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REVIEW PAPER

Bone regeneration with recombinant human bone morphogenetic protein 2: a systematic review

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Abstract
Aim The aim of this work was to perform a systematic literature review on the clinical application of rhBMP-2 in bone reconstruction prior to placing implants.
Materials and Methods A PUBMED search was made about the subject and nine clinical trials were selected according to strict inclusion criteria.
Results Overall success rates of bone regeneration with rhBMP-2 was 81.4% and success of implants placed was 87.4%. Most frequent adverse events were pain, edema and erythema.
Conclusion It was concluded that the treatment with rhBMP-2 foi satisfactory in most cases and the placement of dental implants in the bone regenerated with rhBMP-2 is feasible.

Keywords Bone morphogenetic protein 2 · Bone graft · Dental implants · Rehabilitation

Introduction

Dental implants have been used successfully for the replacement of tooth loss, however, adequate bone dimension is critical to successful placement of implants and their long-term maintenance in patients with severe atrophy of the jaws [1]. In cases of local bone deficiency, a variety of techniques and materials have been used for the reconstruction of bone defects in the maxillofacial area. Traditionally, autologous, allogeneic and xenogeneic bone grafts have been used for this purpose [2].

Current reconstructive strategies include alveolar distraction osteogenesis, bone block grafts and guided bone regeneration (GBR). These techniques have their advantages and disadvantages, including the need for a surgical wound in the donor site and its associated morbidity [3]. Autograft is considered the "gold standard" for its osteoconductive, osteoinductive and osteogenic characteristics. Moreover, according to the literature, the majority of bone substitutes have almost exclusively osteoconductive characteristics [4].

Recombinant human BMP-2 (rhBMP-2) and 7 have been reported as having potential use as bone substitutes in animal models [5]. BMPs stimulate angiogenesis as well as migration, proliferation and differentiation of mesenchymal stem cells into a phenotype of forming bone and cartilage cells [6].

Although rhBMP-2 alone is capable of promoting osteoinduction, a carrier is needed for adequate bone formation. Tipe I Collagen matrices are considered good carriers for growth factors due to the rheological properties, biocompatibility and absorbable nature6. In 2007, the association of rhBMP-2/absorbable collagen sponge (ACS) (INFUSE BONE GRAFT®, Medtronic, Memphis, Tennessee, USA) was approved by the Food and Drug Administration (FDA) as a substitute to autogenous bone for maxillary sinus floor graft and localized regeneration of the alveolar ridge for defects associated with post-extraction sockets [7].

The use of rhBMP-2 out of the indications approved by the FDA is considered "off label" [4]. Off label uses of

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rhBMP-2 includes cleft palate repair [8], reconstruction of severe atrophy of the jaws [9], segmental defects after tumor resection, treatment of osteonecrosis by bisphosphonates and osteoradionecrosis [1, 10] and total reconstruction of severely atrophic maxilla [11].

Although rhBMP-2 proved to be a promising osteoinductive material as a substitute for autogenous bone graft, questions were raised about the safety of using these growth factors. Carragee et al. [12] conducted a systematic review in which they evaluated controlled clinical trials that reported the complications and side effects of rhBMP-2 used in spinal surgery, finding an incidence of 10–50%, which included excessive bone growth, retrograde ejaculation and intense cervical edema with life-threatening airway obstruction. Moreover, the authors claim that high doses of rhBMP-2 may be associated with risk of developing malignant tumors. Woo [13], conducted a survey of adverse effects reported by the FDA in patients who received rhBMP-2 in the maxillofacial region, finding 83 reports of adverse effects, 66.3% of these in "off label" use of the material. In this paper, the authors performed a systematic review of the literature regarding the use of rhBMP-2 to reconstruct alveolar bone prior to the placement of dental implants.

Materials and Methods

Search Strategy

The MEDLINE (PUBMED) database was searched from 1980 through May 2015 for clinical studies evaluating the use of rhBMP-2 for alveolar ridge and maxillary sinus augmentation for implant placement. The search strategy included a combination of the following MeSH terms: "bone morphogenetic protein," "rhBMP-2," "alveolar ridge augmentation," "bone regeneration", "maxillary sinus augmentation" and "dental implants". Cochrane Central Register of Controlled Trials, EMBASE, SciELO, and LILACS were also searched using similar strategy. Hand searching of the main journals in the field of dental implants and oral and maxillofacial surgery completed the search.

Inclusion Criteria

The search was limited to human studies and the following study types: clinical trials, controlled clinical trials, randomized controlled trial (RCT), case reports, clinical trial phase I, II, III, and IV. Only studies published in English were considered. Hand searching of the main journals in the field of dental implants and oral and maxillofacial surgery completed the search.

Exclusion Criteria

Studies in animals, reviews, and systematic reviews of literature. Articles that did not present data relevant to the aim of this study were excluded.

Selection of the Studies

Three reviewers (SBFQ, JQF and VNL) independently assessed the titles and abstracts of all the results identified in electronic databases, verified agreement in the pre-selection of articles, and when there was disagreement, proceeded to the joint reading of the full text of the article to the final selection. Studies that met the criteria for inclusion were obtained. From this search, a collection of studies to be evaluated by the reviewers was created.

Outcomes Evaluated

The primary outcomes evaluated was success rate of rhBMP-2 as a grafting material in reconstruction of alveolar ridge, dental alveolus preservation and inlay maxillary sinus grafts prior to the placement of dental implants. Secondary outcomes were: adverse effects and complications, region of the graft, association or not with other grafting materials, quantity and quality of the newly formed bone, clinical and radiographic follow up, success of implants and implant supported prosthesis in the areas grafted with rhBMP-2.

Data Collection and Analysis

The reviews were not masked regarding the authors or the results of the studies. Data were extracted independently by three reviewers (SBFQ, JQF and VNL) and crossed to verify the agreements and disagreements. Discordant results were resolved by consensus. Data related to the objectives, materials and methods, results and conclusions were extracted and tabulated. The evaluation of these items provided a new set of data for the present study. The results are presented through tables. Due to the heterogeneity of the data collected it was not possible to make a meta-analysis of the results.

Results

Results Regarding the Search of the Articles

The initial search in PUBMED returned 1310 publications related to rhBMP-2. No studies of alternative search strategies were added to this list, since the other research data bases returned the same results found in PUBMED.

After detailed screening it was possible to select 11 studies that met the inclusion criteria of this systematic review. Two of the studies were eliminated because they were sub-analyzes of other already included in the review.

Number of Patients Evaluated and Clinical Applications of rhBMP-2 (Table 1)

The nine clinical studies involved a total of 527 patients of which 282 received rhBMP-2. The other 256 patients formed the control groups in which were used autogenous, allogenic or xenogeneic bone grafts or ACS without rhBMP-2. Regarding clinical applications, five of the selected studies showed applications considered "in label" [14–18] and four of the papers used the rhBMP-2 in off label applications [19–21].

Implant Placement in Areas of Regenerated Bone with rhBMP-2 (Table 2)

A total of 635 implants were placed in 282 patients who received rhBMP-2 associated or not with other grafts materials. The minimum follow-up time was 4 months 15 and the maximum was 5 years and 10 months [17]. The minimum time between the reconstruction and the placement of the implants was 4 months [14], and the maximum 11.5 months [16], with an average time of 6.6 months. Regarding the successful treatment with rhBMP-2 (Table 3), we can separate this data in three different analysis: the success of bone reconstruction, i.e., the number of patients that was possible to place implants without the need for additional bone graft, being 193 of the 237 patients who received rhBMP-2 graft (81.45%); the success rate of the implants placed in the bone regenerated with rhBMP-2 was 87.4% (472 of 540 implants placed), and the success rate of prosthesis with functional load on the implants placed in regenerated areas with rhBMP-2 was 83.6% (128 of 153 patients).

Histological Analysis of Newly Formed Bone (Table 4)

In six of the nine studies included in the review core biopsies were obtained at the time of implant placement [14–17, 19, 21]. Histologically all samples showed bone formation, especially of exuberant trabecular bone, predominantly poorly organized primary bone, lamellar bone in low to moderate amounts, few to moderate osteoblasts and few to absent osteoclasts. The inflammatory infiltrate was scarce, as well as vascular proliferation. In none of the evaluated specimens were found residual bovine type I collagen.

Amount of New Bone Formed (Table 5)

The amount of newly formed bone was evaluated by eight of the nine studies included in this systematic review [13–20, 22]. The average vertical bone formation was 8.01 mm and horizontal bone formation was about 4 mm. Regarding bone quality, few studies evaluated this variable [16, 19]. The evaluation methods were not clear and very heterogeneous, not allowing for a precise conclusion abut the results. In general the newly formed bone has been reported as soft during drilling for implant placement, being predominantly type II/III/IV according to Branemark classification [16].

Safety in the Use of rhBMP-2 (Table 6)

Safety using rhBMP-2 + ACS was assessed in the papers by Cochran et al. [14], Fiorellini et al. [15], Boyne et al.

Table 1 Studies included in the systematic review

No.	Author	Year	Study design	Indication (FDA)	Graft	Region
1	Cochran et al.	2000	MRCT	In label	rhBMP/2 + ACS	Fresh alveolous
2	Jung et al.	2003	RCCT	Off label	rhBMP-2 + XG + CM	Vestibular dehiscence
3	Fiorellini et al.	2005	MRCT	In label	rhBMP-2 + ACS	Fresh alveolous
4	Boyne et al.	2005	MRCCT	In label	rhBMP-2 + ACS	Maxillary sinus
5	Triplett et al.	2009	MRCCT	In label	rhBMP-2 + ACS	Maxillary sinus
6	de Freitas et al.	2013	RCT	Off label	rhBMP-2 + ACS + TM	Horizontal maxillary ridge reconstruction
7	Marx et al.	2013	ECR	Off label	rhBMP-2 + AG + PRP + TM	Horizontal and vertical maxillary ridge reconstruction
8	Coomes et al.	2014	RCCT	In label	rhBMP-2 + ACS	Fresh alveolous
9	Misch et al.	2015	RCS	Off label	rhBMP-2 + ACS + AG + TM	Horizontal and vertical maxillary and mandible ridge reconstruction

MRCT multicentric randomized clinical trial, *RCCT* randomized controlled clinical trial, *MRCCT* multicentric randomized controlled clinical trial, *RCT* randomized clinical trial, *RCS* retrospective clinical study, *XG* xenogenous graft, *CM* collagenous membrane; *TM* titanium mesh, *AG* allogenous graft, *PRP* platelet rich plasma

Table 2 Number of patients, implants, follow up and average time until placement of implants in the cases treated with rhBMP-2

Author	Patients (n)	Implants (n)	Follow up (months)	Implant placement (months)
Cochran et al.	12	13	36	5.8
Jung et al.	11	18	6	Immediate
Fiorellini et al.	40	43	4	NI
Boyne et al.	35	159	52	8.7
Triplett et al.	82	241	58	9
Freitas et al.	12	32	12	6
Marx et al.	20	61	6	6
Coomes et al.	20	18	5	5
Misch et al.	15	50	6	6
Total	282	635	25 (average)	6.6

NI not informed

Table 3 Success rates of reconstruction, implants placed and implant supported prosthesis in reconstructed areas with rhBMP-2

Author	Success/reconstruction (patients)	Success/implants	Success/prosthesis (patients)
Cochran et al.	9 of 12 (75%)	13 of 13 (100%)	10 of 10 (100%)
Fiorellini et al.	30 of 43 (69.7%)	NE	NE
Boyne et al.	30 of 35 (85.7%)	131 of 153 (85.6%)	27 of 35 (77.1%)
Tripplett et al.	67 of 82 (81.7%)	199 of 241 (82.5%)	64 of 81 (79%)
de Freitas et al.	12 of 12 (100%)	32 of 32 100%	12 of 12 (100%)
Marx et al.	18 of 20 (90%)	57 of 61 (93%)	NE
Coomes et al.	12 of 18 (66.6%)	NE	NE
Misch et al.	15 of 15 (100%)	40 of 40 (100%)	15 of 15 (100%)
Total	193 of 237 (81.4%)	472 of 540 (87.4%)	128 of 153 (83.6%)

NE not evaluated

Table 4 Data from studies that performed histological analysis of newly formed bone by rhBMP-2

Author	Lamellar bone	Woven bone	Trabeculate bone	Vascularization	Osteoblasts	Osteoclasts	Inflammation	Collagen remants
Cochran et al.	++	+++	+++	++	+	+	+	−
Jung et al.	+	+	−	−	−	−	−	−
Fiorellini et al.	++	++	+++	+	++	+	−	−
Boyne et al.	++	+	+++	++	++	+	−	−
Triplett et al.	+++	+	+++	+++	+++	+	+	−
Marx et al.	+++	+	+++	+++	+++	−	−	−

− absent, + small amount, ++moderate amount, +++ large amount

[16] and Triplett et al. [17]. This assessment was made by clinical and radiographic follow-up, signs and symptoms of local and systemic alterations (pain, swelling, erythema, infection, etc.), hematological and immunological tests to verify if the patients developed antibodies to any of the rhBMP-2 + ACS association components. Most of the adverse reactions were local and transitory, such as exacerbated edema and erythema. No studies identified antibodies to rhBMP-2, but some patients had antibodies to bovine collagen, however this response was transient and the antibodies were not detected after 2 months. One study [21] evaluated the postoperative edema in patients who received a combination of rhBMP-2 + PRP + allogeneic bone compared to patients who received only autologous graft in the reconstruction of extremely atrophic maxilla, finding statistically significant difference in favor of group using rhBMP-2 in the periods of 3, 8 and 15 days ($p = 0.01$).

Table 5 Average amount of bone formed in height and width in reconstructions with rhBMP-2

Author	Bone formed (height) (mm)	Bone formed (width) (mm)
Cochran et al.	10.4	4.9
Jung et al.	6.8	NI
Fiorelini et al.	NI	3.27
Boyne et al.	10.2	2
Triplett et al.	7.83	NI
de Freitas et al.	NI	3.2
Coomes et al.	4.33	6.59
Misch et al.	8.53	NI
Average	8.01	3.99

NI not informed

Table 6 Data from studies reporting adverse effects and complications in reconstructions with rhBMP-2

Author	Edema	Erythema	Pain	Immune response	Systemic	Infection	Dehiscence/membrane exposure	Total of events per study
Cochran et al.	−	+	+	−	+	+	−	21
Jung et al.	−	−	−	−	−	−	+	1
Fiorellini et al.	+	+	+	+	−	−	−	250
Boyne et al.	+	+	+	+	+	−	+	546
Triplett et al.	+	−	+	+	−	−	−	NI
Freitas et al.	+	+	+	−	−	−	+	NI
Marx et al.	+	−	−	−	−	+	+	NI
Coomes et al.	+	+	−	−	−	−	−	NI
Misch et al.	−	−	−	−	−	−	−	NI
Total studies	6	5	5	3	2	2	4	818

+ present, − absent, *NI* not informed

Discussion

In this systematic review we observed that much of the literature about the use of rhBMP-2 in implant dentistry lacks of appropriate methodology, and the studies presented very small sample sizes. It was possible to select only nine studies that met the inclusion criteria of this review [13–22]. Most of the articles in the initial search were case reports or case series with small sample size, experimental in vitro or animal studies, and studies in areas other than dentistry. This proves that most of the articles published on the subject do not have the criteria to be classified as good scientific information, i.e., controlled and randomized clinical trials with adequate sample and strict evaluation criteria. Therefore, more well-designed randomized controlled clinical trials are needed to give a better basis for clinical use of rhBMP-2 in implant dentistry.

There is much debate regarding the use of "off label" of rhBMP-2. Some studies show a higher incidence of complications with off-label use of Infuse Bone Graft for orthopedic and neurosurgical applications [12]. According to Misch et al. [22], the off-label use is not forbidden, but the patient should be fully informed about the risks and benefits of the technique and must sign an informed consent authorizing the use in the particular case. In four of the studies included in the review, the rhBMP-2 was used off label [19–22]. The success rates, adverse effects were similar to those reported with the use in label of rhBMP-2.

The studies included in this systematic review showed high rates of success in bone regeneration prior to implant placement. The average gain was 8.01 mm height ranging from 4.3318 and 10.4 mm [14]. In width, the average gain was 3.99 mm, ranging from 216 to 6.59 mm [18]. The success rate of osseointegration of implants placed in regenerated bone with rhBMP-2 (87.4%) and implant-supported prostheses submitted to masticatory load (83.65%) can be considered comparable to autogenous bone, with the advantage of not requiring a second surgical site to obtain it, and superior to xenogeneic and allogeneic grafts, due to its osteoinductive capacity, since the first two are only osteoconductive.

Few studies have specifically evaluated the side effects and complications associated with the use of rhBMP-2. As a growth factor with high chemotactic potential to inflammatory cells, it is expected that rhBMP-2 cause large

leakage of fluids into the extravascular space, increasing the capillary permeability and local blood flow, which explains the exuberant edema and erythema present in patients who use rhBMP-2 [12, 13, 21, 22]. In fact, while all reviewed studies emphasize that the edema has no major consequence for the patient, there are reports of life threatening airway obstruction due to excessive soft tissue edema in the cervical spinal fusion surgery [12, 13]. Other serious adverse reactions reported in the orthopedic literature include ectopic calcification, excessive bone formation and increased incidence of cancer in patients grafted with rhBMP-2 [12], however, these severe side effects and complications have never been reported with the use of rhBMP-2 in dentistry.

In conclusion, clinical studies included in this systematic review of the literature showed that rhBMP-2 can be a good alternative to autogenous bone, promoting bone regeneration in height and width suitable to receive dental implants and implant-supported prosthesis with good stability at least 5 years.

Compliance with Ethical Standards

Conflict of interest Author Jannice de Queiroz Fernandes declares that she has no conflict of interest. Author Valthierre Nunes de Lima declares that he has no conflict of interest. Author João Paulo Bonardi declares that he has no conflict of interest. Author Osvaldo Magro Filho declares that he has no conflict of interest. Author Sormani Bento Fernandes Queiroz declares that he has 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. Herford AS, Boyne PJ (2008) Reconstruction of mandibular continuity defects with bone morphogenetic protein-2 (rhBMP-2). J Oral Maxillofac Surg 66(4):616–624
2. Hart KL, Bowles D (2013) Reconstruction of alveolar defects using titanium-reinforced porous polyethylene as a containment device for recombinant human bone morphogenetic Protein 2. J Oral Maxillofac Surg 70:811–820
3. Herford AS, Tandon R, Stevens TW, Stoffella E, Cicciu M (2013) Immediate distraction osteogenesis: the sandwich technique in combination with rhBMP-2 for anterior maxillary and mandibular defects. J Craniofac Surg. 24:1383–1387
4. de Freitas RM, Spin-Neto R, Junior EM, Pereira LAVD, Wikesjö UME, Susin C (2012) Alveolar ridge and maxillary sinus augmentation using rhBMP-2: a systematic review. Clin Implant Dent Related Res 17:e192–e201
5. Katayama Y, Matsuyama Y, Yoshihara H, Sakai Y, Nakamura H, Imagama S, Ito Z, Wakao N, Kamiya M, Yukawa Y, Kanemura T, Sato K, Iwata H, Ishiguro N (2009) Clinical and radiographic outcomes of posterolateral lumbar spine fusion in humans using recombinant human bone morphogenetic protein-2: an average five-year follow-up study. Int Orthop 33:1061–1067
6. Stancoven BW, Lee J, Dixon DR, McPherson JC III, Bisch FC, WikesjoÅN UME, Susin C (2013) Effect of bone morphogenetic protein-2, demineralized bone matrix and systemic parathyroid hormone (1-34) on local bone formation in a rat calvaria critical-size defect model. J Periodont Res. 48:243–251
7. McKay WF, Peckham SM, Badura JM (2007) A comprehensive clinical review of recombinant human bone morphogenetic protein-2 (INFUSE Bone Graft). Intern Orthop. 31(6):729–734
8. Francis CS, Mobin SSN, Lypka MA, Rommer E, Yen S, Urata MM, Hammoudeh JA (2013) rhBMP-2 with a demineralized bone matrix scaffold versus autologous iliac crest bone graft for alveolar cleft reconstruction. Plast Reconstr Surg 131:1107
9. Misch CM, Wang H-L (2011) Clinical applications of recombinant human bone morphogenetic protein-2 for bone augmentation before dental implant placement. Clin Adv Periodont 1:118–131
10. Carter TG, Brar PS, Tolas A, Beirne OR (2008) Off-label use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for reconstruction of mandibular bone defects in humans. J Oral Maxillofac Surg 66:1417–1425
11. Spagnoli DB, Marx RE (2011) Dental implants and the use of rhBMP-2. Oral Maxillofac Surg Clin N Am 23:347–361
12. Carragee EJ, Hurwitz EL, Weiner BK (2011) A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. Spine J. 11:471–491
13. Woo EJ (2012) Adverse events reported after the use of recombinant human bone morphogenetic protein 2. J Oral Maxillofac Surg 70:765–767
14. Cochran DL, Jones AA, Lilly LC, Fiorellini JP, Howell H (2000) Evaluation of recombinant human bone morphogenetic protein-2 in oral applications including the use of endosseous implants: 3-year results of a pilot study in humans. J Periodontol 71:1241–1257
15. Fiorellini JP, Howell TH, Cochran D, Malmquist J, Lilly LC, Spagnoli D et al (2005) Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. J Periodontol 76:605–613
16. Boyne PJ, Lilly LC, Marx RE, Moy PK, Nevins M, Spagnoli DB, Triplett RG (2005) De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation. J Oral Maxillofac Surg 63:1693–1707
17. Triplett RG, Nevins M, Marx RE, Spagnoli DB, Oates TW, Moy PK et al (2009) Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation. J Oral Maxillofac Surg 67:1947–1960
18. Coomes AM, Mealey BL, Huynh-Ba G, Barboza-Arguello C, Moore WS, Cochran DL (2014) Buccal bone formation after flapless extraction: a randomized, controlled clinical trial comparing recombinant human bone morphogenetic protein 2/absorbable collagen carrier and collagen sponge alone. J Periodontol 85:525–535
19. Jung RE, Glauser R, Scharer P, Hammerle CH, Sailer HF, Weber FE (2003) Effect of rhBMP-2 on guided bone regeneration in humans. Clin Oral Implants Res 14:556–568
20. de Freitas RM, Susin C, Spin-Neto R, Marcantonio C, Wikesjö UME, Pereira LAVD, Marcantonio E Jr (2013) Horizontal ridge augmentation of the atrophic anterior maxilla using rhBMP-2/ACS or autogenous bone grafts: a proof-of-concept randomized clinical trial. J Clin Periodontol 40:968–976
21. Marx RE, Armentano L, Olavarria A, Samaniego J (2013) rhBMP-2/ACS grafts versus autogenous cancellous marrow grafts in large vertical defects of the maxilla: an unsponsored randomized open-label clinical trial. Int J Oral Maxillofac Implants 28:e243–e251
22. Misch CM, Jensen OT, Pikos MA, Malmquist JP (2015) Vertical bone augmentation using recombinant bone morphogenetic protein, mineralized bone allograft, and titanium mesh: a retrospective cone beam computed tomography study. Int J Oral Maxillofac Implants 30:202–207