ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Review Article

rhBMP-2 Effectiveness in Alveolar Ridge Augmentation, Ridge Preservation and Maxillary Sinus Lift: Meta-Analyses

Bassam M Kinaia[1]*, Christopher Pham[2], Hana Gadalla[3], Omar Mario Masabni[4], Maanas Shah[5], Kashif Naqvi[6], Michael Haddow[7], Karishma Choksi[8], Abdullah Othman[9], Krupa Patel[10] and Anthony L Neely[11]

[1]Director and Associate Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[2]Postgraduate Periodontal Resident, Graduate Periodontics Program, University of Southern California, CA, USA

[3]Clinical Assistant Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[4]Postgraduate Periodontal Resident, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[5]Faculty, Periodontology Department, Hamdan Bin Mohammed College of Dental Medicine, Dubai, UAE.

[6]Private Practice, Redford, MI, USA

[7]Clinical Associate Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[8]Clinical Assistant Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[9]Clinical Assistant Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

[10]Private Practice, Sterling Heights, MI, USA

[11]Associate Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA

***Corresponding Author:** Bassam M Kinaia, Director and Associate Professor, Division of Graduate Periodontics, University of Detroit Mercy School of Dentistry, Detroit, MI, USA.

Received: December 18, 2018; **Published:** January 11, 2019

Abstract

Context: Alveolar bone deficiencies adversely affect proper dental implant placement in a correct restorative position. Thus, localized ridge augmentation (RA), ridge preservation (RP), and maxillary sinus lift (SL) using bone grafts or biological agents such as recombinant human bone morphogenetic protein-2 (rhBMP-2) are often employed to restore the bone.

Aim and Objective: This systematic review assesses the effects of using rhBMP-2 on bone changes in RA, RP and SL.

Materials and Methods: Literature reviews of the COCHRANE and MEDLINE electronic databases and hand searching up to January 2017 was carried out. Three reviewers independently and in triplicates identified eligible studies and assessed the data and methodological quality using specific data extraction and assessment forms. This systematic review was conducted according to the PRISMA and MECIR guidelines.

Results: The search identified 189 potential publications. After review of abstracts and titles, 33 articles qualified for full text review. Only 6 studies satisfied the inclusion criteria. Two studies evaluated bone width in ridge augmentation with rhBMP-2 versus without rhBMP-2 (ACS, bone graft or no treatment) at the crest and apex. Difference in means was 1.043 mm [SD 0.318 (95% CI, 0.420 to 1.666)] at crest, and 0.271 mm [SD 0.358 (95% CI, -0.431 to 0.974)] at apex showing slightly better bone width with rhBMP-2 with statistical significance for the crest width only. Two studies evaluated bone width in ridge preservation with rhBMP-2 versus without rhBMP-2 (ACS or bone graft only). Difference in means was 0.662 mm [SD 0.535 (95% CI, -0.484 to 1.809)] showing significantly greater increase in bone width in patients treated with rhBMP-2. Two studies evaluated bone height in sinus lift with rhBMP-2 versus conventional bone grafting. Difference in means was -1.593 mm [SD 0.315 (95% CI, -2.210 to -0.976)] in favor of conventional bone grafts. Heterogeneity was noted among the studies.

Conclusion: The studies presented in these meta -analyses show that rhBMP-2 is an effective alternative to bone grafts alone in restoring alveolar ridge deficiencies. The use of rhBMP-2 in ridge augmentation showed slightly better bone width compared to its use in ridge preservation. The use of rhBMP-2 in ridge augmentation and ridge preservation was effective in maintaining bone width compared to patients treated without rhBMP-2 (ACS, bone graft or no treatment). However, rhBMP-2 was less effective in sinus lift bone height gain compared to patients receiving bone grafts. The aforementioned results should be interpreted with caution. Moreover, definitive conclusions regarding rhBMP-2 cannot be made due to limited number of studies and heterogeneity present.

Keywords: *Recombinant Human Morphogenetic Protein; Alveolar Ridge Augmentation; Dental Implants; Bone Graft; Maxillary Sinus; Systematic Review*

Abbreviations

RA: Ridge Augmentation; RP: Ridge Preservation; SL: Sinus Lift; rhBMP-2: Recombinant Human Bone Morphogenetic Protein-2; ACS: Acellular Collagen Sponge; PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis; MECIR: Methodological Expectations of Cochrane Intervention Reviews

Introduction

Alveolar bone deficiency is a common finding post extraction and can adversely affect the ideal prosthetic placement of dental implants. The literature cites compromised implant stability or esthetic dilemmas around implants placed in alveolar ridges with insufficient bone [1-5]. Post extraction, approximately 50% of bone volume is lost with the most happening in the initial 6 - 12 months [6]. Therefore, procedures aimed at bone regeneration and preservation post-extraction are important to maintain adequate bone quantity and quality for proper implant placement. In deficient ridges, guided bone regeneration (GBR) via alveolar ridge augmentation (RA) or sinus lift (SL) are routinely used [7]. Ridge preservation (RP) involves placement of bone graft concurrently with extraction to maintain better bone volume [8]. Numerous types of bone grafts, growth and differentiating factors are used for RA, RP and SL [2,9]. Though bone grafts are widely used with considerable success and safety, research has continued to explore biologically active molecules such as recombinant human bone morphogenetic protein- 2 (rhBMP-2) that is a differentiating factor used in bone regeneration with high osteoinductive properties [10-12]. The use of rhBMP-2 with a carrier "acellular collagen sponge (ACS)" promotes chemotaxis, proliferation, and differentiation of undifferentiated cells into osteoblasts [13]. The first human pilot study using rhBMP-2 in sinus lift augmentation demonstrated 100% new bone formation [10]. The newly regenerated bone was deemed adequate for only 73% of the patients [10].

The literature cites conflicting reports for the effect of rhBMP-2 effect on bone growth. Some studies show significant benefits of rhBMP-2 on increasing bone height and width [14-16], while others demonstrate either considerable shrinkage using rhBMP-2 alone or no increase in alveolar ridge width or height [12]. To improve rhBMP-2 efficacy in space maintenance, a later study proposed that graft shrinkage can be prevented by adding a bone graft to the ACS [17]. Implant survival with rhBMP-2 is approaching 100% and is comparable to implants placed in regenerated bone [2]. Although the literature cites promising potential for use of rhBMP-2 in RA, RP and SL, the results are inconclusive. The objective of this meta-analysis is to systematically assess the effect of rhBMP-2 in alveolar ridge augmentation, ridge preservation, and sinus lift procedures and report on adverse effects associated with rhBMP-2.

Material and Methods

Information Sources

This meta-analyses were performed following the "Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement" [18], the "Cochrane Collaboration recommendations" [19] and the "Methodological Expectations of Cochrane Intervention Reviews (MECIR)" [20].

The focused PICO Question was:

- P: Completely or partially edentulous healthy patients with alveolar ridge deficiency.
- I: Regenerative therapies using rhBMP-2 for alveolar ridge augmentation, ridge preservation or maxillary sinus lift.
- C: Change in ridge dimensions using rhBMP-2 compared to other regenerative therapies.
- O: The primary outcome was to calculate difference in ridge width or height in millimeters (mm). The secondary outcome was adverse effects associated with rhBMP-2.

Screening process

An electronic search of two electronic databases "the National Center for Biotechnology Information PubMed, Medline, and the Cochrane Collaboration Library" was completed in triplicates independently by three reviewers (BMK, CP, and KN). Publications in English

from 1966 up to January 2017 were selected. In addition to the online search, a hand search of references of reviews related to the topic of rhBMP-2 and regenerative therapies was conducted.

The following search terminology was performed using Boolean operators: "(BMP and bone grafting) OR (BMP and dental implants) OR (rhBMP-2 AND dental implants) OR (rhBMP-2 AND socket preservation) OR (rhBMP-2 AND maxillary sinus) OR ((rhbmp-2) OR (recombinant human morphogenetic protein 2) AND ("Alveolar Ridge Augmentation"[Mesh]))) OR ((rhbmp-2) OR recombinant human morphogenetic protein 2) AND ("Graft Survival"[Mesh]))) OR ((growth factor) OR (rhbmp-2) OR recombinant human morphogenetic protein 2) AND dental)) OR ((rhbmp-2) OR (recombinant human morphogenetic protein 2) AND periodontal))".

Eligibility criteria

The inclusion criteria included manuscripts that had to be: 1) Clinical trials, randomized controlled trials, controlled clinical trials, case reports, or case series 2) published in English; 3) conducted on human participants; 4) have at least five participants; 5) primary treatment outcomes reported on clinical, radiographic findings, and/or adverse effects related to rhBMP-2; and 6) a minimum of 3 months follow-up.

The manuscripts were excluded if: 1) inclusion criteria not matched; 2) they had missing data relevant to the treatment outcomes.

Risk for bias

An excel data-collection form was used independently by three reviewers (BMK, CP and KN) to collect the following study information: 1) author and year of publication; 2) study category; 3) randomization technique; 4) treatment groups; 5) patient demographics; 6) clinical or radiographic bone formation; 7) carrier type; 8); regenerative procedure and materials used; 9) adverse effects; and 10) follow-up time.

The data was screened and evaluated independently according to the MECIR [20] and PRISMA [18] parameters. If a disagreement occurred, it was resolved by discussion. When a selected publication was missing relevant data, the corresponding authors were contacted to seek complete ascertainment of the data.

Qualitative assessment

The Cochrane Assessment of Allocation Concealment [21] and the Jadad-Score Calculation [22] were used for methodological assessment. The Cochrane Assessment used grades "A, B, C, D" for the validity and randomization of the studies where grade A and B had low risk for bias, and C and D had high risk for bias. The Jadad scale used points "0, 1, 2, 3, 4, 5" with of 3 to 5 signifying high study quality.

Statistical analysis

The mean new bone formation measured in millimeters was the basis for data analyses. Mean differences were compared using Hedges g statistic for meta- analysis and 95% confidence intervals (CI) were calculated. Statistically significant differences were reported when $p < 0.05$. Meta-analyses were carried out using Comprehensive Meta-Analysis statistical software. Random effects models were used to correct for heterogeneity between studies.

Study of heterogeneity

The value of I2 measured heterogeneity with value of 75% or higher representing higher heterogeneity due to the moderate insensitivity of the Q statistic [23].

Results

Study selection

The electronic search identified 187 articles and the hand search added 2 more for a total of 189 studies. Based on title and abstract review, 33 relevant studies were selected for full text review. From the 33 studies, 27 did not meet the inclusion criteria and the remaining 6 studies reported data and exhibited a test and control arm allowing a series of meta-analyses to be performed (Figure 1). Kappa statistic

was used to calculate the inter-observer agreement (Kappa value = 0.8907, SE = 0.0566, 95% CI = 0.78 to 1.00). Characteristics of the 6 studies [24-29] are summarized in table 1.

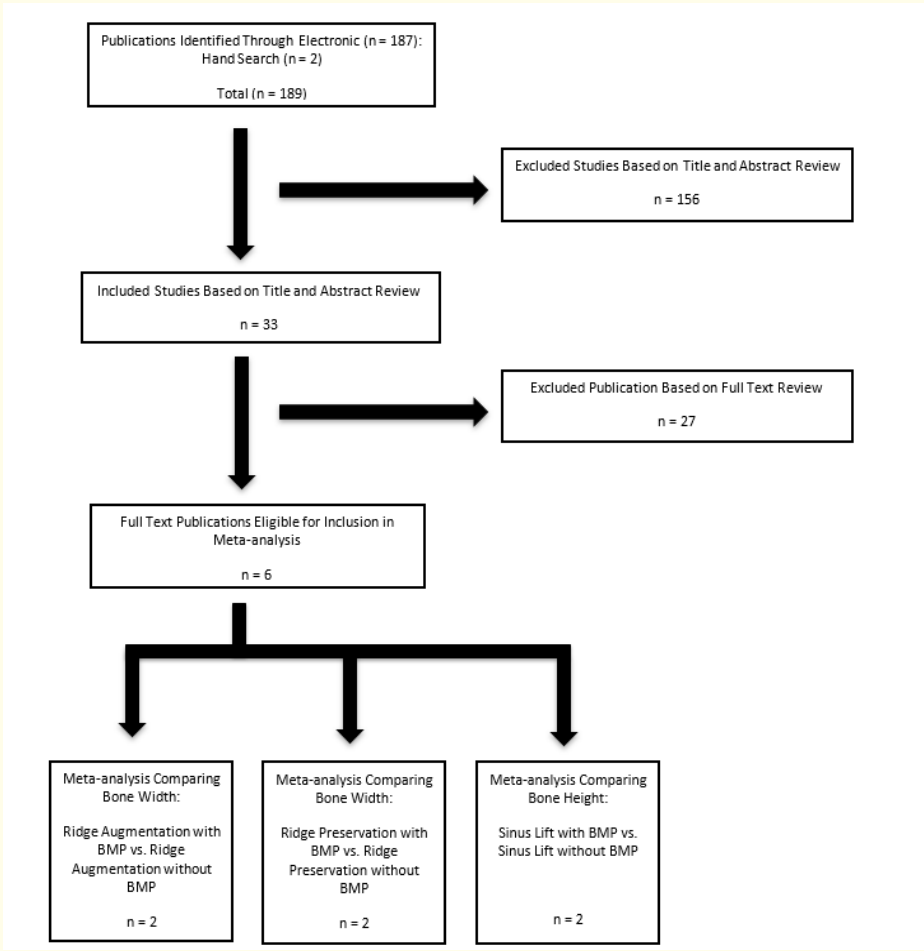

Figure 1: *Flow chart for identification of publications according to PRISMA principles for systematic reviews.*

Qualitative assessment

All 6 studies were randomized clinical trials (RCTs) [24-29]. All 6 RCTs scored high (Grade A to B according to the Cochrane allocation of concealment. Five RCTs [24,25,27-29] scored high on the Jadad score (Score of 1 - 3) and only one [26] study scored low (4 out of 5) (Table 1).

Author/Year	**de Freitas., et al. (2013) [24]**	
Study Design	RCT	
Treatment Groups (Intervention)	Alveolar Ridge Augmentation: rhBMP-2/ACS	Alveolar Ridge Augmentation: Autogenous
Number of Patients (Mean/Range of Age in Years)	12 (42.4)	12 (47.7)
Concentration BMP (mg/mL)	1.5	(NC/NA)
Total Dose per Site (mg)	4.2	(NC/NA)
Carrier Type	ACS	(NC/NA)
Bone Volume (cm^3)	(NC/NA)	(NC/NA)
Bone Height (mm)	(NC/NA)	(NC/NA)
Bone Width (mm) at Crest (C) Apex (A)	 C: 1.5 ± 0.7 A: 1.7 ± 0.9	 C: 0.9 ± 0.5 A: 1.8 ± 1.1
Bone Density	(NC/NA)	(NC/NA)
New Bone (%)	(NC/NA)	(NC/NA)
Re-evaluation Time (Months)	6	6
Number of Implants	32	30
Type of Definitive Restoration (Time Delivered in months)	(NC/NA)	(NC/NA)
Implant Survival Rate	100	100
Allocation Concealment	Grade A	
Jadad Score	3	

Author/Year	Fiorellini., et al. (2005) [25]			
Study Design	RCT			
Treatment Groups (Intervention)	Alveolar Ridge Augmentation: rhBMP-2/ACS	Alveolar Ridge Augmentation: rhBMP-2/ACS	Alveolar Ridge Augmentation: ACS Only	No Treatment
Number of Patients (Mean/Range of Age in Years)	22 (47.4)	21 (47.4)	17 (47.4)	20 (47.4)
Concentration BMP (mg/mL)	0.75	1.50	(NC/NA)	(NC/NA)
Total Dose per Site (mg)	0.9	1.9	(NC/NA)	(NC/NA)
Carrier Type	ACS	ACS	(NC/NA)	(NC/NA)
Bone Volume (cm^3)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Bone Height (mm)	-0.62 ±1.39	- 0.02 ± 1.2	- 1.0 ± 1.4	-1.17 ± 1.23
Bone Width (mm) at Crest (C) Apex (A)	 C: 1.76 ± 1.67 A: 2.29 ± 1.07	 C: 3.27 ± 2.53 A: 2.68 ± 1.37	 C: 0.82 ± 1.4 A: 1.82 ± 1.5	 C: 0.57 ± 2.56 A: 1.65 ± 2.06
Bone Density	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
New Bone (%)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Re-evaluation Time (Months)	4	4	4	4
Number of Implants	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Type of Definitive Restoration (Time Delivered in months)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Implant Success Rate	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Implant Survival Rate	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Observation Period After Loading (months)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Allocation Concealment	Grade B			
	3			

Author/Year	Boyne., et al. (2005) [26]			Triplett., et al. (2009) [29]	
Study Design	RCT			RCT	Prospective
Treatment Groups (Intervention)	Sinus Augmentation: rhBMP-2/ACS	rhBMP-2+ACS	Sinus Augmentation: Autogenous OR Autogenous + Allogenous	rhBMP-2+ACS	Clinical Trial autogenous + allogenous bone
Number of Patients (Mean/Range of Age in Years)	18 (57)	17 (52)	13 (57)	82 (53.6)	78 (51.4)
Concentration BMP (mg/mL)	0.75	1.5	(NC/NA)	1.5	0
Total Dose per Site (mg)	8.9	20.8	(NC/NA)	12.9	0
Carrier Type	ACS	ACS	(NC/NA)	ACS	(NC/NA)
Bone Volume (cm^3)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Bone Height (mm)	9.47 ± 5.72	10.16 ± 4.7	11.29 ± 4.12	7.83 ± 3.52	9.46 ± 4.11
Bone Width (mm) at Crest (C) Apex (A)	 C: 2.02 ± 2.73 A: 11.86 ± 5.15	 C: 1.98 ± 2.41 A: 10.78 ± 4.63	 C: 4.66 ± 2.75 A: 10.56 ± 3.17	 N/A	 N/A
Bone Density (at 4 months)	84 ± 50 mg/cc	137 ± 77 mg/cc	350 ± 243 mg/cc	283	200
New Bone (%)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Re-evaluation Time (Months)	4	6	4	6	6
Number of Implants	83	73	63	240	243
Type of Definitive Restoration (Time Delivered in months)	Single Tooth + FPD + Over Denture	Single Tooth + FPD + Over Denture	Single Tooth + FPD + Over Denture	(NC/NA)	(NC/NA)
Implant Success Rate	71	71	52	83	90
Implant Survival Rate	88	79	81	87	87
Observation Period After Loading (months)	36	36	36	(NC/NA)	(NC/NA)
Allocation Concealment	Grade B			Grade B	
	4			1	

Author/Year	Kim., et al. (2014) [27]		Coomes., et al. (2014) [28]	
Study Design	RCT	RCT	RCT	RCT
Treatment Groups (Intervention)	rhBMP2 + Injectable demineralized bone matrix gel	Injectable demineralized bone matrix gel alone	rhBMP-2+ACS	Collagen Sponge
Number of Patients (Mean/Range of Age in Years)	29 (50.37)	30 (51.18)	14	17
Concentration BMP (mg/mL)	0.05	0	1.5	0
Total Dose per Site (mg)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Carrier Type	Resorbable Membrane + Allo bone graft	Resorbable Membrane	ACS	(NC/NA)
Bone Volume (cm^3)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Bone Height (mm)	-1.17 ± 0.82	-1.5 ± 1.07	(NC/NA)	(NC/NA)
Bone Width (mm) at Crest (C) Apex (A)	 C: -1.06 ± 1.26 A: -0.23 ± 0.45	 C: -1.21 ± 1.31 A: -0.37 ± 0.61	C: -2.07±1.17	C: -3.4±1.73
Bone Density	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
New Bone (%)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Re-evaluation Time (Months)	3	3	5	5
Number of Implants	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Type of Definitive Restoration (Time Delivered in months)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Implant Success Rate	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Implant Survival Rate	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Observation Period After Loading (months)	(NC/NA)	(NC/NA)	(NC/NA)	(NC/NA)
Allocation Concealment	Grade A		Grade A	
Jadad Score	2		2	

Table 1: *Characteristics of the 6 studies included in the systematic review.*

Prosp CT: Prospective Clinical Trial; RCT: Randomized Clinical Trial; NC/NA: Not Clear or Not Available; ACS: Acellular Collagen Sponge; rhBMP-2: Recombinant Human Bone Morphogenic Protein-2.

Intergroup meta-analysis

The 6 studies included a total of 467 patients (ages 18 to 79) with 4 to 36 months follow-up. Of the patients treated in the rhBMP-2 group, 66, 55 and 128 had RA, RP and sinus lifts, respectively.

Meta-analysis: Alveolar ridge augmentation with or without rhBMP-2 reporting on bone width

Two studies [24,25] evaluated the effects of rhBMP-2 in RA on alveolar bone width measured at the crest and the apex of the ridge compared to control patients receiving ACS or autogenous bone alone. Patients received rhBMP-2 with concentrations of 0.75 mg/mL and 1.50 mg/mL [25] and 1.50 mg/mL [24] and were reevaluated after four-six months. The treatment groups varied in concentration of rhBMP-2, and were pooled together (22 received 0.75 mg/mL, and 33 received 1.50 mg/mL) for both studies [24,25]. The rhBMP-2 group (test) had 35 patients while the control group included 49 patients. The difference in means at the crest was 1.043 mm [SD 0.318 (95% CI, 0.420 to 1.666)] showing greater horizontal bone gain at the crest in patients treated with rhBMP-2. The difference in horizontal bone gain was statistically significant (p = 0.615) without heterogeneity between the studies (I2 = 0.00%) (Figure 2A). The difference in means at the apex was 0.271 mm [SD 0.358 (95% CI, -0.431 to 0.974)] showing greater horizontal bone gain in patients with rhBMP-2. There was no statistical difference (p = 0.135) with slight heterogeneity between the studies (I^2 = 38.12%) (Figure 2B).

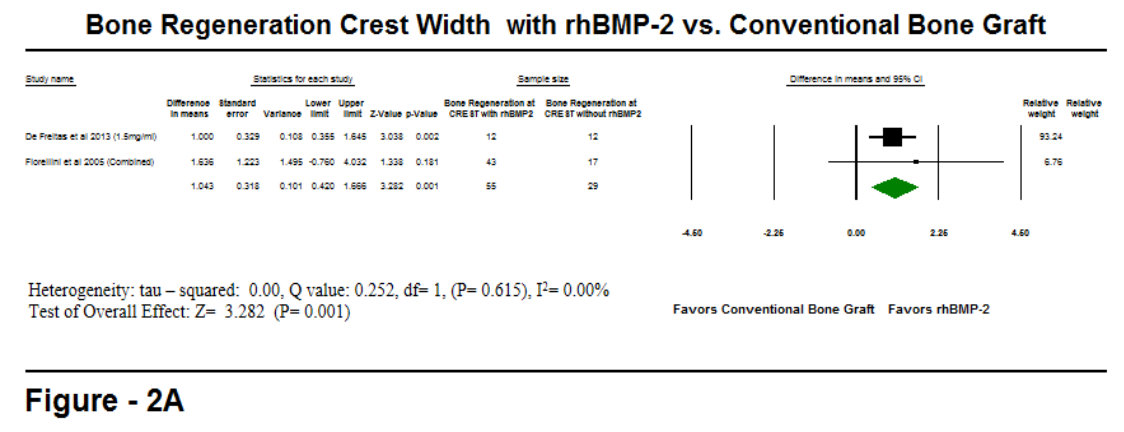

Figure - 2A

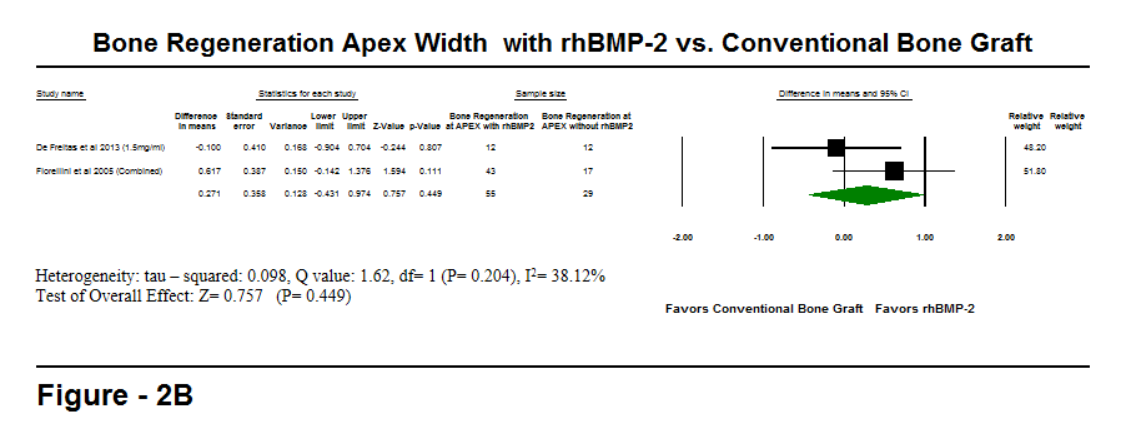

Figure - 2B

Figure 2: *Forest plot comparing bone width: A) conventional versus rhBMP-2 alveolar ridge augmentation at the crest. B) conventional versus rhBMP-2 alveolar ridge augmentation at the apex. (df = degrees of freedom; I2 = Heterogeneity).*

Meta-analysis: Ridge preservation with or without rhBMP-2 reporting on bone width

Two studies [28,30] evaluated the effects of rhBMP-2 on alveolar bone width in patients receiving RP. Coomes., *et al.* [28] utilized 1.50 mg/mL rhBMP-2/ACS in 14 patients and compared it to ACS alone in 17 patients. Kim., *et al.* [30] utilized 0.05 mg/mL rhBMP-2 with a demineralized bone matrix (DBM) carrier in 29 patients compared to DBM alone in 30 patients with follow up of three to five months. Whereas the treatment groups varied in rhBMP-2 concentration and carrier, they were pooled together to allow enough data for analysis. The difference in means was 0.662 mm [SD 0.535 (95% CI, -0.484 to 1.809)] indicating greater increase in alveolar bone width in patients treated with rhBMP-2. There was no statistical difference ($p = 0.257$) and substantial heterogeneity was noted between the studies ($I^2 = 70.76\%$) (Figure 3).

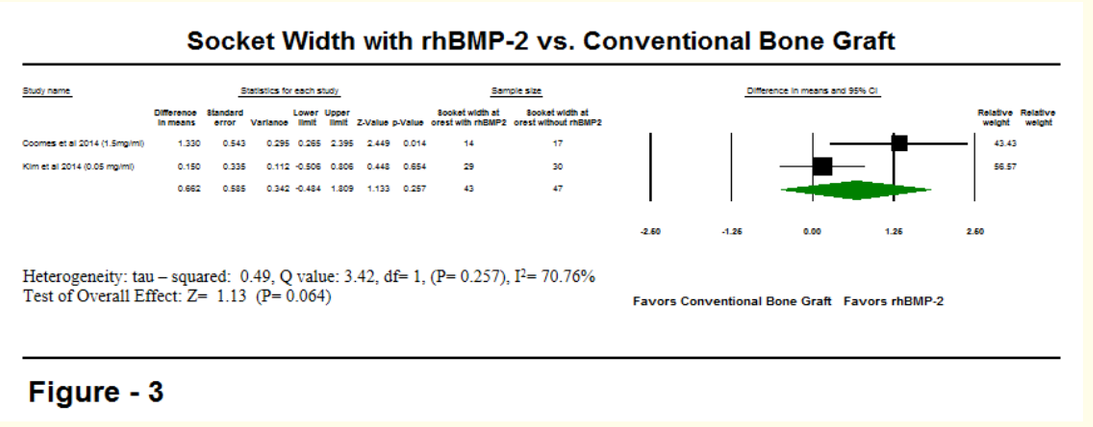

Figure 3: *Forest plot comparing bone width: conventional versus rhBMP-2 ridge preservation. (df = degrees of freedom; I2 = Heterogeneity).*

Meta-analysis: Maxillary sinus lift with or without rhBMP-2 reporting on bone height

Two studies [26,29] exhibited test and control arms allowing a meta-analysis to be conducted. The studies evaluated the effects of rhBMP-2/ACS in sinus augmentation procedures versus conventional bone grafts on bone height. Triplett., *et al.* [29] compared 1.50 mg/mL rhBMP-2/ACS to an autograft. Boyne., *et al.* [26] compared 0.75 mg/mL and 1.50 mg/mL rhBMP-2/ACS to autogenous only or a combination of autogenous and allogenic bone graft.

The different concentration groups were pooled together to allow a more robust analysis. A total of 18 received 0.75 mg/ml, and 99 received 1.50 mg/ml. The difference in means was -1.593 mm [SD 0.315 (95% CI, -2.210 to -0.976)]. There was greater increase in bone height in patients treated with the bone graft compared to rhBMP-2/ACS. The difference in bone height was statistically significant ($p < 0.05$). No heterogeneity was noted between the studies ($I^2 = 0.00\%$) (Figure 4).

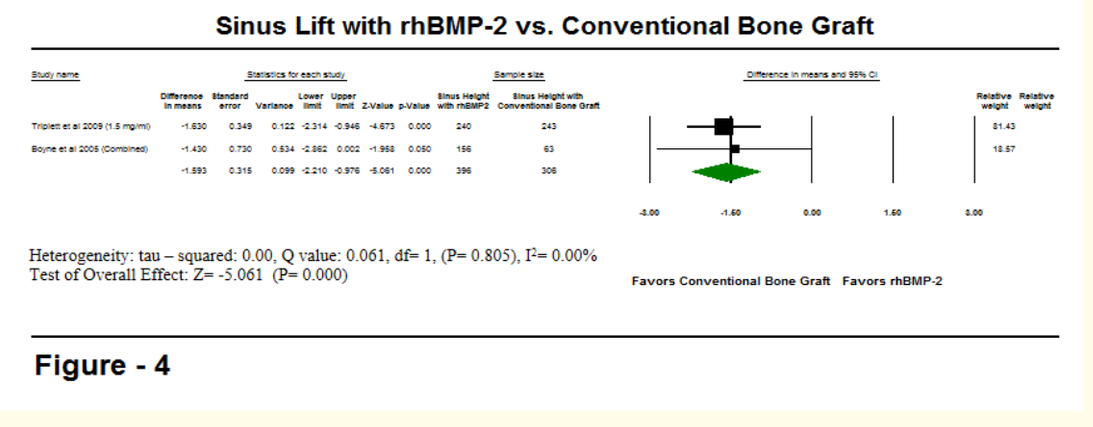

Figure : *Forest plot comparing bone height: conventional versus rhBMP-2 sinus lift. (df = degrees of freedom; I2 = Heterogeneity).*

Adverse events

While no safety issues were associated with use of rhBMP-2, higher post-surgical events such as edema, oral pain and erythema were reported. Two studies [25,29] reported greater frequency of oral edema in groups treated with rhBMP-2 compared to control groups. Fiorellini., *et al.* [25] reported 250 events for 78 of the 80 enrolled patients, with the most frequent being oral edema (75%), mouth pain (68%), and oral erythema (46%) and these events were higher compared to the extraction only group. In addition, groups treated with 1.50 mg/mL of rhBMP-2 (n = 14) experienced greater frequency of oral edema compared to the 0.75 mg/mL group (n = 7) [26]. With regard to pain, patients in the bone graft group experienced greater pain with the autograft harvest site compared to rhBMP-2 [26].

With regard to long-term efficacy of rhBMP-2, an early study [12] evaluated the use of rhBMP-2 in RA versus RP on alveolar bone height with a three- year follow-up [15]. There were a total of 5 patients in the RA group and 6 in the RP group. The study utilized 0.43 mg/mL concentration of rhBMP-2 with ACS. The difference in means was -0.086 mm [SD 0.754 (95% CI, - 1.564 to -1.392)] indicating slightly better bone height in RA compared to RP. However, the difference was not statistically significant (p = 0.909) without heterogeneity between the studies (I^2 = 0.00%).

Discussion

Recombinant human bone morphogenetic protein (rhBMP-2) with a proven ability to induce bone growth, was approved by the Food and Drug administration based on superior results in spinal fusion procedures [31]. This systematic review focuses on highlighting the efficacy of rhBMP-2 in three different treatment scenarios.

Intergroup meta-analysis

Meta-analysis: Alveolar ridge augmentation with or without rhBMP-2 reporting on bone width

The first meta-analysis included two studies comparing the use of rhBMP-2 in RA versus control showing greater horizontal bone width for the rhBMP-2 group wit mean difference of 1.043 mm at the crest and 0.271 mm at the apex [24,25]. A recent systematic review [32], included two studies reporting on bone width in RA using rhBMP-2 without conducting a meta -analysis. One study reported no difference between the rhBMP-2 and the autogenous bone groups [24], while the second study showed better bone width gain with the rhBMP-2 group (-3.40 + 1.73) compared to the control (autogenous) group (-2.07 + 1.17) [28]. Although, the current meta -analysis shows that the rhBMP-2 group has a better outcome, one should be remember that the slight heterogeneity (I^2 = 38.12%) observed between the studies at the apex could skew the results.

Meta-analysis: Ridge preservation with or without rhBMP-2 reporting on bone width

Alveolar ridge preservation is a well-documented procedure [28,30]. Recent reviews reported better bone width maintenance with RP 1.89 mm [33] and 1.31 to 1.54 mm [34] compared to extraction alone. The current meta-analysis showed bone gain of 0.662 mm favoring the rhBMP-2 group. This finding is in agreement with a recent systematic review that showed a volumetric gain of 0.104 cm^3 [35]. Although the rhBMP-2 shows promising results (0.662 mm gain), it is noteworthy that bone grafting alone has shown superior results (1.31 to 1.89 mm gain) compared to extraction alone [34,35]. This could be related to the fact that bone grafts take longer to resorb with better space maintenance compared to rhBMP-2 [17].

Meta-analysis: Maxillary sinus lift with or without rhBMP-2 reporting on bone height

Although the use of autogenous bone has been the gold standard, literature has shown that up to 55% of resorption can occur in the first 6 months in autogenous bone augmented sinus lift procedures [36]. A prospective clinical trial utilizing xenograft and a resorbable collagen membrane in the control group to augment the sinus resulted in mean residual graft values of ranging from 22.78 to 10.83% [37]. The use of rhBMP-2 has initially showed promising results as an alternative to bone graft. The current meta-analysis showed a

mean difference of -1.593 mm in favor of the bone graft compared to the rhBMP-2 group. A recent systematic review evaluated different concentrations of rhBMP-2 using pooled estimate instead of meta-analysis and reported similar results in favor of the bone graft group (-0.50 mm; P = 0.00) [32].

The current meta-analysis collapsed the two concentrations of rhBMP-2 and only reported rhBMP-2. While separating subjects would allow evaluation of the effect of rhBMP-2 at different concentrations, too few subjects were available to make this feasible. Kelly., *et al.* 2015 showed minimal heterogeneity (I^2 = 18.67) in their study compared to none in the present analysis (I^2 = 0%) [32].

Adverse effects

The use of rhBMP-2 in RA and RP seems to be less dimensionally stable with the loss of alveolar bone height after 3 years [15]. Assessment of the mean change in alveolar bone height and width from pre- to post- implantation in the alveolar ridge indicated a decrease in bone height (-0.8 mm) and width (- 3.6 mm) during the three-year follow-up period. The difference in means was -0.086 mm [SD 0.754 (95% CI, -1.564 to -1.392)] indicating slightly better bone height in RA compared to RP. In a recent publication [38] machined surface implants using bone xenograft and collagen membrane (GBR) were compared to standard implant placement without GBR. The 5-to 15-year follow-up examination revealed loss of interproximal marginal bone level that averaged 0.23 ± 0.70 mm for the GBR group and 0.28 ± 0.63 mm for the control group. Conventional grafting methods around dental implants have shown alveolar bone loss in long term follow-up studies and the results are comparable with rhBMP-2 studies [24,25].

Limitation and Recommendations for Future Research

The primary objective of the current review was to quantitatively evaluate the amount of bone augmentation obtained using rhBMP-2 in RA, RP and SL. While there were numerous publications on the use of rhBMP-2, only six could be included in this investigation because of inconsistencies in methods and reported data.

Conclusion

Clinical documentation of the effect of rhBMP-2 for ridge augmentation procedures and adverse events is sparse. Inadequacies in study design limit the use of these investigations. Hence, there is a need for additional RCTs evaluating rhBMP-2 for intra-oral bone augmentation in well-defined clinical studies. The significant high cost of rhBMP-2 may have contributed to the limited number of clinical studies utilizing it in intraoral ridge augmentation procedures. Meta-analyses and a systematic review were done to evaluate the bone changes after utilizing rhBMP-2 on RA, RP and SL. Within the limitations of the methodologies used, the studies presented in these meta-analyses show that rhBMP-2 is an effective alternative to bone grafts in restoring alveolar ridge deficiencies (height and width). The use of rhBMP-2 in ridge augmentation showed slightly better bone width compared to its use in ridge preservation. The use of rhBMP-2 in ridge augmentation and ridge preservation was effective in maintaining bone width compared to patients treated without rhBMP-2 (ACS, bone graft or no treatment). However, rhBMP-2 was less effective in sinus lift bone height gain compared to patients receiving bone grafts. Due to limited number of studies the results should be interpreted with caution and definitive conclusions regarding rhBMP-2 cannot be made.

Conflict of Interest

The authors declare that they have no conflicts of interest. No author received any monetary compensation for this manuscript.

Footnote

‖ Statistical thinking for managerial decisions: pooling the means, variances. ¶ Number Crunchers Statistical Software Program, NCSS, Kaysville, UT.

Bibliography

1. Cordaro L., *et al*. "Inlay-onlay grafting for three-dimensional reconstruction of the posterior atrophic maxilla with mandibular bone". *International Journal of Oral and Maxillofacial Surgery* 39.4 (2010): 350-357.

2. Jensen SS and H Terheyden. "Bone augmentation procedures in localized defects in the alveolar ridge: clinical results with different bone grafts and bone-substitute materials". *The International Journal of Oral and Maxillofacial Implants* 24 (2009): 218-236.

3. Evans CD and ST Chen. "Esthetic outcomes of immediate implant placements". *Clinical Oral Implants Research* 19.1 (2008): 73 -80.

4. Chen ST., *et al*. "Consensus statements and recommended clinical procedures regarding surgical techniques". *The International Journal of Oral and Maxillofacial Implants* 24 (2009): 272-278.

5. Chen ST and D Buser. "Clinical and esthetic outcomes of implants placed in postextraction sites". *The International Journal of Oral and Maxillofacial Implants* 24 (2009): 186-217.

6. Schropp L., *et al*. "Bone healing and soft tissue contour changes following single-tooth extraction: a clinical and radiographic 12-month prospective study". *The International Journal of Periodontics and Restorative Dentistry* 23.4 (2003): 313-323.

7. Eickholz P., *et al*. "Long-term results of guided tissue regeneration therapy with non-resorbable and bioabsorbable barriers. I. class II furcations". *Journal of Periodontology* 72.1 (2001): 35-42.

8. Worch KP., *et al*. "A multidisciplinary approach to the diagnosis and treatment of early-onset periodontitis: a case report". *Journal of Periodontology* 72.1 (2001): 96-106.

9. Lindhe J., *et al*. "Clinical periodontology and implant dentistry". 4th edition. Oxford, UK: Blackwell Munksgaard (2003): 667.

10. Boyne PJ., *et al*. "A feasibility study evaluating rhBMP-2/absorbable collagen sponge for maxillary sinus floor augmentation". *The International Journal of Periodontics and Restorative Dentistry* 17.1 (1997a): 11-25.

11. Cochran DL., *et al*. "Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants". *Journal of Periodontology* 70.2 (1999): 139-150.

12. Howell TH., *et al*. "A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation". *The International Journal of Periodontics and Restorative Dentistry* 17.2 (1997): 124-139.

13. Lee JB., *et al*. "Combined periodontal-prosthodontic treatment of early-onset periodontitis--an alternative to implant therapy". *The International Journal of Periodontics and Restorative Dentistry* 20.6 (2000): 604-611.

14. Jung RE., *et al*. "Effect of rhBMP-2 on guided bone regeneration in humans". *Clinical Oral Implants Research* 14.5 (2003): 556-568.

15. Cochran DL., *et al*. "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". *Journal of Periodontology* 71.8 (2000): 1241-1257.

16. Boyne PJ., *et al*. "A feasibility study evaluating rhbmp-2/absorbable collagen sponge for maxillary sinus floor augmentation". *The International Journal of Periodontics and Restorative Dentistry* 17.1 (1997b): 11-25.

17. Tarnow DP., *et al*. "Maxillary sinus augmentation using recombinant bone morphogenetic protein-2/acellular collagen sponge in combination with a mineralized bone replacement graft: a report of three cases". The *International Journal of Periodontics and Restorative Dentistry* 30.2 (2010): 139-149.

18. Moher D., *et al*. "PRISMA Statement". *Epidemiology* 22.1 (2011): 128.

19. Higgins JP., *et al*. "The cochrane collaboration's tool for assessing risk of bias in randomised trials". *BMJ (Clinical Research Edition)* 343 (2011): d5928.

20. Higgins Julian PT., *et al*. "Methodological expectations of cochrane intervention reviews (MECIR)". London (2016).

21. Higgins J and Green S. "Assessment of study quality". The Cochrane Handbook for Systematic Reviews of Interventions 4.2.6. Chichester, UK: John Wiley and Sons, Ltd (2006): 79-84.

22. Jadad AR., *et al*. "Assessing the quality of reports of randomized clinical trials: is blinding necessary?" *Controlled Clinical Trials* 17.1 (1996): 1-12.

23. Higgins JP and SG Thompson. "Quantifying heterogeneity in a meta-analysis". *Statistics in Medicine* 21.11 (2002): 1539-1558.

24. de Freitas RM., *et al*. "Horizontal ridge augmentation of the atrophic anterior maxilla using rhBMP- 2/ACS or autogenous bone grafts: a proof-of -concept randomized clinical trial". *Journal of Clinical Periodontology* 40.10 (2013): 968-975.

25. Fiorellini JP., *et al*. "Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation". *Journal of Periodontology* 76.4 (2005): 605-613.

26. Boyne PJ., *et al*. "De novo bone induction by recombinant human bone morphogenetic protein-2 (rhBMP-2) in maxillary sinus floor augmentation". *Journal of Oral and Maxillofacial Surgery* 63.12 (2005): 1693-1707.

27. Kim JH., *et al*. "Extraction sockets: erratic healing impeding factors". *Journal of Clinical Periodontology* 41.1 (2014): 80-85.

28. Coomes AM., *et al*. "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". *Journal of Periodontology* 85.4 (2014): 525-535.

29. Triplett RG., *et al*. "Pivotal, randomized, parallel evaluation of recombinant human bone morphogenetic protein-2/absorbable collagen sponge and autogenous bone graft for maxillary sinus floor augmentation". *Journal of Oral and Maxillofacial Surgery* 67.9 (2009): 1947-1960.

30. Kim YJ., *et al*. "Ridge preservation using demineralized bone matrix gel with recombinant human bone morphogenetic protein-2 after tooth extraction: a randomized controlled clinical trial". *Journal of Oral and Maxillofacial Surgery* 72.7 (2014): 1281-1290.

31. Burkus JK., *et al*. "Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2". *Spine* 27.21 (2002): 2396-2408.

32. Kelly MP., *et al*. "Systematic review and meta-analysis of recombinant human bone morphogenetic protein-2 in localized alveolar ridge and maxillary sinus augmentation". *Journal of Oral and Maxillofacial Surgery* 74.5 (2016): 928-939.

33. Avila-Ortiz G., *et al*. "Effect of alveolar ridge preservation after tooth extraction: a systematic review and meta-analysis". *Journal of Dental Research* 93.10 (2014): 950-958.

34. Willenbacher M., *et al*. "The Effects of Alveolar Ridge Preservation: A Meta-Analysis". *Clinical Implant Dentistry and Related Research* 18.6 (2016): 1248-1268.

35. Moslemi N., *et al*. "Outcomes of alveolar ridge preservation with recombinant human bone morphogenetic protein-2: a systematic review". *Implant Dentistry* 27.3 (2018): 351-362.

36. Handschel J., *et al*. "A Histomorphometric Meta-analysis of sinus elevation with various grafting materials". *Head and Face Medicine* 5 (2009): 12.

37. Yu H., *et al*. "A prospective randomized controlled trial of the two-window technique without membrane versus the solo-window technique with membrane over the osteotomy window for maxillary sinus augmentation". *Clinical Implant Dentistry and Related Research* 19.6 (2017): 1099-1105.

38. Benic GI., *et al*. "Primary ridge augmentation with collagenated xenogenic block bone substitute in combination with collagen membrane and rhBMP-2: A pilot histological investigation". *Clinical Oral Implants Research* 28.12 (2017): 1543-1552.

Volume 18 Issue 2 February 2019