone regeneration by offering a biologically driven alternative to traditional autogenous bone grafting techniques. Its osteoinductive capacity enables predictable de novo bone formation even in severely atrophic maxillary sites, thereby expanding the therapeutic possibilities for implant-supported rehabilitation in complex clinical scenarios.

The use of rhBMP-2 contributes to reduced surgical morbidity by eliminating the need for secondary donor sites, while also allowing for volumetric bone reconstruction compatible with subsequent implant placement. Nevertheless, its clinical effectiveness is closely dependent on appropriate case selection, optimized dosing, and suitable carrier systems. Variability in surgical protocols and reported adverse responses highlights the importance of standardized clinical guidelines and cautious implementation.

Overall, rhBMP-2 should be regarded as a complementary regenerative strategy rather than a universal substitute for autogenous grafts. Continued refinement of delivery systems, along with well-designed clinical trials and long-term outcome assessments, will be

essential to fully establish its role within evidence-based maxillary reconstruction and contemporary regenerative dentistry.

REFERENCES

Ahlmann, E., Patzakis, M., Roidis, N., Shepherd, L., & Holtom, P. (2002). Comparison of anterior iliac crest bone grafting to other techniques. Journal of Bone and Joint Surgery, 84(9), 1689–1694.

Boyne, P. J., Marx, R. E., Nevins, M., et al. (2005). A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation. International Journal of Periodontics & Restorative Dentistry, 25(6), 511–521.

Carreira, A. C., Alves, G. G., & Zambuzzi, W. F. (2014). Bone morphogenetic proteins: Structure, biological function and therapeutic applications. Archives of Biochemistry and Biophysics, 561, 64–73. https://doi.org/10.1016/j.abb.2014.07.011

Chen, G., Deng, C., & Li, Y. P. (2012). TGF-β and BMP signaling in osteoblast differentiation and bone formation. International Journal of Biological Sciences, 8(2), 272–288. https://doi.org/10.7150/ijbs.2929

Esposito, M., Grusovin, M. G., Coulthard, P., & Worthington, H. V. (2006). The efficacy of various bone augmentation procedures for dental implants. Cochrane Database of Systematic Reviews, CD003607. https://doi.org/10.1002/14651858.CD003607.pub2

Fernandes, J. de Q., et al. (2018). Bone regeneration with recombinant human bone morphogenetic protein-2: A systematic review. Journal of Maxillofacial and Oral Surgery, 17(1), 13–23. https://doi.org/10.1007/s12663-017-1045-4

James, A. W., et al. (2016). rhBMP-2 adverse events: A systematic review. Tissue Engineering Part B: Reviews, 22(4), 284–297. https://doi.org/10.1089/ten.TEB.2015.0357

Misch, C. E., & Wang, H.-L. (2011). Clinical applications of rhBMP-2 in oral and maxillofacial reconstruction. Journal of Oral and Maxillofacial Surgery, 69(2), 464–473. https://doi.org/10.1016/j.joms.2010.06.182

Reddi, A. H. (2005). BMPs: From bone morphogenetic proteins to body morphogenetic proteins. Cytokine & Growth Factor Reviews, 16(3), 249–250. https://doi.org/10.1016/j.cytogfr.2005.05.001

Urist, M. R. (1965). Bone: Formation by autoinduction. Science, 150(3698), 893–899. https://doi.org/10.1126/science.150.3698.893

Younger, E. M., & Chapman, M. W. (1989). Morbidity at bone graft donor sites. Journal of Orthopaedic Trauma, 3(3), 192–195.