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REVIEW ARTICLE

Scientific evidence on the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in oral and maxillofacial surgery

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Abstract

Purpose This study aimed to identify the main indications for the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for bone repair and maintenance in the maxilla and mandible through a review of clinical trials evaluating the viability of using rhBMP-2 to delay the installation of dental implants, thus allowing satisfactory bone formation and long-term osseointegration.

Methods Literature search of the PubMed/Medline databases was performed using the following MeSH index terms— "bone morphogenetic protein 2" and "dentistry". Only clinical trials necessarily published in English, related to dentistry, and focused on bone reconstruction in critical defects, post-extraction alveoli, increasing the atrophic alveolar ridge, or surgery for maxillary sinus elevation were included, regardless of the age, sex, ethnicity, associated morbidities, or period of publication.

Results Of the 17 studies identified based on the search filters, 2 were excluded. Therefore, 15 studies were finally included in this review.

Conclusions Based on the results of our review, we concluded that the use of rhBMP-2 for the preservation of the alveolar ridge after tooth extraction or for increasing the local defects is safe and viable. The use of rhBMP-2/Bio-Oss® for the elevation of the maxillary sinus membrane is unnecessary; however, it can improve and accelerate the maturation process in cases of guided bone regeneration in peri-implant defects. Compounds comprising rhBMP-2, allogenic bone, and plasma-rich platelet (PRP) can act as autograft substitutes in mandibular critical defects.

Keywords Atrophy · Biocompatible materials · Bone morphogenetic protein 2 · Bone regeneration

Introduction

First described in 1965, bone morphogenetic protein (BMP) is a member of the transforming growth factor-β1 family. Subsequent research led to the purification of bone extracts for the isolation of BMPs, which are osteoinductive proteins that stimulate endochondral and intramembranous bone formation and might lead to the differentiation of mesenchymal cells [1–5].

The bone formation ability and safety of recombinant human bone morphogenetic protein-2 (rhBMP-2) associated with absorbable collagen sponge (ACS), as well as the safety of their osteoinductive carrier components have been extensively investigated and are well known [6–9]. The application of rhBMP-2/ACS has been reported to have resulted in normal bone induction at the site of implantation—a process which involves the migration and proliferation of mesenchymal cells at the site of implantation, followed by their differentiation into osteoprogenitor cells [10].

The regeneration of any type of tissue requires the presence of the classic "tissue engineering triangle," which includes a source of cells, a signal for bone formation, and a matrix.

The implantation of rhBMP-2/ACS has been proven to be an appropriate signal for induction of bone formation in both

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lumbar vertebral [11] and tibial fractures, as well as in alveolar ridge preservation [10–13] and elevation of the maxillary sinus membrane [14–17].

It has been shown that rhBMP-2/ACS exhibits chemoattraction towards osteoprogenitor and stem cells, which serve as sources of bone-forming cells [18]. Lyophilized cancellous allograft and xenogeneic bones are commonly used as osteoconductive matrices [19]. Platelet-rich plasma (PRP) is known to contain several growth factors and cell adhesion molecules (fibrin, fibronectin, and vitronectin) [10, 12], and the convergence of these three materials is an example of the formation of the "tissue engineering triangle."

Literature describes several possibilities for the application of rhBMP-2, including its widespread application in the treatment of jaw defects. However, studies are still necessary for the evaluation of the viability of this material. Therefore, this study aimed to identify scientific evidence regarding the main indications for the application of rhBMP-2 for bone repair and maintenance in the maxilla and mandible. This was accomplished through a review of clinical trials evaluating the viability of using rhBMP-2 to delay the installation of dental implants, thus allowing satisfactory bone formation and long-term osseointegration after functional loading.

Clinically, the main purpose of this review was to provide oral maxillofacial surgeons and implant specialists a current protocol of the rational use of rhBMP-2 in the reconstruction of atrophic jaws.

Materials and methods

For this literature review, we searched the PubMed/Medline databases for clinical trials involving the use of rhBMP-2, without any restriction of the time period, using the MeSH index terms "bone morphogenetic protein 2" and "dentistry".

Limiting the search to studies related to dentistry published in English identified 243 relevant references. These results were again filtered to identify only clinical trials involving the use of rhBMP-2 for different purposes and defects, as described below:

- Critical defects
- Post-exodontic alveoli
- Increasing the atrophic alveolar ridge
- Maxillary sinus elevation
- Cleft lip and palate

Studies were included regardless of the following factors:

- Age
- Gender
- Ethnicity

- Associated comorbidities

Studies not related to the following subjects were excluded:

- Bone reconstruction
- Patients with systemic disorders that could affect the results
- In vivo studies
- In vitro studies

Results

A search of the PubMed/Medline databases for the index terms revealed 17 studies after the application of the limits and inclusion/exclusion criteria. Careful evaluation of the full texts of these studies led to the exclusion of a study related to the use of rhBMP-2 in bone defects caused by periodontal pockets [20], as well as another related to its use in maxillary bone gain for nasolabial soft tissue support [21]. Finally, 15 studies were included in this review, of which, 7 involved the use of rhBMP-2 with or without other biomaterials, apart from the evaluation of different concentrations of rhBMP-2 in the treatment of anterior atrophic maxilla and/or post-exodontics alveolus; 4 studies involved the application of rhBMP-2 in the elevation of the maxillary sinus, 2 in peri-implant defects, and 2 in defects of critical size.

The demographic and clinical characteristics evaluated in the selected studies are described in detail in Tables 1, 2, 3, 4, 5, and 6; they included the number of patients participating in the study; sex; mean age (in years); regions of the jaw subjected to reconstruction; results of evaluation in terms of different concentrations of rhBMP-2 and/or comparison to other already acclaimed biomaterials; results of bone formation analyzed by microscopy; results of measurement of marginal bone gain/loss, either in terms of height or thickness, based on imaging findings (X-rays or computed tomography); antibody formation potential (anti-rhBMP-2, anti-bovine collagen type I, or anti-human collagen type I antibodies) evaluated through hematological examination; and implant survival rates and complications.

Discussion

Among the clinical trials reviewed in the present study, the results of those involving the use of rhBMP-2 in the treatment of atrophic ridges of the anterior maxilla or post-exodontic alveolus indicated alveolar bone maintenance, in general, regardless of the type of material used, isolated or combined use of rhBMP-2 in association with demineralized bone matrix, or type of control (blood clot or ACS only) [13, 22–26]. These

Table 1 Features evaluated in 7 of 15 studies selected for literature review

Study	Patient	Sex	Age (average years)	Region	Groups evaluated
Boyne; Marx; Nevins et al., [14]	12	4 M 8 F	51	Maxillary sinus (unilateral)	Sinus lift and filled with rhBMP-2/ACS
Howell; Fiorellini; Jones et al.,[22]	12	4 M 2 F	55	Anterior of maxilla and post-extraction socket	Group I: post-extraction sockit (rhBMP-2/ACS) Group II: alveolar ridge augmentation (rhBMP-2/ACS)
Cochran; Jones; Lilly et al., [23]	12	–	–	Anterior of maxilla and post-extraction socket	Group I: post-extraction sockit (rhBMP-2/ACS) Group II: alveolar ridge augmentation (rhBMP-2/ACS)
Jung; Glauser; Scharer et al., [28]	11	7 M 4 F	53	5 patients (maxilla) 6 patients (jaw) on peri-implant defects	Group control (BIO-OSS® + BIO-GIDE®) Group test (BIO-OSS ® + rhBMP-2 + BIO-GIDE®)
Bianchi; Fiorellini; Howell et al., [24]	20	12 M 8 F	+/−53.2	Post-extraction sockit	Group I: rhBMP-2/ACS 1.50 mg/ml Group II: rhBMP-2/ACS 0.75 mg/ml Group III: ACS (placebo) Group IV: no treatment
Fiorellini; Howell; Cochran et al., [25]	80	43 M 37 F	47.4	Post-extraction sockit	Group I: rhBMP-2/ACS 1.50 mg/ml Group II: rhBMP-2/ACS 0.75 mg/ml Group III: ACS (placebo) group IV: no treatment
Boyne; Lilly; Marx et al., [15]	48	19 M 29 F	55	Maxillary sinus	Group I: autogenous bone or autologous + allogenous Group II: rhBMP-2/ACS 0.75 mg/ml Group III: rhBMP-2/ACS 1.50 mg/ml

Table 2 Features evaluated in 7 of 15 studies selected for literature review

Study	Unit bone formation (microscopic evaluation)	Bones maintaining height/width	Antibody formation potential	Implant survival rate	Complications
Boyne; Marx; Nevins et al., [14]	–	Average of bone height augmentation at 4 months by CT = 8.51 mm	9 patients developed anti-rhBMP-2, human collagen type 1	100 %	Sinusitis (4 patients) rhinitis (2 patients)
Howell; Fiorellini; Jones et al.,[22]	–	Periapical radiography (maintained bone height) CT at 4 months (socket 0.31 mm ridge 0.16 mm)	All patients (antibody formation potential below the limits)	–	–
Cochran; Jones; Lilly et al., [23]	–	Periapical radiography (distance between the apex of the implant and the ridge crest 8–12 months after prosthetic function: average of the height decreased 1.43 mm mesial and 1.84 mm distal)	–	100 %	Colitis-2 cases (17 % in group I)
Jung; Glauser; Scharer et al., [28]	–	Loss of bone height after 6 months of implant installation: group control = 0.4 mm group test = 0.2 mm ($p < 0.01$)	–	100 %	–
Bianchi; Fiorellini; Howell et al., [24]	–	Comparative CT bone volume augmentation between pre and post-extraction of 4 months: group I: 0.192 cm^3 group II: 0.106 cm^3 group III: 0.084 cm^3 group IV: 0.104 cm^3 (group I>II, III e IV-$p < 0.05$; group II=III=IV-$p > 0.05$)	–	–	–
Fiorellini; Howell; Cochran et al., [25]	–	Comparative CT bone lost post-extraction—4 months: height and width B-P 25, 50 and 75 % in mm (respectively) group I: −0.02; +3.27; +3.97; +2.68 group II: −0.62; +1.76; +2.45; +2.29 group III: −1; +0.82; +1.79; +1.82 group IV: −1.17; +0.57; +1.62; +1.65 (height $p = 0.029$ and width V-P 25 % $p = 0.000$; 50 % $p = 0.001$; 75 % $p > 0.05$)	11 patients developed formation of antibodies (anti-bovine collagen type I)	–	–
Boyne; Lilly; Marx et al., [15]	–	Comparative CT augmentation in mm of height; width B-P (¼, ½ and ¾) respectively—4 months group I: 11.29; 4.66; 10.17; 10.56 group II: 9.47; 2.02; 8.54; 11.86 group III: 10.16; 1.98; 7.8; 10.78 (there was statistical difference only in width ¼—$p = 0.013$)	2 patients (group III) developed formation of antibody anti-rhBMP-2; 3 patients (group I), 2 (group II), 4 (group III) developed formation of antibody anti-bovine collagen type I	75 to 80 % after 3 years use of the prosthesis	Dehiscence (15 %—group I; 11 %—group II; 6 %—group III); sinusitis (31 %—group I; 17 %—group II; 6 %—group III)

Table 3 Features evaluated in 4 of 15 studies selected for literature review

Study	Patient	Sex	Age (average years)	Region	Groups valuated
Jung; Windisch; Eggenschwiler et al., [29]	11	4 M 7 F	53	Peri-implant defects	Group control (BIO-OSS® + BIO-GIDE®) Group test (BIO-OSS ®+ rhBMP-2 + BIO-GIDE®)
Triplett; Nevins; Marx et al., [19]	160	71 M 89 F	Above 18	Maxillary sinus	Group control: autogenous bone Group test: rhBMP-2
Kao; Kubota; Nevins et al., [16]	22	13 M 9 F	50.8	Maxillary sinus	Group I: rhBMP-2 + Bio-Oss® (80/20); Group II: Bio-Oss®
Freitas; Susin; Spin-Neto et al., [26]	24	12 M 12 F	45.5	Anterior of maxilla	Group control: autogenous bone Group test: rhBMP-2/ACS 1.5 mg/ml (4.2 mg for region)

results also indicated the superiority of rhBMP-2 in the treatment of post-exodontic alveoli with previous vestibular bone loss [27].

Regarding the measurement of alveolar bone loss for the evaluation of the bone height (distance between the implant apex and alveolar ridge crest) and width (V-P), average bone losses of 1.84 and 1.43 mm in height were noted at the distal and mesial regions, respectively, within a minimum period of 3–4 months after implant installation [22, 26] and a maximum period of 12 months after functional rehabilitation with implant-supported prostheses; there were no statistically significant differences in efficacy between rhBMP-2 and bone substitutes or blood clot control, in the treatment of post-exodontic alveoli [22, 24, 26].

It was evident from the results of the evaluated studies that the concentration of rhBMP-2 (0.75 or 1.5 mg/ml) influenced the osteoinductive activity of BMP-2 in post-exodontic alveolar defects. Patients treated with the lowest concentration of rhBMP-2 (0.75 mg/ml) showed no statistically significant differences in terms of the bone volume, height, or width when compared to the control groups (isolated ACS or blood clot); however, the patients treated with higher concentrations of rhBMP-2 (1.5 mg/ml) exhibited significantly higher values of the same parameters when compared to the control groups ($p < 0.05$) [24]. Another study also reported higher values of V-P alveolar bone width at an rhBMP-2 concentration of 1.5 mg/ml, in comparison with the other evaluated groups ($p < 0.05$) [25]. Therefore, the use of rhBMP-2 at a concentration of 1.5 mg/ml presents significant applicability in clinical dental practice for the treatment of these defects.

Therefore, at least in the treatment of post-exodontic alveolar defects and small maxillary atrophy, differences in the concentration of rhBMP-2 do not substantially influence bone repair. In these situations, the use of any bone substitute with osteoconductive properties seems to produce satisfactory results by allowing osseointegrated implant installation and long-term bone maintenance; this statement is supported by clinical investigations reporting a 100 % survival rate of the installed implants [23, 26].

One of the challenges for guided bone regeneration is the use of biomaterials in the treatment of peri-implant defects. Exposure of implant threads because of physiological resorption after exodontia by pathological or traumatic processes is usually observed. Even in the absence of fenestration, particulate bone reconstruction is necessary if the thickness of the vestibular cortex is less than 1.5 mm [28, 29]. Regarding alveolar bone maintenance, clinical studies have reported no statistically significant differences between the efficacies of lyophilized bovine bone (Bio-Oss®) and bovine collagen membrane (Bio-Gide®) in the treatment of peri-implant defects, regardless of their association with rhBMP-2.

In periapical radiographic images acquired 6 months after implant installation [28] and after 3 and 5 years of prosthetic rehabilitation [29], the loss of neoformed bone in the peri-implant defects was minimal, with no statistically significant differences between the two treatment groups (Bio-Oss® vs. Bio-Oss®/rhBMP-2). Therefore, in such defects, only osteoconductive bone substitutes are indicated, and supplementation with rhBMP-2 may be dispensed with.

Another area widely discussed in literature is the use of biomaterials for the elevation of the maxillary sinus membrane in order to increase the bone height in the posterior maxilla. Because of the physiological characteristic of the maxillary sinus to keep expanding during an individual's life, it is common to observe maxillary sinus pneumatization with decreased alveolar ridge height following exodontia of the upper posterior teeth. Surgery for sinus membrane elevation is indicated in cases where the residual ridge height is 5 mm or less [17].

In this context, several studies have reported that the use of rhBMP-2/ACS is highly favorable for the gain and maintenance of bone height in osseointegrated implants [14–16, 19]. The results of CT analysis, with a minimum follow-up period of 4 months, showed an increase of 8.51 mm in bone height with rhBMP-2 [14]. Another study reported that rhBMP-2 (1.5 mg/ml) produced results similar to those with autogenous bone graft, increasing the bone width to ¼th the bone height reached after sinus membrane elevation ($p = 0.013$) [15]. In another study, based on the results of CT evaluation of the

Table 4 Features evaluated in 4 of 15 studies selected for literature review

Study	Unit bone formation (microscopic evaluation)	Bones maintaining height/width	Antibody formation potential	Implant survival rate	Complications
Jung; Windisch; Eggenschwiler et al., [29]	–	Comparative periapical radiographs (initial, 3 and 5 years—the marginal bone level to the prosthetic component) Group control: initial × 3 years: −0.02 mm in the mesial; 0.10 mm in distal. 3 × 5 years: −0.08 mm in the mesial; −0.04 Mm distal. Group test: initial × 3 years: −0.04 mm in the mesial; −0.08 Mm in the distal; 3 × 5 years: −0.03 mesial; −0.06 distal ($p > 0.05$)	–	100 %	No complications
Triplett; Nevins; MARX et al., [19]	–	Comparative CT average bone density 6 months after grafting: autologous (283 mg/cm^3) density greater than rhBMP-2 (200 mg/cm^3)—$p < 0.0001$; 6 months after functional loading): rhBMP-2 (358 mg/cm^3)> autologous (298 mg/cm^3 $p = 0.0132$); 12 months after functional load: rhBMP-2 (153 mg/cm3)> autogenous (16 mg/cm3 $p < 0.0001$).	2 patients developed anti-rhBMP-2; 25 of the control goup developed anti-bovine collagen type I; 24 of the test group.	79 %	–
Kao; Kubota; Nevins et al., [16]	% neoformed bone: group I: 16.04 %; group II: 24.85 % ($p = 0.0014$); Bio-Oss residual particles: group I: 15.70 %; group II: 39.70 % ($p = 0.0001$), Medullary bone: group I: 68.26 %; group II: 35.45 % ($p = 0.0001$),	–	–	100 %	–
Freitas; Susin; Spin-Neto et al., [26]	–	CT baseline, 3 and 6 months after grafting to measure the width BP (2.6 and 10 mm of bone crest): Goup control: initial: 4; 5.3; 8.4 mm. 3 months: 0.9; 3.1; 2.0 mm. 6 months: 0.5; 2.9; 1.8 mm. Group test: initial: 3.6; 4.3; 7.9 mm. 3 months 1.5; 3.0; 1.9 mm. 6 months: 1.5 mm; 2.9 mm; 1.7 mm.	–	100 %	–

Table 5 Features evaluated in 4 of 15 studies selected for literature review

Study	Patient	Sex	Age (average years)	Region	Groups evaluated
Marx; Armentano; Olavarria et al., [10]	40	10 M 30 F	60	Extensive bone defects in maxilla (1 × 1 cm)	Group control: autogenous (tibia or iliac crest) Group test: rhBMP-2 + autogenous + PRP
Marx; Harrell, [12]	40	–	57	Mandibular defects (6–8 cm)	Group A: 1-BMA+TNC+CD34+CFU; 2- rhBMP-2/ACS; 3-bone marrow allogeneus; 4-BMA+CD44+CD90+CD105+TNC+CFU. Group B: similar to group A, but greater cells number (TNC, CD34+ e CFU).
Kim; Lee; Kim et al., [13]	69	34 M 35 F	50	Post-extraction sockit	Group control: DBM + porcine collagen gel type I Group test: rhBMP-2 + DBM + porcine collagen gel type I
Coomes; Mealey Huynh-Ba et al., [27]	38	21 M 17 F	Above 18	Post-extraction sockit	Group control: collagen sponge Group test: rhBMP-2/ACS

bone density, autogenous bone superiority was observed at 6 months after grafting with autogenous bone or rhBMP-2/ACS, while the density values at 6 and 12 months after functional loading were significant higher in the rhBMP-2 group compared with the autogenous bone graft group ($p < 0.05$) [19]. Therefore, in these situations, it may be concluded the BMP causes an increase in the density of the neoformed bone over time, which leads to a more positive prognosis of rehabilitative treatment with implants. Despite the osteogenic, osteoconductive, and osteoinductive properties of autogenous bone, its application in the maxillary sinus promotes, beyond bone apposition, remodeling over time. The results of the studies reviewed here indicated increased remodeling with autogenous bone grafts compared to rhBMP-2 [14–16, 19].

The combination of osteoconductive bone substitutes with rhBMP-2 for the elevation of the sinus membrane is probably not necessary. In a clinical trial involving 22 patients who underwent elevation of the sinus membrane and received grafts with either rhBMP-2/Bio-Oss® in a 4:1 ratio or only Bio-Oss®, the percentage of neoformed bone was greater in the group treated with Bio-Oss®, which confirms our previous statement. These results may be attributed to an increase in osteoclast differentiation caused by the release of rhBMP-2 [16], which also promotes increased regulation of the activator receptor of the nuclear factor-kappa B (NF-kB), the main factor responsible for osteoblast differentiation and a very important factor for osteoinduction. Interactions between the components of osteoclastogenesis and osteoblastogenesis are influenced by the behavior of rhBMP-2. The activation of the receptor activator of nuclear factor Kappa-B ligand (RANKL) and osteoprotegerin (OPG) systems at the same time by rhBMP-2 by negative feedback mechanisms leads to an increase or decrease of the bone mass. This interaction complex is based on the interactions in the central signaling pathway in bone remodeling [30].

The greatest obstacle for maxillary bone reconstruction is certainly the availability of bone for achieving satisfactory repair in case of extensive damage. Such defects have been treated with autogenous block grafts harvested from the oral cavity (mental region and mandibular ramus); for the treatment of total maxillary defects, extraoral donor regions such as the cranial vault, iliac crest, tibia, fibula, ribs, radius, and ulna are used. However, surgical morbidity associated with the necessity of a secondary donor site as well as the contraindication for general anesthesia in systemically compromised patients makes the search for other alternatives a subject for further research.

In a clinical trial involving the study of 40 patients with atrophic maxillary defects with dimensions of 1×1 cm [10], there were no differences in terms of the area of the neoformed bone between the control (autogenous bone; tibia or iliac crest) and test (rhBMP-2 + allograft bone + PRP) groups ($p = 0.95$), which indicated the similar

Table 6 Features evaluated in 4 of 15 studies selected for literature review

Study	Unit bone formation (microscopic evaluation)	Bones maintaining height/width	Antibody formation potential	Implant survival rate	Complications
Marx; Armentano; Olavarria et al., [10]	Bone area: group control: 54 % group test: 59 % (p = 0.95)	—	—	Group control: 90 % Group test: 85 %	Group control; group test respectively, graft loss (2. 2) Infection (2.2) Titanium mesh exposure (3. 3)
Marx; Harrell, [12]	Bone regeneration: group A—40 %; group B –100 % (p = 0.006). Average trabecular bone: group A —36 %; group B —67 % (p = 0.01).	TC 6 months after graft—bone density: goupA—424 HU; group B—737 HU (p = 0.01)	—	—	—
Kim; Lee; Kim et al., [13]	—	Comparative CT between the average of the baseline and 3 months after grafting for measuring mm in of the height and width B-P {1.3 and 5 mm of bone crest} (respectively): group control: −1.50;−1.21;−0.58;−0.37 Goup test: −1.17;−1.06;−0.43;−0.23 (p > 0.05 for all)	1 patients has developed anti-rhBMP-2	—	—
Coomes; Mealey Huynh-Ba et al., [27]	—	Comparative CT between the average of the initial and 5 months Group control: 3.5 to 9 mm Group test: 2 to 9,5 mm (p = 0.018)	—	100 %	—

efficacies of the two graft treatments. Two cases in each group experienced early titanium mesh exposure, initially related to the lack of vascularization in the graft, leading to the loss of those four grafts. Additionally, late mesh exposure occurred in three cases in each group; however, since the grafts had by then vascularized, the sites were successfully sutured, thus explaining the absence of infection or graft loss.

In terms of bone reconstruction, mandibular defects still represent a challenging situation for maxillofacial surgeons. Mandibular defects result from high impact facial traumas that cause extensive damage and subsequent resorption as well as from bone resection caused by pathological lesions [31]. Unfortunately, for graft reconstruction, free autogenous graft is not a favorable alternative in most of these cases. In such situations, microvascularized grafts are the best option for treatment. However, the presence of a highly specialized multidisciplinary team is vital for the removal of the microvascularized graft, which, in addition to surgical morbidity, hampers the implementation of this approach.

A recently published study involving 40 patients with large mandibular defects (6–8 cm) reported that reconstruction with rhBMP-2/ACS in association with bone marrow aspirates and undifferentiated mesenchymal cells (including tenascin-C (TNC), $CD34^+$, and CFU) 6 months after grafting resulted in a favorable bone density for implant installation (737 Hounsfield units [HU]: measure unit for radiodensity used in computed tomoghraphic scans). TNC represents the total nucleated cells in the bone marrow aspirate; CD34 is a hematopoietic progenitor cell antigen, which represents a protein encoded by the *CD34* gene, expressed in the early hematopoietic and vascular-associated tissues; CFU is the number of colony-forming units of CD^+ cells—a measure of the number of $CD34^+$ cells in the bone marrow aspirate. These results are encouraging since they indicate a viable alternative for large reconstructions. Despite this body of results obtained from randomized clinical trials, which are considered highly reliable in terms of scientific evidence, there is still a necessity for further studies on this subject in order to evaluate the concentration of the osteoprogenitor cells and extent of clinical tolerance, as well as to perform long-term monitoring after functional loading.

Despite the high success rates of rhBMP-2 application, the development of immunological factors such as anti-rhBMP-2, anti-bovine collagen type I, and anti-human collagen type I antibodies needs to be considered. These factors could potentially affect the safety and efficacy of rhBMP-2. However, the risks of immune system interactions involving rhBMP-2 seem to be low [13, 29]. Therefore, further evaluation of the production of antibodies in response to rhBMP-2 should be performed to monitor the long-term safety of rhBMP-2 application.

Conclusions

Based on the results of our review of clinical studies involving the use of rhBMP2 in dentistry, it was concluded the following that:

1. The use of rhBMP-2/ACS for the preservation of the alveolar ridge after tooth extraction or for increasing the local defects is safe and viable.
2. The use of rhBMP-2/Bio-Oss® in maxillary sinus membrane elevation is unnecessary. It can, however, improve and accelerate the maturation process in cases of guided bone regeneration in the treatment of peri-implant defects. However, the use of rhBMP-2 for long-term bone maintenance is unnecessary.
3. Compounds comprising rhBMP-2, allogenic bone, and PRP might act as substitutes for autogenous grafts in maxillary critical defects.
4. In large mandibular defects (6–8 cm), the use of rhBMP-2/ACS, bone marrow aspirates, and undifferentiated mesenchymal cells together results in favorable bone density for implant installation.

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