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EFFECT OF RECOMBINANT HUMAN BONE MORPHOGENIC PROTEIN-2 AS AN ADJUNCT IN GUIDED BONE REGENERATION AND IN SUBJECTS WITH PERIODONTITIS- A SYSTEMATIC REVIEW AND METANALYSIS

Periodontology

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ABSTRACT

Aim: Periodontal therapy aims to preserve teeth in health and function. While autografts are the gold standard for bone regeneration, their limitations have led to using substitutes and growth factors like bone morphogenetic protein-2 (BMP-2). BMP-2 is highly osteo inductive and, when combined with carriers, enhances bone regeneration. Despite promising animal data, comprehensive human studies are limited. This systematic review and meta-analysis assessed rhBMP-2's efficacy in adult periodontitis patients. **Methods:** The review followed PRISMA 2020 guidelines and was registered in PROSPERO (CRD42024543617). Electronic databases were searched for studies evaluating rhBMP-2 as an adjunct for bone and periodontal regeneration in periodontitis. Outcomes included alveolar height and width changes, new bone formation, defect depth, probing depth (PD), clinical attachment level (CAL), and gingival index (GI). Study quality was assessed using the Cochrane ROB-2 tool. Meta-analysis employed standardized mean difference (SMD) and a random-effects model via Review Manager (RevMan) 5.3, with significance at $p < 0.05$. **Results:** Nine randomized controlled trials were included, with seven in meta-analysis. Pooled data showed rhBMP-2 improved clinical, aesthetic, and satisfactory outcomes, including greater bone formation and regeneration. It also enhanced alveolar ridge preservation and was effective in complex defects. Included studies had low to moderate risk of bias, and funnel plots indicated minimal publication bias. **Conclusion:** RhBMP-2 is an effective, minimally invasive method to improve bone and periodontal regeneration with few complications and enhanced post-surgical bone formation. However, larger clinical trials with longer follow-up are needed to confirm these results and provide stronger evidence.

KEYWORDS

Alveolar Ridge Augmentation, Bone Morphogenetic Protein, Bone Regeneration, Periodontal Regeneration, Systematic Review, Tooth Extract

INTRODUCTION

The primary goal of periodontal therapy is to create conditions that maintain the patient's dentition in health, comfort, and function.[1] Despite many availabletreatments, clinicians seek more predictable, less technique-sensitive regenerative options that promote faster tissue repair and suit various periodontal defects.[2] Synthetic barrier membranes help support the right progenitor cells at the wound site.[3]

Urist, Reddi, and Huggins discovered that devitalized and demineralized bone matrix can induce heterotrophic osteogenesis.[4] Bone morphogenetic proteins-2 (BMP-2), found within the bone matrix, possess osteogenic and osteoinductive properties that stimulate new bone formation [5].

Guided regeneration is a common outpatient dental procedure, enhanced by substitute materials.[6] Autogenous bone grafts remain the gold standard due to superior osteogenesis but have limitations like donor site surgery, complications, and limited supply.[7][8] Consequently, allogenic, xenogenic, and alloplastic grafts are used alone or combined for bone regeneration.[9]

Unlike conventional bone substitutes that are osteoconductive or weakly osteoinductive, bone morphogenetic proteins (BMPs) possess strong osteoinductive abilities and are studied as novel graft materials for bone regeneration.[10] As potent cytokines, they drive bone development by inducing mesenchymal progenitor cells to become osteoblasts.[11]

BMPs, a family of over 20 proteins in the transforming growth factor-β family, regulate key fetal and postnatal functions.[12] Recombinant human BMP-2 (rhBMP-2) has shown significant bone and cementum regeneration in dogs, with animal studies confirming enhanced periodontal healing using BMP-2 and BMP-7 in defects.[13][14][15]

Recombinant human BMP-2 (rhBMP-2) alone induces bone formation, but its osteoinductive effect is greatly enhanced when delivered with a biomaterial carrier.[10] The carrier provides a 3D scaffold for osteogenic cell growth and controlled growth factor release, defining the space for new mineralized tissue.[11] In dogs, rhBMP-2 with a collagen foam carrier increased bone formation in intra-bony defects without side effects like ankylosis or bone resorption.[12]To date, no comprehensive qualitative or quantitative analysis exists on the efficacy of recombinant human bone morphogenetic protein-2 (rhBMP-2) as an adjunct for guided bone and periodontal regeneration in periodontitis patients. This systematic review was conducted to evaluate rhBMP-2's effectiveness in adults with periodontitis through a novel meta-analysis.

Rationale

The study aims to evaluate recombinant human bone morphogenetic protein-2 (rhBMP-2) as an alternative to autografts for bone and periodontal regeneration. While autografts are effective, their limitations have prompted exploration of rhBMP-2, which shows strong bone-inducing properties in animal studies. However, comprehensive human evidence is lacking. This review and meta-analysis address this gap by assessing clinical trial data on rhBMP-2's efficacy in adult periodontitis patients, aiming to provide clearer guidance for its use as a less invasive, effective regenerative therapy.

Objective

The objective of this study is to systematically review and meta-analyze randomized controlled trials to evaluate the efficacy of recombinant human bone morphogenetic protein-2 (rhBMP-2) as an adjunct for guided bone and periodontal regeneration in adult periodontitis patients compared to other biomaterials.

METHODS

The focused research question using the PICO format was: “Does recombinant human bone morphogenetic protein-2 (rhBMP-2) differ in efficacy from other biomaterials for periodontal and bone regeneration?”

- P (Participants): Patients requiring alveolar ridge preservation or augmentation
- I (Intervention): Use of rhBMP-2
- C (Comparison): Other biomaterials
- O (Outcome): Bone regeneration measured by changes in alveolar height, width, new bone formation, and initial defect depth; periodontal regeneration assessed by probing depth (PD), clinical attachment level (CAL), and gingival index (GI).

Eligibility Criteria: studies were selected based on following criteria's

a) Inclusion Criteria: following were the inclusion criteria

1. Studies published in English

2. Studies from January 2000 to December 2023 with sufficient data on rhBMP-2 efficacy versus other biomaterials for periodontal and bone regeneration
3. Studies reporting outcomes on alveolar height and width changes, new bone formation, initial defect depth, and periodontal regeneration via probing depth (PD), clinical attachment level (CAL), and gingival index (GI)
4. Randomized controlled trials (RCTs), comparative, and prospective studies
5. Open access journal publications
6. Articles providing outcomes as mean and standard deviation (SD)

b) Exclusion Criteria: following were the exclusion criteria

1) Studies conducted before 2000
2) Articles not in English
3) reviews, abstracts, letter to the editor, editorials, animal studies and in vitro studies were excluded
4) Articles not from open access journals

Search Strategy

A comprehensive electronic search was conducted up to December 2023 for English-language studies from 2000 to 2023 using PubMed, Google Scholar, and EBSCOhost. Additional searches included clinical trial databases and grey literature via Google Scholar, Greylist, and OpenGrey. Keywords and MeSH terms related to alveolar ridge augmentation, rhBMP, bone and periodontal regeneration, and study types were combined using Boolean operators.

Selection Process

Screening was done in two phases by two authors: first, titles and abstracts were reviewed to exclude ineligible articles; then, full texts were independently assessed. Disagreements were resolved by discussion or a third reviewer, with final decisions by consensus. Authors were contacted for missing information.

Data Collection Process

For all included studies, data extracted included author(s), country, year, sample size, study design, interventions, comparators, assessed parameters, follow-up duration, and conclusions.

Study Risk of Bias Assessement

Two authors conducted a two-phase screening: first, titles and abstracts were reviewed to exclude irrelevant studies; then, full texts were assessed independently. Disagreements were resolved through discussion or by a third reviewer. Final decisions were made by consensus, and authors were contacted for additional information when needed.

Effect Measure

The study used standardized mean difference (SMD) with a random-effects model to compare rhBMP-2 and other biomaterials ($p < 0.05$).

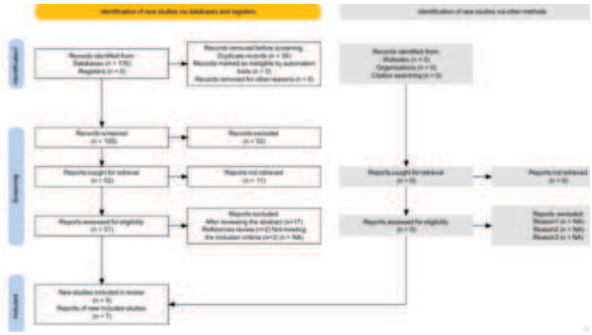
Synthesis Method

After duplicate removal, references were screened and ineligible studies excluded. Full texts were assessed, and nine studies were included in the review, with seven in the meta-analysis (see Figure 1).

Study Characteristics

Table 1 summarizes data from nine [21]-[29]randomized controlled trials (RCTs) involving 353 patients, all assessing recombinant human bone morphogenetic protein-2 (rhBMP-2) for bone and periodontal regeneration. Four studies were conducted in South Korea [22][24][26][27], four in India [24][25][26][27], and one[21] in the USA. RhBMP-2 was compared to various biomaterials including absorbable collagen sponge (ACS), demineralized bone matrix (DBM), open flap debridement (OFD), bovine-derived xenograft (BDX), bovine bone, polylactic glycolic acid (PLGA), platelet-rich fibrin (PRF), tricalcium phosphate (TCP), and hyaluronic acid (HA). Bone regeneration outcomes included changes in alveolar height, width, new bone formation, and defect depth; periodontal regeneration was measured by probing depth (PD), clinical attachment level (CAL), and gingival index (GI). Results indicated that rhBMP-2 produced better clinical, aesthetic, and satisfactory outcomes, with greater bone formation and regeneration, improved alveolar ridge preservation, and effectiveness in complex bone defects.

RESULTS



Study Selection:
Figure 1 PRISMA FLOWCHART

Table 1

Author, years of study	Country	Study design	Sample size	Intervention	Comparator	Follow up duration	Parameters assessed	Conclusion
Fiorellini et al., 200521	USA	RCT	80	FhBMP-2 + ACS	ACS	Baseline and 4 months	Alv. Bone height and width change	FhBMP-2+ ACS can increase amount of bone formation
Kim et al., 201422	South Korea	RCT	69	FhBMP-2 + DBM	DBM	Baseline and 3 months	Alv. Bone height and width	FhBMP-2 + DBM can be used in clinical applications
Vandana et al., 201623	India	RCT	32	FhBMP-2 + OFD	OFD	3,6 and 9 months	PD, CAL radiographic changes	FhBMP-2 + can improve periodontal regeneration
Nam et al., 201724	South Korea	RCT	20	FhBMP-2	BDX	Baseline and 4 months	Change in bone volume, absorption rate, vertical augmentation	FhBMP-2 can be used for bone augmentation in complicated bone defects
Vandana et al., 201725	India	RCT	32	FhBMP-2	PRF + OFD	Baseline and 6 months	CAL, PD, defect fill	FhBMP-2 has shown better outcome in treating intra-bony defects
Shim et al., 201826	South Korea	RCT	20	FhBMP-2	Bovine bone	Baseline and 3 months	Alv. Height and width, new bone formed	FhBMP-2 showed greater new bone formation post - surgery
Jo et al., 201927	South Korea	RCT	64	FhBMP-2 + ACS	FhBMP + TCP/HA	1,2 and 4 months	Alv. Height and width and complication	FhBMP-2 + ACS has better alveolar ridge preservation
Sneha et al., 202128	India	RCT	32	FhBMP-2	PRF	HPD, VPD, GI, PI, bone fill	Baseline, 3 and 6 months	FhBMP-2 can be used as graft material in furcation defects
Agrawal et al., 202329	India	RCT	24	FhBMP-2	PLGA	PI, PBI, CAL, VPD, HPD	Baseline and 6 months	FhBMP-2 provided better satisfactorily and clinically feasible results

Risk of Bias in Studies:

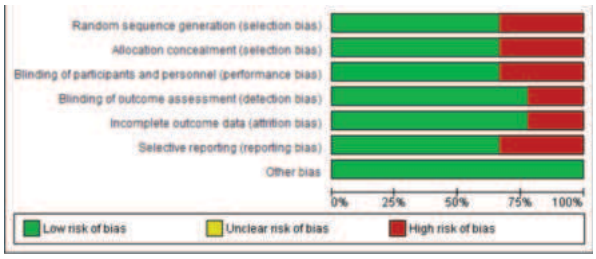


Figure 2: showing risk of bias graph: presented as percentages across all included studies.

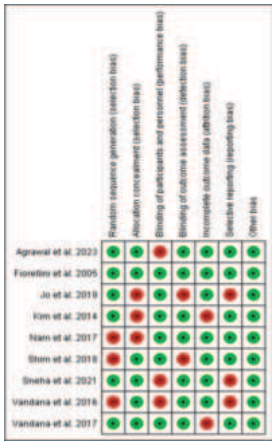


Figure 3: Risk of Bias of Individual study

Results of Synthesis

Meta-analysis assessed rhBMP-2's efficacy versus other biomaterials for bone regeneration—including alveolar height, width changes, new bone formation, and defect depth—and periodontal regeneration via probing depth (PD), clinical attachment level (CAL), and gingival index (GI), as shown in Figures 4-23

1) Change in Alveolar Bone Height

Three studies21,25 containing data on 136 patients, of which (n=48) patients were evaluated by RhBMP and (n=69) patients by other modalities for change in alveolar bone height. As shown in Figure 4. the SMD is -1.00 (-2.17 – 0.17) and the pooled estimates signifies that change in alveolar bone height on an average was 1.00 times higher in RhBMP group (p>0.05).

Figure 4: Comparison for Change in Alveolar Bone Height

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 5.

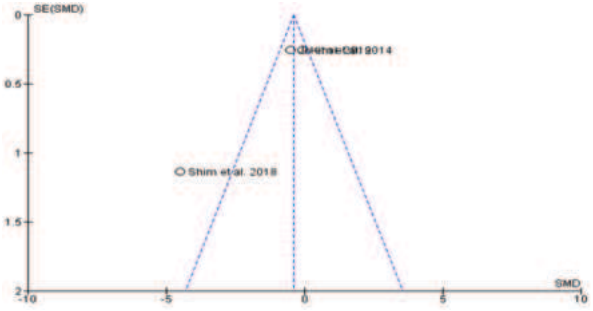


Figure 5: Showing Begg's Funnel plot demonstrating absence of publication bias.

2) Change in Alveolar Bone Width

Two studies21,25 containing data on 73 patients, of which (n=36) patients were evaluated by RhBMP and (n=37) patients by other modalities for change in alveolar bone width. As shown in Figure 6. the SMD is -0.23 (-0.69 – 0.23) and the pooled estimates signifies that change in alveolar bone width on an average was 0.23 times higher in RhBMP group (p>0.05).

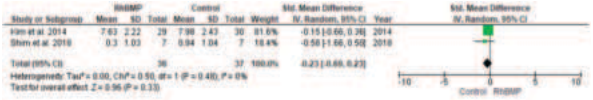


Figure 6: Comparison for Change in Alveolar Bone Width

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 7.

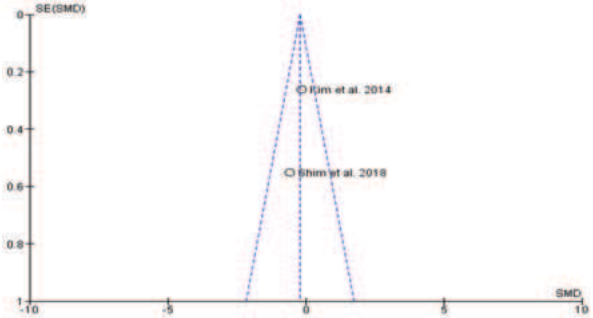


Figure 7: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

3) Amount of New Bone Formation

Two studies21,25 containing data on 39 patients, of which (n=19) patients were evaluated by RhBMP and (n=20) patients by other modalities for amount of new bone formation. As shown in Figure 8. the SMD is 0.71 (-0.51 – 1.94) and the pooled estimates signifies that amount of new bone formation on an average was 0.71 times higher in RhBMP group (p>0.05).

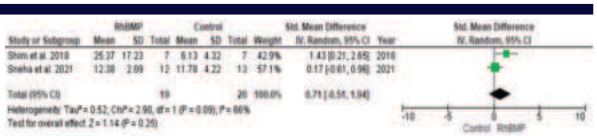


Figure 8: Comparison For New Bone Formation

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 9.

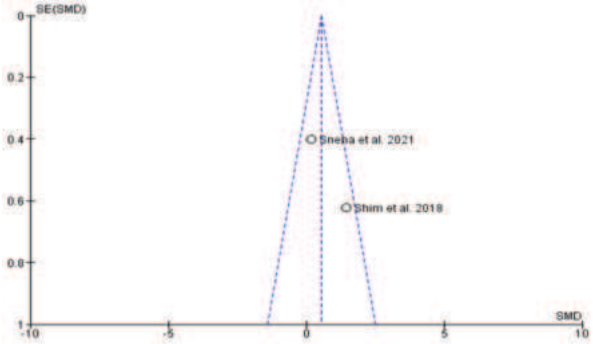


Figure 9: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

4) Alveolar Width Change at 25% ESL

Two studies21,25 containing data on 100 patients, of which (n=51) patients were evaluated by RhBMP and (n=49) patients by other modalities for alveolar width change at 25% extraction socket level (ESL). As shown in Figure 10. the SMD is 0.55 (-0.36 – 1.46) and the pooled estimates signifies that increase in alveolar width change at 25% extraction socket level on an average was 0.55 times higher in RhBMP group (p>0.05).

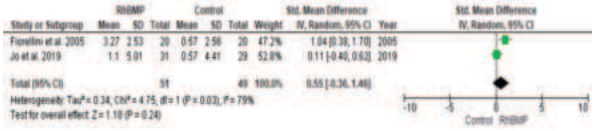


Figure 10: Comparison for GT at 1 Month

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 11.

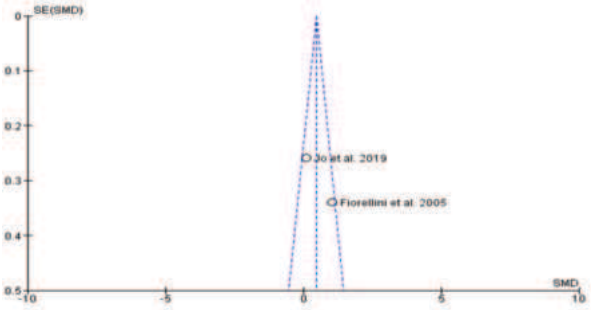


Figure 11: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

5) Alveolar Width Change at 50% ESL

Two studies21,25 containing data on 100 patients, of which (n=51) patients were evaluated by RhBMP and (n=49) patients by other modalities for alveolar width change at 50% extraction socket level (ESL). As shown in Figure 12. the SMD is 0.51 (-0.24 – 1.26) and the pooled estimates signifies that increase in alveolar width change at 50% extraction socket level on an average was 0.51 times higher in RhBMP group (p>0.05).

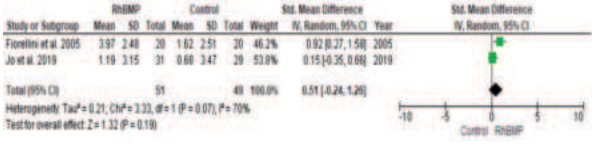


Figure 12: Comparison For Alveolar Width Change at 50% Extraction Socket Level

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 13.

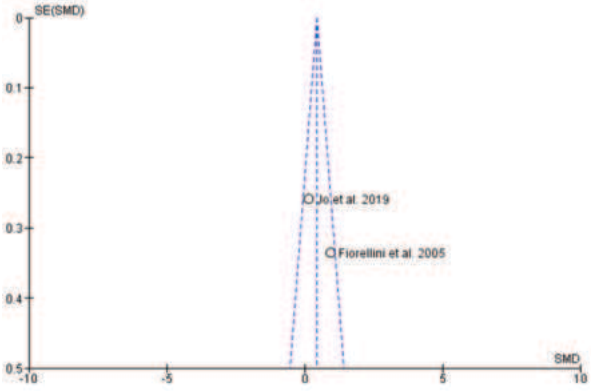


Figure 13: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

6) Alveolar Width Change at 75% ESL

Two studies21,25 containing data on 100 patients, of which (n=51) patients were evaluated by RhBMP and (n=49) patients by other modalities for alveolar width change at 75% extraction socket level (ESL). As shown in Figure 14. the SMD is 0.36 (-0.04 – 0.76) and the pooled estimates signifies that increase in alveolar width change at 75% extraction socket level on an average was 0.36 times higher in RhBMP group (p>0.05).

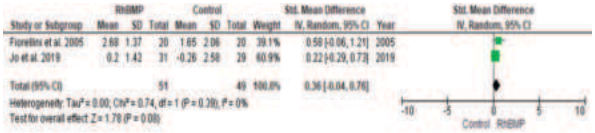


Figure 14: Comparison For Alveolar Width Change at 75% Extraction Socket Level

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 15.

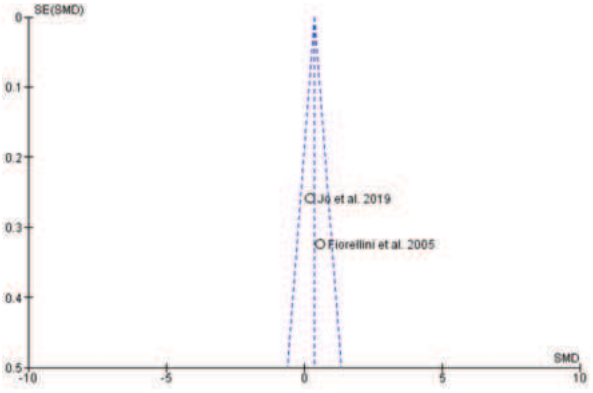


Figure : Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

7) Initial Defect Depth

Two studies21,25 containing data on 64 patients, of which (n=32) patients were evaluated by RhBMP and (n=32) patients by other modalities for initial defect depth. As shown in Figure 16. the SMD is 0.42 (-0.58 – 1.42) and the pooled estimates signifies that decrease in initial defect depth on an average was 0.42 times higher in RhBMP group (p>0.05).

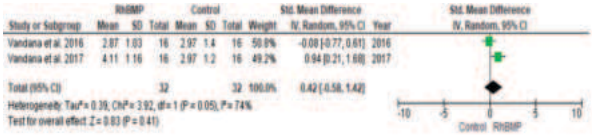


Figure 16: Comparison For Initial Defect Depth

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 17.

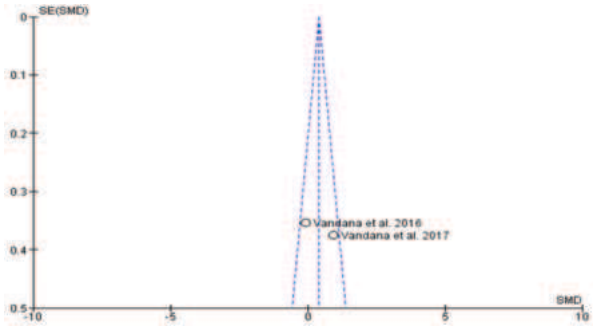


Figure 4: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

A) Periodontal Regeneration

1) Probing Pocket Depth (PPD)

Two studies21,25 containing data on 64 patients, of which (n=32) patients were evaluated by RhBMP and (n=32) patients by other modalities for reduction in PPD. As shown in Figure 18. the SMD is 1.31 (-1.57 – 4.20) and the pooled estimates signifies that reduction in PPD on an average was 1.31 times higher in RhBMP group (p>0.05).

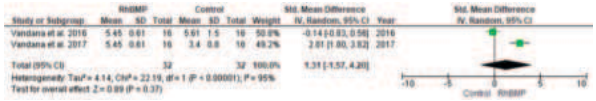


Figure 18: Comparison For Reduction in PPD

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 19.

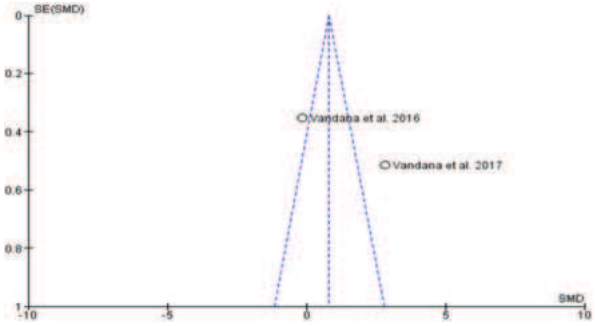


Figure 19: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

2) Clinical Attachment Level (CAL)

Two studies21,25 containing data on 64 patients, of which (n=32) patients were evaluated by RhBMP and (n=32) patients by other modalities for gain in CAL. As shown in Figure 20. the SMD is 1.25 (-1.19 – 3.69) and the pooled estimates signifies that gain in CAL on an average was 1.25 times higher in RhBMP group (p>0.05).

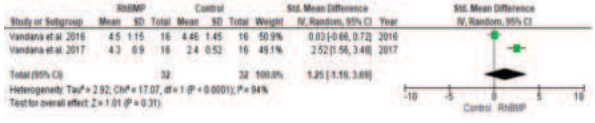


Figure 20: Comparison For Gain in CAL

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 21.

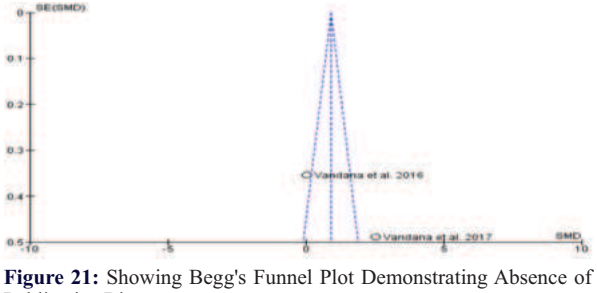


Figure 21: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

3) Gingival Index (GI)

Two studies21,25 containing data on 57 patients, of which (n=28) patients were evaluated by RhBMP and (n=29) patients by other modalities for reduction in GI. As shown in Figure 22. the SMD is 2.44 (-2.22 – 7.11) and the pooled estimates signifies that reduction in GI on an average was 2.44 times higher in RhBMP group (p>0.05).

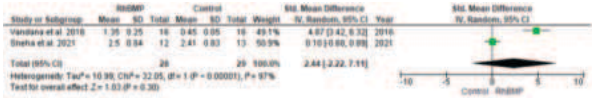


Figure 22: Comparison for Reduction in GI

The funnel plot did not show significant asymmetry, indicating absence of publication bias as shown in Figure 23.

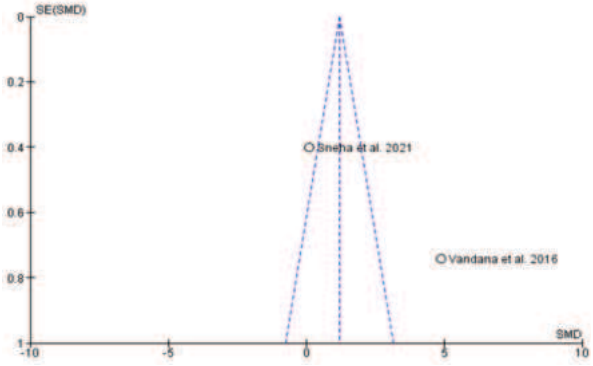


Figure 23: Showing Begg's Funnel Plot Demonstrating Absence of Publication Bias.

DISCUSSION

de Queiroz Fernandes et al. [30] conducted a systematic review on the clinical efficacy of recombinant human bone morphogenetic protein (rhBMP) for bone regeneration before implant placement. Nine RCTs met eligibility criteria, revealing an 82% success rate for bone regeneration and around 87% for implant success. Common complications included pain, edema, and erythema. The study concluded rhBMP treatment yielded satisfactory results, making implant placement feasible.

Moslemi et al. [31] reviewed whether rhBMP-2 placement in extraction sockets reduces alveolar ridge changes. Seven RCTs were analyzed, but heterogeneity prevented meta-analysis. Findings showed rhBMP-2 was more effective in preserving ridge width than height. Specifically, 1.5 mg/ml rhBMP-2 with absorbable collagen sponge was notably effective for sockets with over 50% buccal bone dehiscence, suggesting clinical efficacy in alveolar width preservation.

Medikeri et al. [32] evaluated rhBMP-2 versus other biomaterials for intra-bony defects in periodontitis patients. Reviewing RCTs from 1980 to 2017, they found significant improvements in radiographic bone fill, clinical attachment level (CAL), and pocket depth reduction with rhBMP-2. The authors concluded rhBMP-2 could serve as a useful adjunct to standard grafting procedures for periodontal regeneration.

This systematic review and meta-analysis offer a comprehensive qualitative and quantitative assessment of rhBMP-2 as an adjunct in guided bone and periodontal regeneration for periodontitis patients. Studies included RCTs up to December 2023 comparing rhBMP-2 with various biomaterials such as absorbable collagen sponge, demineralized bone matrix, open flap debridement, bovine-derived xenografts, polylactic glycolic acid, platelet-rich fibrin, tricalcium phosphate, and hyaluronic acid. Meta-analysis showed rhBMP-2 provided superior clinical, aesthetic, and satisfactory outcomes, with increased bone formation, better alveolar ridge preservation, and efficacy in complex bone defects. Studies exhibited low to moderate risk of bias, and funnel plots indicated no significant publication bias.

The review's strength lies in adherence to PRISMA guidelines, extensive literature search, robust data synthesis, and quality assessment using the Cochrane ROB-2 tool. Most studies had low to moderate bias risk, supporting high overall evidence quality with minimal variability.

However, limitations include sparse literature comparing rhBMP-2 with other biomaterials for combined bone and periodontal regeneration, resulting in only nine studies being included. More large-scale, randomized controlled, prospective, or follow-up studies are needed to better establish comparative efficacy.

Systematic reviews and meta-analyses are the best available evidence but depend on the quality of included studies. Given the short observation periods and known bias risks, current evidence is sufficient to support therapeutic recommendations on rhBMP-2 efficacy for periodontal and bone regeneration in adults.

CONCLUSION

RhBMP-2 was found to be an effective method for enhancing bone and periodontal regeneration, notable for being minimally invasive with few complications and resulting in increased bone formation after surgery. However, further clinical and comparative studies with larger sample sizes and longer follow-up are needed to strengthen the evidence and confirm these findings.

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