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SYSTEMATIC REVIEW

Preclinical application of recombinant human bone morphogenetic protein 2 on bone substitutes for vertical bone augmentation: A systematic review and meta-analysis

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ABSTRACT

Statement of problem. Recombinant human bone morphogenetic protein 2 (rhBMP-2) has been introduced to clinical practice because of its osteoinductive capacity. However, the evidence of its efficacy in vertical bone augmentation procedures is not clear.

Purpose. The purpose of this systematic review and meta-analysis was to investigate the efficacy of rhBMP-2 in vertical bone augmentation and to establish whether its addition in preclinical experiments (animal studies) would be sufficient to justify further clinical and histometric studies.

Material and methods. An electronic search of 3 databases, PubMed/MEDLINE, EMBASE, and Web of Science, and a manual search of the reference list of relevant studies were performed. Only randomized controlled trials regarding animal studies comparing the efficacy of bone grafts supplemented with and without rhBMP-2 in vertical bone augmentation procedures were included and reviewed.

Results. Nine studies were included. The results of the meta-analysis showed that the pooled weighted mean difference (WMD) of the percentage of newly formed bone was 9.97% (95% confidence interval [CI]=−0.79% to 20.72%; P=.070), the WMD of the percentage of residual materials was −21.31% (95% CI=−70.62% to 28.00%; P=.400), the WMD of the augmented bone height was 1.70 mm (95% CI=−0.23 to 3.63 mm; P=.080), the WMD of the augmented bone height for studies with space-providing barriers was 1.00 mm (95% CI=0.43 to 1.57 mm; P<.001), and the WMD of the percentage of regenerated tissue was 17.07% (95% CI=8.52% to 25.62%; P<.001).

Conclusions. The application of rhBMP-2 in bone substitutes did not enhance new bone formation and residual graft resorption in vertical bone augmentation procedures. Tissue regeneration and the augmented bone height were significantly improved by the additional use of BMP-2. (J Prosthet Dent 2019;122:355-63)

When there is vertical alveolar bone loss, bone must often be increased before an implant can be placed[1]; this represents a major problem in implant dentistry.[2] An autologous bone graft is regarded as the gold standard for increasing bone because it has excellent biological and mechanical properties.[3,4] However, with current grafting techniques, an autologous bone graft has problems of morbidity of the donor site, postoperative pain, and limited availability.[5,6] At present, a number of substitutes for a bone graft are available. The ideal substitute should be biocompatible, osteoconductive, and osteoinductive.[7] The osteoinductivity of a bone substitute can be improved by using an osteoinductive protein. Bone morphogenetic proteins (BMPs) are a subfamily of the transforming growth factor-β superfamily. Their osteoinductivity was first noted by Urist[8] in 1965. Since then, their roles in the regulation of bone induction, maintenance, and repair have been investigated.[9-13] Studies in animals and humans have confirmed that using the

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recombinant human bone morphogenetic protein 2 (rhBMP-2) induces and enhances the regeneration of bone.[14-18] The Food and Drug Administration has approved the use of rhBMP-2 (Infuse Bone Graft; Medtronic) for lumbar interbody fusions, sinus, and alveolar ridge defects associated with sockets resulting from tooth extraction.[19]

With the increasing clinical use of rhBMP-2, a number of worrying and well-documented side effects have been reported. These include adipogenesis,[20] postoperative inflammation,[21] ectopic bone formation,[22] and osteoclast-mediated bone resorption.[23,24] These are caused mainly by the high doses of rhBMP-2 necessary to produce the desired results. Although efforts have been made in recent years to develop an appropriate carrier for rhBMP-2 to reduce its side effects and increase its efficacy,[25-28] using it clinically is still controversial.

In addition, vertical bone augmentation means replacing a 1-wall defect rather than a space-providing defect. Compression of the soft tissue can limit bone formation.[29,30] If the augmented space is not carefully maintained, the outcome of the vertical bone augmentation is hard to predict.[31,32]

At present, little is known about using rhBMP-2 for vertical bone augmentation in humans, but several experiments have been carried out on animals.[2,3,33] Therefore, a systematic review and meta-analysis of animal studies that used rhBMP-2 for vertical bone augmentation were conducted to help justify further clinical and histometric studies.

MATERIAL AND METHODS

The electronic databases including PubMed/MEDLINE, EMBASE, and Web of Science were scanned for the title and abstract of relevant papers in English from the earliest publication to July 2017 (Fig. 1). Searches were performed using the following medical subject headings (MeSH terms, represented as mh) and keywords: ((bone morphogenetic protein 2)[mh] OR (BMP-2) OR (rhBMP-2)) AND ((bone substitutes)[mh] OR (block bone substitute) OR (particulate substitute)) AND ((alveolar ridge augmentation)[mh] OR (vertical bone augmentation) OR (bone formation)). A manual search of the reference list of relevant studies was also performed as a supplement of the electronic search.

The inclusion criteria and exclusion criteria are listed in Table 1. All the studies identified by the electronic searches were examined to determine their eligibility for the present review. The full text of the study was obtained for those articles which appeared to meet the criteria for inclusion in the survey and for those articles which had insufficient data in the title and abstract to enable a clear decision. For the latter group, the list of references was searched manually to find any

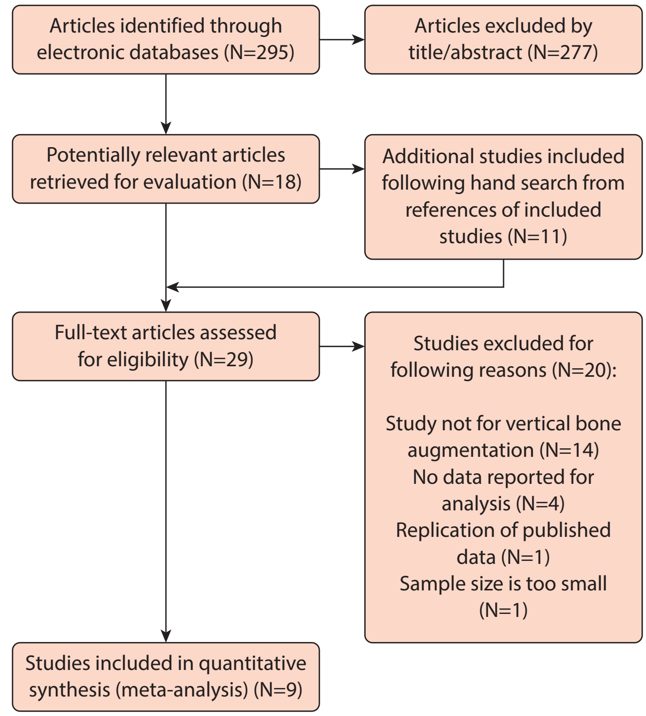

Figure 1. Flowchart of article selection process.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	1. Articles only of randomized controlled trials regarding animal experiments included and reviewed. 2. Test groups to use bone grafts applied with rhBMP-2 for vertical bone augmentation. 3. Control groups to use the same bone grafts alone (without rhBMP-2) for vertical bone augmentation. 4. Animals used were adults. 5. Numbers of grafts stated. 6. Numbers and types of test animals stated. 7. Data reported for at least one of the following: percentage of newly formed bone, percentage of residual grafting, augmented bone height, percentage of regenerated tissue in original grafting material, or sufficient reporting of data to (re)calculate these. 8. Follow-up periods stated.
Exclusion criteria	1. Studies not published as full articles excluded 2. In vitro studies, reviews, case reports, and duplicate publications also excluded, but bibliographies of these studies screened for potential articles that could be included. 3. Studies also excluded if they used one of the following: cell culture, bone transport models, injectable materials, and studies reporting on vertical bone augmentation after or simultaneously with insertion of implants.

potentially relevant articles. They were then added to the results of the electronic search. The eligibility of an article was considered independently by 2 reviewers (F.T., L.W.). If they disagreed, a third reviewer (N.S.) was consulted.

For each study, the following data were recorded if applicable: study design, first author, year of publication, number of animals, number of augmented sites, sample size, dose of rhBMP-2, type of grafting material, barrier type, healing period, newly formed bone, percentage of residual grafting material in the regenerated tissue, augmented bone height, and percentage of regenerated tissue in the original grafting material. For studies involving more than 1 growth factor, only the results using rhBMP-2 were extracted. Authors of the relevant articles were contacted for more detailed data if necessary.

The risk of bias of the included articles was assessed independently by 2 reviewers (F.T., L.W.) using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool for animal studies,[34] which is based on the Cochrane Risk of Bias tool[35] for randomized clinical trials and has been adjusted for animal intervention studies. The domains are sequence generation, baseline characteristics, allocation concealment, random housing, blinding for performance bias, random outcome assessment, blinding for detection bias, incomplete outcome data, and selective outcome reporting. A risk of bias judgment ("high," "low," or "moderate") was decided based on each domain. If each domain of SYRCLE was judged as "-" (low risk), the risk of bias of the study was scored as "low." If only one domain was judged as "?" (unclear risk), the risk of bias of this study was scored as "moderate." Otherwise, the risk of bias of the study was scored as "high." Any disagreement was resolved through a discussion to reach a consensus.

The investigated outcomes for the meta-analysis were the percentage of newly formed bone in the regenerated tissue, the percentage of residual grafting material in the regenerated tissue, the augmented bone height, and the percentage of regenerated tissue in the original grafting material. Adverse effects were not analyzed because they were not systematically reported in any of the articles. The pooled weighted mean difference (WMD) between the results with and without rhBMP-2 was assessed separately using software (RevMan v5.3; The Nordic Cochrane Centre). For the assessment of each result, the contribution of each article was weighed. For studies with several treatment arms, the results of all arms were combined. Heterogeneity was assessed with the chi-square test and the I^2 test. I^2 value is the percentage of the observed variance that reflects real differences between studies. Lower I^2 values represent less heterogeneity. For studies with an I^2 value higher than 50%, a random-effect model was applied to minimize the bias caused by methodological differences in the studies. Otherwise, a fixed-effect model was chosen. Forest plots were generated to represent graphically the differences in the 4 results for all the included articles. Confidence intervals (CIs) were reported at 95% levels (α=.05). The present study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[36]

RESULTS

The selection process is shown in Figure 1. Two hundred ninety-five articles were identified through electronic search. After screening the titles and abstracts, 18 articles were selected for an evaluation of the whole text. The reference lists of these 18 articles were also examined, and as a result, 11 more articles were added to the 18 articles, giving a total of 29 articles. Of these 29 articles, 20 were excluded for reasons shown in Figure 1. The remaining 9 studies[2,3,33,37-42] were included in this systematic review.

The main features and conclusions of the included studies are presented in Table 2. The volume size of samples used for the surgery was reported, except for 3 studies.[2,39,41] The surgery of vertical bone augmentation was performed using space-providing barriers (titanium cylinders or titanium meshes) in only 4 of the articles.[2,3,38,41]

The results of the included studies were determined using a histomorphometric analysis for 7 studies, using a microcomputed tomography for 1 study[2] and with macroscopic measurements using a digital caliper for 1 study.[3] The duration of the study varied from 2 weeks to 4 months. The grafting materials used were not all the same and neither were the concentrations of rhBMP-2. In 7 studies, a low concentration ($\leq$1.0 mg/mL)[19] of rhBMP-2 was used, while 2 studies[2,3] used a high concentration (>1.0 mg/mL).[19] Subgroup meta-analysis regarding the concentrations of rhBMP-2 was not possible because of the limited number of relevant results.

The assessment of the risk of bias for the included studies is given in Table 3. The bias in the selection and in performance is low in most studies because the national or international guidelines for animal experiments were followed. Blinding for detection bias was rarely mentioned, and therefore, the detection bias is difficult to judge for most of the articles. Any specimen loss was clearly stated in all the articles, and almost all the studies maintained the study protocol, leading to a low risk of attrition bias and reporting bias. The study by Polo et al[3] showed a high reporting bias because part of the results regarding newly formed bone was missing. The results regarding the newly formed bone in this study were, therefore, excluded from this review. To summarize, 1 study was considered to have a low risk of bias, 5 studies were considered to have a moderate risk of bias, and the remaining 3 studies were considered to have a high risk of bias. Funnel plots to assess the publication bias could not be made because the number of articles was less than 10.[43]

Five studies[37,39-42] that reported the percentage of newly formed bone in the regenerated tissue were included for the meta-analysis (Fig. 2). A sixth study by

Table 2. Features of included articles

	Subjects			Surgical Sites				
Study	Animal	Surgery Sites	No. of Animals	No. of Surgical Sites (C vs T)	Control Group Intervention vs Test Group Intervention	Size (mm^3)	Barriers	Healing Period
Murata et al, 2000	Rats	Calvaria	20	5 vs 5	Atelocollagen vs atelocollagen+rhBMP-2	NA	NA	2 weeks
				5 vs 5				4 weeks
Kawakatsu et al, 2008	Dogs	Mandibles	6	6 vs 6	PGS vs PGS+0.4 mg/ml BMP-2	30×8×6	NA	16 weeks
Jung et al, 2008	Rabbits	Calvaria	10	10 vs 10	PEG matrix+HA/TCP vs PEG matrix+HA/TCP+10 μg/ml rhBMP-2	NA	Titanium cylinder	8 weeks
				10 vs 10	PEG matrix+HA/TCP vs PEG matrix+HA/TCP+30 μg/ml rhBMP-2			
Kim et al, 2010	Rabbits	Calvaria	10	5 vs 5	DBBB vs DBBB+6 μg rhBMP-2	ϕ6×4	NA	12 weeks
				5 vs 5	CHBB vs CHBB+5 μg rhBMP-2	ϕ6×4		
Kim et al, 2012	Rabbits	Calvaria	14	7 vs 7	BCP vs BCP+10 μg rhBMP-2	ϕ8×3	NA	8 weeks
				7 vs 7	BCP/collagen vs BCP/collagen+10 μg rhBMP-2			
Schmitt et al, 2013	Pigs	Calvaria	11	5 vs 5	Bio-Oss block vs Bio-Oss block+8 μg/ml rhBMP-2/Tissucol	20×10×10	NA	30 days
				5 vs 4				60 days
Polo et al, 2013	Rabbits	Calvaria	22	10 vs 12	BBM vs BBM+1.5 mg/ml rhBMP-2/ACS	ϕ5×5	Titanium cylinder	14 weeks
				10 vs 11	BCP vs BCP+1.5 mg/ml rhBMP-2/ACS			
				10 vs 12	β-TCP vs β-TCP+1.5 mg/ml rhBMP-2/ACS			
				10 vs 12	CL vs CL+1.5 mg/ml rhBMP-2/ACS			
Ikeno et al, 2013	Rabbits	Calvaria	5	5 vs 5	PM vs PM+25 μg/ml rhBMP-2	ϕ6×7	Titanium cylinder	8 weeks
Hsu et al, 2017	Dogs	Mandibles	3	11(3) vs 11(3)[b]	Human allografts vs human allografts+1.5 mg/ml rhBMP-2/ACS	NA	Titanium meshes	4 months

ACS, absorbable collagen sponge; BBM, bovine bone mineral; BCP, block-type biphasic calcium phosphate; β-TCP, beta-tricalcium phosphate; C, control group; CHBB, corticocancellous human bone block; CL, blood clot; DBBB, deproteinized bovine bone block; GBR, guided bone regeneration; HA/TCP, hydroxyapatite/tricalcium phosphate; N, number; NA, not applicable; PEG, polyethylene glycol; PGS, poly gelatin sponge; PM, PuraMatix, a synthetic self-assembling peptide; T, test group; % of newly formed bone, percentage of newly formed bone; % of residual materials, percentage of residual grafting material in regenerated tissue; % of regenerated tissue, percentage of regenerated tissue in original grafting material; ϕ, diameter. [a]Values were calculated by authors. [b]Although 11 dogs were used in Hsu's study, only 3 dogs were euthanized for microcomputed tomography analysis. In this systematic review, data of augmented bone height from those 3 dogs were collected.

Kawakatsu et al[33] reported the results of newly formed bone in square millimeter. This could not be converted into a percentage and so could not be compared with other studies nor used in the meta-analysis. The pooled WMD of the percentage of newly formed bone was 9.97% (95% CI=−0.79% to 20.72%; P=.070). There was a high degree of heterogeneity (P<.001 for chi-square test; I^2=93%) in the selected studies.

Three studies[37,39,42] reported the percentage of residual materials in the regenerated tissue from histomorphometric measurements (Fig. 3). The pooled WMD of the percentage of residual materials was −21.31% (95% CI=−70.62% to 28.00%; P=.400). A high degree of heterogeneity (P<.001 for chi-square test; I^2=98%) among selected studies was noticed.

Four studies[2,33,37,38] reported the augmented bone height (Fig. 4). The pooled WMD of the augmented bone height was 1.70 mm (95% CI=−0.23 to 3.63 mm; P=.080; P<.001 for chi-square test; I^2=94%). Of the 4 studies, 2 studies[2,38] used space-providing titanium barriers. A subgroup analysis for the augmented bone height among studies conducted with space-providing barriers was conducted. The pooled weighted mean in group with rhBMP-2 was 1.00 mm (95% CI=0.43 to 1.57 mm) higher than that in the control group. The difference was statistically significant (P<.001). Low heterogeneity (P=.430 for chi-square test, I^2=0%) among the selected studies was noticed. This result shows that when surgery was performed using a titanium barrier, the augmented bone height in the group with rhBMP-2 increased compared with the group without rhBMP-2.

Only 2 studies[3,38] reported the percentage of regenerated tissue in the original grafting material (Fig. 5). The pooled WMD of the percentage of regenerated tissue was 17.07% (95% CI=8.52% to 25.62%; P<.001). This result means that a higher percentage of regenerated tissue was found when rhBMP-2 was used. There was a low degree of heterogeneity (P=.260 for chi-square test, I^2=20%) between these 2 studies.

DISCUSSION

The purpose of this systematic review and meta-analysis was to investigate if using rhBMP-2 with the bone

Table 2. *(Continued)* Features of included articles

Outcomes (C/T)				
% of Newly Formed Bone	% of Residual Materials	Augmented Bone Height (mm)	% of Regenerated Tissue	Main Conclusions
0 ±0/49.3 ±7.4	94.4 ±1.1/40.5 ±8.2	NA	NA	Onlay implant of rhBMP-2 and atelocollagen should be biologically novel effective system for bone augmentation.
0 ±0/92.5+2.0	88.3 ±3.0/2.0 ±0.8	NA	NA	
NA	NA	0.22 ±0.28/4.3 ±0.9	NA	RhBMP-2/PGS promoted substantial bone formation and provided sufficient space for bone formation with no immune or other adverse reactions, which might be effective for vertical ridge augmentation.
15.16 ±7.95/26.32 ±8.56	NA	NA	NA	RhBMP-2 significantly enhances bone regeneration in rabbits when delivered by synthetic PEG matrix containing HA/TCP.
15.16 ±7.95/30.15 ±7.63	NA	NA	NA	
4.89 ±2.37/16.61 ±6.13	41.02 ±15.84/53.48 ±18.24	1.85 ±0.55/1.89 ±0.55	NA	Vertical bone augmentation was not enhanced by application of rhBMP-2 or DBBB alone. In CHBB groups, which showed better result, there were no significant differences between test and control groups.
29.83 ±6.97/30.85 ±7.45	91.01 ±4.56/94.05 ±5.75	4.00 ±0.34/4.11 ±0.41	NA	
26.9 ±10.0/40.9 ±3.2	NA	NA	NA	BCP-collagen blocks with rhBMP-2 facilitate 3-dimensional vertical bone augmentation.
23.3 ±6.6/49.9 ±1.8	NA	NA	NA	
3.92 ±1.14/4.88 ±1.09	32.34 ±6.88/31.56 ±4.80	NA	NA	In chosen setting and time frame, de novo bone formation did not increase with additional use of BMP-2.
10.02 ±5.43/9.33 ±3.92	33.38 ±0.45/33.15 ±6.95	NA	NA	
NA	NA	NA	66.3 ±20.73/91.7 ±9.09[a]	RhBMP-2/ACS significantly increases bone formation in rabbit calvarium GBR model when combined with any of β-TCP, BCP, and BBM.
NA	NA	NA	78.1 ±12.05/94.4 ±5.91[a]	
NA	NA	NA	70.1 ±19.94/93.3 ±5.82[a]	
NA	NA	NA	41.7 ±24.88/57.9 ±35.40[a]	
NA	NA	3.47 ±0.57/4.39 ±0.39	48.94 ±11.33/58.06 ±14.84	PuraMatrix combined with rhBMP-2 significantly enhanced bone regeneration in bone augmentation model in rabbits.
NA	NA	3.49 ±0.66/5.15 ±1.40	NA	RhBMP-2 combined with allograft allows increase of vertical gain compared with non-rhBMP-2 sites.

substitutes gave better vertical bone augmentation than those without rhBMP-2. Only randomized controlled trials were included in this study because the randomized controlled trial shows higher level of evidence than other study designs such as cohort and case-control studies.

Seven of the 9 articles[2,3,33,38-41] reported a positive result which favored the use of rhBMP-2. Two articles[37,42] reported that the vertical bone augmentation was not enhanced by the application of rhBMP-2 in their experiments. The results of the meta-analysis demonstrated that the tissue regeneration was significantly improved with rhBMP-2. When a space-providing titanium barrier was used, the augmented bone height was also increased by using rhBMP-2. These positive results can be attributed to the osteoinductive efficacy of rhBMP-2. However, no statistically significant difference was found in the percentage of newly formed bone and residual materials between the groups with and without rhBMP-2. This contradicts the clear facts that BMP-2 promotes osteogenic differentiation in vitro[13,18] and induces new bone formation at ectopic sites in vivo.[17,18]

This finding may be because, when analyzing the percentage of newly formed bone and the percentage of residual materials, a high heterogeneity was noticed among the selected studies. This is because of the different grafting materials, surgical procedures, doses and concentrations of rhBMP-2, animal models, and healing periods used in these studies. These differences may have affected the final outcomes and lead to high heterogeneity among the studies.

In addition, BMP-2 can not only induce osteogenic programming by upregulating the expression of series of transcription factors, such as runt-related transcription factor 2 in osteoblasts[11,12] but also enhance bone resorption by activating osteoclasts by upregulating cyclooxygenase-2 and the receptor activator of nuclear kappa-B ligand.[23,24] As Schorn et al[44] reported in a study of vertical bone regeneration with the simultaneous insertion of implants, the negative feedback mechanisms of the rhBMP-2 signaling cascade can put a brake on new bone formation. In a vertical bone augmentation model in rats, Kinard et al[45] reported increased osteoclastic bone resorption in groups releasing BMP-2 and that the level

Table 3. Risk of bias assessment for included articles

Criteria (Hooijmans et al,[34] 2014)	Murata et al,[39] 2000	Kawakatsu et al,[33] 2008	Jung et al,[41] 2008	Kim et al,[37] 2010	Kim et al,[40] 2012	Schmitt et al,[42] 2013	Polo et al,[3] 2013	Ikeno et al,[38] 2013	Hsu et al,[2] 2017
Sequence generation (selection bias)	?	?	+	+	+	+	+	+	?
Baseline characteristics (selection bias)	+	+	+	+	+	+	+	+	+
Allocation concealment (selection bias)	?	?	+	+	+	+	+	+	-
Random housing (performance bias)	+	+	+	+	+	+	+	+	+
Blinding (performance bias)	+	+	+	+	+	+	+	+	+
Random outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+
Blinding (detection bias)	?	?	?	?	+	?	?	?	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	-	+	+
Selective outcome reporting (reporting bias)	+	+	+	+	+	+	+	+	+
Estimated potential risk of bias	High	High	Moderate	Moderate	Low	Moderate	High	Moderate	High

+, low risk of bias; ?, unclear risk of bias; -, high risk of bias.

Study or Subgroup	Graft+rhBMP-2 Mean	SD	Total	Graft Alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Murata et al. 2000	70.9	23.33	10	0	0	10		Not estimable	2000
Jung et al. 2008	28.24	8.13	20	15.16	7.95	10	25.4%	13.08 (7.00, 19.16)	2008
Kim et al. 2010	23.73	9.88	10	17.36	14.03	10	21.8%	6.37 (−4.27, 17.01)	2010
Kim et al. 2012	45.4	5.29	14	25.1	8.35	14	26.0%	20.30 (15.12, 25.48)	2012
Schmitt et al. 2013	6.86	3.44	9	6.97	4.9	10	26.8%	−0.11 (−3.89, 3.67)	2013
Total (95% CI)			**63**			**54**	**100.0%**	**9.97 (−0.79, 20.72)**	

Heterogeneity: τ^2=108.85; χ^2=42.14, *df*=3 (*P*<.00001); I^2=93%
Test for overall effect: Z=1.82 (*P*=.07)

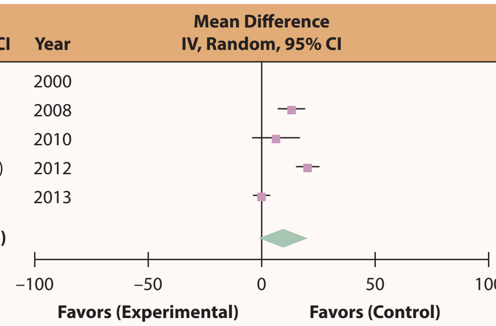

Figure 2. Meta-analysis for percentage of newly formed bone in regenerated tissue among selected studies. Pooled WMD of percentage of newly formed bone, 9.97% (95% CI=−0.79% to 20.72%). Difference between groups not statistically significant (*P*=.070). High degree of heterogeneity (*P*<.001 for chi-square test; I^2=93%) among selected studies was noticed. CI, confidence interval; IV, inverse variance; rhBMP-2, recombinant human bone morphogenetic protein 2; SD, standard deviation; WMD, weighted mean difference.

Study or Subgroup	Graft+rhBMP-2 Mean	SD	Total	Graft Alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Murata et al. 2000	21.25	21.02	10	91.35	3.86	10	33.6%	−70.10 (−83.35, −56.85)	2000
Kim et al. 2010	73.77	24.9	10	66.02	28.55	10	32.0%	7.75 (−15.73, 31.23)	2010
Schmitt et al. 2013	32.27	5.51	9	32.86	4.63	10	34.4%	−0.59 (−5.19, 4.01)	2013
Total (95% CI)			**29**			**30**	**100.0%**	**−21.31 (−70.62, 28.00)**	

Heterogeneity: τ^2=1835.65; χ^2=96.07, *df*=2 (*P*<.00001); I^2=98%
Test for overall effect: Z=0.85 (*P*=.40)

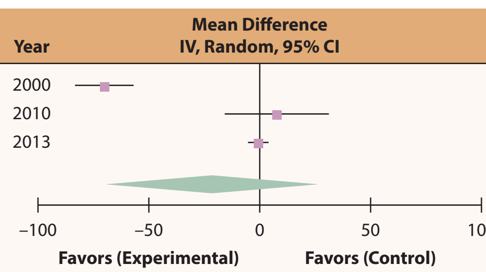

Figure 3. Meta-analysis for percentage of residual materials in regenerated tissue among selected studies. Pooled WMD of percentage of residual materials, −21.31% (95% CI=−70.62% to 28.00%). Difference between groups not statistically significant (*P*=.400). High degree of heterogeneity (*P*<.001 for chi-square test; I^2=98%) among selected studies was noticed. CI, confidence interval; IV, inverse variance; rhBMP-2, recombinant human bone morphogenetic protein 2; SD, standard deviation; WMD, weighted mean difference.

of bone augmentation was not significantly different between the groups with and without BMP-2 after healing for 4 weeks. Although this article was excluded from this review because of insufficient data reported, it explained the results in the present review. Therefore, when applied in vitro or for ectopic sites, BMP-2 showed a clear osteoinductive efficacy in the absence of osteoclasts. When applied at orthotopic bone sites, the results are ambiguous.[23]

The side effects of osteoclastic bone resorption can be reduced, and the efficacy of rhBMP-2 can be enhanced by using a proper carrier for a slow and sustained delivery of rhBMP-2.[27,28] In a study reporting negative results, Kim et al[37] attributed the absence of significant differences between the corticocancellous human bone block (CHBB)/rhBMP-2 group and CHBB group to the small effect of CHBB on the maintenance and release of rhBMP-2. They suggested that the addition of a carrier

Study or Subgroup	Graft+rhBMP-2 Mean	SD	Total	Graft Alone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kawakatsu et al. 2008	4.3	0.9	6	0.22	0.28	6	26.1%	4.08 (3.33, 4.83)	2008
Kim et al. 2010	3	1.26	10	2.93	1.21	10	25.1%	0.07 (−1.01, 1.15)	2010
Ikeno et al. 2013	4.39	0.39	5	3.47	0.57	5	26.5%	0.92 (0.31, 1.53)	2013
Hsu et al. 2017	5.15	1.4	3	3.49	0.66	3	22.2%	1.66 (−0.09, 3.41)	2017
Total (95% CI)			**24**			**24**	**100.0%**	**1.70 (−0.23, 3.63)**	

Heterogeneity: τ^2=3.56; χ^2=53.05, *df*=3 (*P*<.00001); I^2=94%
Test for overall effect: Z=1.72 (*P*=.08)

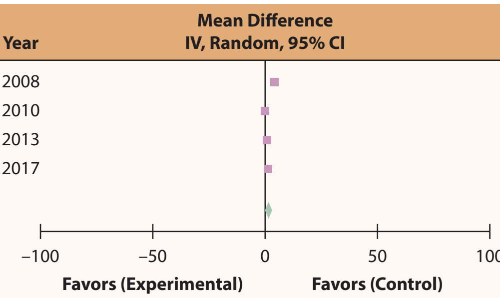

Figure 4. Meta-analysis for comparison of augmented bone height among selected studies. Pooled WMD of augmented bone height, 1.70 mm (95% CI=−0.23 to 3.63 mm). Difference between groups not statistically significant (*P*=.080). High degree of heterogeneity (*P*<.001 for chi-square test; I^2=94%) among selected studies was noticed. CI, confidence interval; IV, inverse variance; rhBMP-2, recombinant human bone morphogenetic protein 2; SD, standard deviation; WMD, weighted mean difference.

Study or Subgroup	Graft+rhBMP-2 Mean	SD	Total	Graft Alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Ikeno et al. 2013	58.06	14.84	5	48.94	11.33	5	27.3%	9.12 (−7.25, 25.49)	2013
Polo et al. 2013	84.11	24.01	47	64.05	23.59	40	72.7%	20.06 (10.03, 30.09)	2013
Total (95% CI)			**52**			**45**	**100.0%**	**17.07 (8.52, 25.62)**	

Heterogeneity: χ^2=1.25, *df*=1 (*P*=.26); I^2=20%
Test for overall effect: Z=3.91 (*P*<.0001)

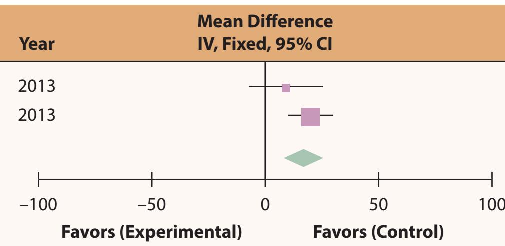

Figure 5. Meta-analysis for percentage of regenerated tissue in original grafting material. Pooled weighted mean of percentage of regenerated tissue in group with rhBMP-2, 17.07% (95% CI=8.52% to 25.62%) higher than that in control group. Difference between groups statistically significant (*P*<.001). Low degree of heterogeneity (*P*=.260 for chi-square test; I^2=20%) among selected studies was noticed. CI, confidence interval; IV, inverse variance; rhBMP-2, recombinant human bone morphogenetic protein 2; SD, standard deviation.

which maintained and gave a controlled released of rhBMP-2 could improve the vertical bone augmentation. Similarly, in a study investigating the effect of rhBMP-2 around endosseous implants reported by Jones et al,[46] no significant difference in sites with or without rhBMP-2 regarding new bone area or percentage of defect fill was found after 12 weeks. The authors suggested that sustained stimulation of bone growth might require additional delivery or the prolonged release of the rhBMP-2.

Another reason affecting the results was also reported. Kawakatsu et al,[33] Kim et al,[37] and Schmitt et al[42] reported that, because the vertical bone augmentation is the reestablishment of a 1-wall defect rather than of a space-providing defect, bone grafting materials were not able to provide or maintain a space adequately. This could result in a limited bone formation because of soft tissue compression. Studies[31,32] have reported that stable maintenance of the augmented space is essential for successful bone regeneration. Interestingly, for all the statistically significant results achieved in this review (the augmented bone height for studies with barriers and the percentage of regenerated tissue), most of the studies involved[2,3,38] used space-providing titanium barriers.

The current review presents several limitations. First, the number of the included studies is only 9. Second, the meta-analysis showed a high degree of heterogeneity among the studies when analyzing the percentage of newly formed bone, the percentage of residual materials, and the augmented bone height. This can be attributed to the large variation in the procedures used in the studies. There were differences in the grafting materials, surgical procedures, doses and concentrations of rhBMP-2, animal models, and healing periods. In addition, 6 of the 9 studies had more than 1 treatment arm. Three studies used several types of grafting materials,[3,37,40] 1 study used 2 concentrations of rhBMP-2[41] and 2 studies allowed different times for healing.[39,42] The combination of the data from these studies can also contribute to the moderate or high degree of heterogeneity. A subgroup analysis is an option when the heterogeneity is moderate or high.[31] However, because of the small number of studies, only 1 subgroup analysis was made and that was on the augmented bone height for studies with titanium barriers. The results of the remaining meta-analysis with moderate or high heterogeneity should be interpreted with caution. Further standardized studies are needed.

Third, no adverse effects of using rhBMP-2 for vertical bone augmentation were reported in the included studies. This may be because of the small sample sizes and the limited time for healing in these studies. In addition, the aims of these studies were to investigate the effect of using rhBMP-2 for vertical bone augmentation. Any side effects may have been overlooked. Further studies assessing the risk of adverse events after application of rhBMP-2 for vertical bone augmentation are therefore needed.

This study suggested a possible method for vertical bone augmentation, but the results are not strong enough to support the current use of rhBMP-2 in routine clinical practice. The presence of space-providing barrier and proper carrier for rhBMP-2 may be important to optimize the osteoinductive efficacy of rhBMP-2. This study also motivates clinicians and researchers to explore further the application of rhBMP-2 for vertical bone augmentation in humans.

CONCLUSIONS

Based on the findings of this systematic review and meta-analysis, the following conclusions were drawn:

1. Until now, the application of rhBMP-2 in bone substitutes has not enhanced bone formation and residual graft resorption in vertical bone augmentation procedures.
2. Tissue regeneration was significantly improved by the additional use of BMP-2.
3. With the application of space-providing barriers, the augmented bone height was also significantly enhanced by the use of BMP-2.
4. These results are not strong enough to support the use of rhBMP-2 in routine clinical practice because of the limitations of the study.
5. Further higher quality clinical studies are needed to come to a definite conclusion.

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Noteworthy Abstracts of the Current Literature

Remake rates for single-unit crowns in clinical practice: Findings from The National Dental Practice-Based Research Network

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Purpose. Some crowns returned from the laboratory are clinically unacceptable, and dentists must remake them. The objectives of this study were to: (1) quantify the remake rate of single-unit crowns; and (2) identify factors significantly associated with crown remakes and intraoral fit.

Material and methods. Dentists participating in the National Dental Practice-Based Research Network recruited patients needing crowns and documented fabrication techniques, patient characteristics, and outcomes. Crowns were considered clinically acceptable or rejected. Also, various aspects of the clinical fit of the crown were graded and categorized as 'Goodness of Fit (GOF).' Dentist and patient characteristics were tested statistically for associations with crown acceptability and GOF.

Results. More than 200 dentists participated in this study (N=205) and evaluated 3750 single-unit crowns. The mean age (years) of patients receiving a crown was 55. The remake rate for crowns was 3.8%. The range of rejection rates among individual practitioners was 0% to 42%. Most clinicians (118, or 58%) did not reject any crowns; all rejections came from 42% of the clinicians (n=87). The most common reasons for rejections were proximal misfit, marginal errors, and esthetic failures. Fewer years in practice was significantly associated with lower crown success rates and lower fit scores. GOF was also associated with practice busyness and patient insurance status, patient gender (dentists reported better fit for female patients), and patient ethnicity.

Conclusions. The crown remake rate in this study was about 4%. Remakes and crown GOF were associated with certain dentist and practice characteristics.