Outcomes of Alveolar Ridge Preservation With Recombinant Human Bone Morphogenetic Protein-2: A Systematic Review

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Purpose: *The main focused question of this systematic review was as follows: Does the application of recombinant human bone morphogenetic protein-2 (rhBMP-2) placed in extraction sockets reduce the alveolar ridge changes?*

Methods: *A systematic literature search was performed up to February 2017. Clinical studies published in English were included. Outcome variables of interest were as follows: changes in alveolar ridge width and height, the quality of new bone, patient's safety, adverse events, and postoperative complications.*

Results: *Seven articles were included. Because of the vast heterogeneity and high risk of bias among the studies, performing a meta-analysis deemed not feasible. Application of rhBMP-2 in the extraction socket was more effective in the reduction of ridge width compared with that of ridge height. The superiority of 1.5 mg/mL rhBMP-2/absorbable collagen sponge over the carrier alone on alveolar ridge width/height remodeling was more significant when it was applied in the sockets with ≥50% buccal bone dehiscence. The limited available data showed that rhBMP-2 did not improve the quality of new bone. Antibodies against rhBMP-2 were detected in the serum in 1 trial.*

Conclusions: *Within the limits of this review, 1.5 mg/mL rhBMP-2 might be beneficial for preserving the alveolar ridge width within extraction sockets given as to whether the cost-effectiveness is justifiable. Studies with lower risk of bias should be performed to confirm the above findings. (Implant Dent 2018;27:351–362)*

Key Words: recombinant protein, tooth extraction, alveolar process, alveolar ridge augmentation, intercellular signaling peptides and proteins

After tooth extraction, a continuous loss of bone occurs in the alveolar bone process. This tissue loss would result in substantial dimensional changes of the alveolar ridge over time.[1,2] Approximately 50% reduction of the ridge width has been reported within 12 months after tooth extraction from which the highest rate (30%) took place during the first 3 months.[3] As a consequence, the center of the edentulous ridges may shift toward lingual side that may impede predictable implant placement. Early alveolar bone loss is substantially greater in ridges with <1 mm or in the presence of buccal bone fenestration and dehiscence.[4] It may bring more concerns in the esthetic zone because in the frontal tooth region, the buccal plate is frequently <1 mm.[5,6] Clinical consequences of these physiological hard and soft tissue changes may affect the outcomes of the reconstructive procedures.[7]

To reduce the early dimensional alterations of alveolar ridges, alveolar ridge preservation after tooth extraction has gained popular interest in recent years.[7,8] A variety of biomaterials and technique have been used for alveolar ridge preservation. Based on the results of a systematic review, although placement of xenografts in the extraction sockets resulted in the most amount of buccolingual ridge preservation, the amount of newly formed vital bone

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was the lowest when compared with other bone materials.[9] However, a recent Bayesian network meta-analysis comparing different bone grafts reported that "autogenous bone marrow" and "freeze-dried bone allografts plus membrane" were most effective in reducing alveolar ridge width and height changes, respectively.[10] Generally, bone regeneration is composed of a well-organized series of biological events of bone induction and conduction, involving (1) specific cell types; (2) the scaffold; and (3) expression of signaling molecules (like cytokines and growth factors).[11,12] An integral component of tissue engineering, ie, growth factors include a large family of polypeptide molecules that regulate cell responses such as cell attachment/adhesion, cell survival, proliferation, chemotaxis, and differentiation.[13] Among them, bone morphogenetic proteins (BMPs) have been studied extensively regarding their pivotal role in bone formation.

BMPs can stimulate angiogenesis, proliferation, differentiation, and migration of stem cells from the surrounding tissues into cartilage and bone-forming cells in an area of injury. They regulate the expression of many target genes involved in bone physiology, such as alkaline phosphatase, osteocalcin, osteopontin, and osterix.[13–15] More than 20 BMPs have been described, and many of them have osteogenic ability. Recombinant technologies have been introduced to provide controlled concentrations of BMP.[16–18] Howell et al[19] were pioneers of using recombinant human BMP-2 (rhBMP-2) for management of extraction sockets and reported the technical feasibility of rhBMP-2/absorbable collagen sponge (ACS) for alveolar ridge preservation. In 2007, rhBMP-2 placed on ACS was FDA-approved for alveolar ridge augmentations, for defects associated with extraction sockets, and for sinus augmentations. *In vitro* and *in vivo* studies have shown osteoinductive capacity of rhBMP-2.[13,20]

In a systematic review on the clinical efficacy of rhBMP-2/ACS in maxillary sinus floor/alveolar ridge augmentation, it was concluded that rhBMP-2/ACS is comparable with autogenous bone graft.[21] Another recent systematic review indicated that application of rhBMP-2 in localized ridge augmentation was effective in terms of increasing ridge height. However, rhBMP-2 was not as effective as allograft or autogenous bone graft in maxillary sinus floor augmentation.[22] To the best of our knowledge, the outcomes of application of rhBMP-2 in alveolar ridge preservation have not been systematically reviewed. Therefore, the primary aim of this systematic review was to answer the following question: "Does the application of rhBMP-2 in the extraction sockets reduce the alveolar ridge changes and/or improve the bone quality compared with that of its carrier alone?"

MATERIALS AND METHODS

PICO Question

Does the application of rhBMP-2 in the extraction sockets reduce the alveolar ridge changes and/or improve the bone quality compared with that of its carrier alone?

- Population: individuals needed socket grafting.
- Intervention: use of rhBMP-2 in the extraction socket.
- Comparison: rhBMP-2 group compared with placebo group.
- Outcomes: changes in alveolar ridge width and height and quality of the newly formed bone.

Inclusion and Exclusion Criteria

Randomized clinical trials (RCTs), prospective/retrospective studies, and case series on at least 5 cases using rhBMP-2 for ridge preservation with a follow-up of at least 3 months and published in English were included. Animal studies or studies in which rhBMP-2 was used for a purpose other than ridge preservation were excluded.

Search Strategy

An electronic search was performed in MEDLINE, SCOPUS, Web of Science, Cochrane, and Google Scholar databases. Keywords used in electronic database search included ("recombinant human bone morphogenetic protein-2" OR "recombinant human bone morphogenic protein-2" OR "bone morphogenetic protein-2" OR "bone morphogenic protein-2") AND ("alveolar ridge preservation" OR "ridge preservation" OR "socket graft" OR "socket grafting" OR "extraction socket" OR "socket preservation" OR "socket augmentation" OR "socket management"). The process was repeated until no further new articles could be identified. The last electronic search was performed on January, 2017. In addition, a hand search of the most relevant journals was performed. The screening of titles and abstracts for potential inclusion in the review was undertaken by 2 reviewers (N.M. and S.R.) independently. Selected studies were read carefully and analyzed for the eligibility criteria. Differences between reviewers were resolved by discussion and consensus. The following outcome measures were extracted:

Primary outcome was alveolar ridge quantity (changes in alveolar ridge width and height) and alveolar ridge quality (density of newly formed bone based on computed tomography (CT) images and histologic/histomorphometric analyses), and safety, adverse events, and complications (vital signs, abnormal or ectopic bone induction, antibody development, inflammatory and foreign body responses, and implant failure) were secondary outcome variables. Two reviewers (N.M. and H.R.) extracted the data, and in case of any disagreement, it was resolved between the reviewers after a discussion.

Quality Assessment

Cochrane collaboration tool was used to identify potential risk of bias for the randomized controlled trials. The risk of bias within each study was categorized as follows: low risk of bias if all criteria were met, unclear risk of bias if 1 criterion was missing, and high risk of bias if at least 2 criteria were missing.[23] In addition, a quality appraisal tool using a modified Delphi tool was used to assess the risk of bias for case series studies. A study with more than 70% yes response was considered as a case series with "acceptable quality."[24]

RESULTS

The search process is illustrated in Figure 1. Among 10 articles assessed for possible eligibility, 2 case reports on less than 5 cases were excluded.[25,26] Among 8 remained articles, 2 reported the outcomes in the same cohort with different follow-up periods.[19,27] Thus, the 1 with the longer follow-up was included.[27] Finally, 7 studies including 4 RCTs and 3 case series were included in this systematic review (Fig. 1). Major heterogeneity in between the studies including different inclusion criteria of the sockets, methods of evaluation, and different dosages of rhBMP-2 rendered conducting a meta-analysis impossible.

Six studies (4 RCTs and 2 case series) reported data regarding alveolar ridge width and height changes (Table 1). Quality of the newly formed bone was assessed in 4 studies of which 1 was an RCT (Table 2). Data regarding patients' safety were reported in 2 RCTs[28,29] and 1 case series.[27] Three studies evaluated postoperative healing and complications after application of rhBMP-2 in the extraction sockets[28,30,31] (Table 3). None of the included studies evaluated implant success or failure except 1 study in the abstract.[32]

The follow-up period in the included studies was from 3 months to 3 years. rhBMP-2 used in most studies was produced by a genetically engineered Chinese hamster ovary cell line.[19,26,28–31,33] Only in 1 included study, rhBMP-2 was derived from *Escherichia coli*.[34]

Risk of Bias Assessment

All of the four-included randomized controlled trials were identified with high risk of bias (Table 4). The risk of bias of case series studies was considered high as none of the studies met more than 70% of the criteria of the quality assessment tool (Table 5).

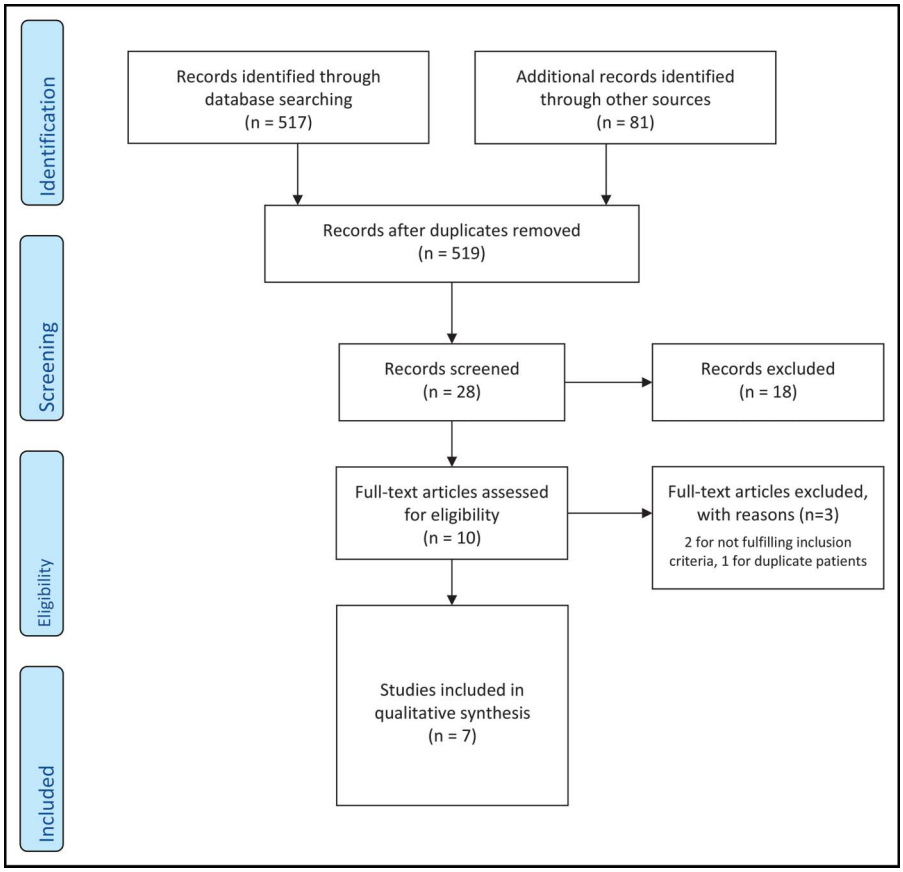

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram of search strategy outlines the number of articles identified, screened, eligible, and included in this review.

Alveolar Bone Quantity

Because of the lack of control group, the case series were not eligible to be used for comparing the bone quantity and quality changes in rhBMP-2 and control groups. Two controlled clinical trials included extraction sockets associated with ≥50% buccal bone dehiscence. ACS[26,27,29–31,33] or bone substitute materials (allograft or alloplast) were used as the carriers for rhBMP-2.[28,34] Generally, in terms of maintenance of alveolar ridge width, 3 clinical trials were in favor of rhBMP-2 over the placebo group[29,30,34] and 1 RCT did not find such an influence.[28]

A multicenter double-blind placebo-controlled study demonstrated that 4 months after socket grafting in the sockets of ≥50% buccal bone defect, radiographic socket width (at 25% extraction socket length) was maintained better with higher dose rhBMP-2/ACS (1.5 mg/mL) compared with that of lower dose rhBMP-2 (0.75 mg/mL)/ACS, ACS alone, or no treatment group (3.3 ± 2.5, 1.8 ± 1.7, 0.8 ± 1.4, and 0.6 ± 2.6, respectively). Evaluation of the alveolar bone height showed that the sites in the 1.5 mg/mL rhBMP-2/ACS group maintained the palatal wall of the extraction socket, whereas the other study groups experienced significant decreases. Moreover, the number of sites needed secondary bone augmentation during implant placement was fewer in 1.5 mg/mL rhBMP-2/ACS group.[29]

Another RCT rhBMP-2/ACS on the extraction sockets with ≥50% buccal bone dehiscence reported greater mean clinical ridge width (6.0 ± 1.58 vs 4.62 ± 1.36 mm) and mean clinical buccal plate reconstruction (4.75 ± 2.65 vs 1.85 ± 3.58 mm) in the sockets that received rhBMP-2/ACS (1.5 mg/mL) compared with that of ACS alone.[30]

Using *E. coli*-derived rhBMP-2, Huh et al indicated that radiographic changes in alveolar bone width (at 25% extraction socket length) was statistically greater in the rhBMP-2–coated ß-TCP/HA group compared with ß-TCP/HA alone group (1.28 ± 1.39 vs 0.01 ± 1.15 mm). Alveolar bone height was lost in both groups,

Table 1. Characteristics of the Studies Evaluating Alveolar Ridge Width and Height Change

Study/ Design	Sample Size for This Outcome Measure/ Location	Socket Anatomy	Study Groups and Surgical Protocol	Measurement Method	RWC and RHC	Outcome
Cochran (2000), 2-center case series	6 patients (7 sites); maxillary bicuspids/ anterior teeth	NA	0.43 mg/mL rhBMP-2/ACS After flap elevation graft was placed in the socket, no primary closure of the socket	Clinical measurement at baseline and during implant placement (16–30 wk after ridge preservation)	RHC: –0.8 ± 1.5 mm RWC: –3.6 ± 3.1 mm	—
Fiorellini et al (2005), 8-center RCT	80 patients (95 sites); bicuspids/ anterior teeth	≥50% buccal dehiscence	Groups: a: 1.50 mg/mL rhBMP-2/ACS; b: 0.75 mg/mL rhBMP-2/ACS; c: ACS alone; and d: no treatment	CT scans were taken within 4 d and at 4 mo after ridge preservation	RHC: group a: –0.02 ± 1.20; group b: –0.62 ± 1.39; group c: –1.00 ± 1.40; group d: –1.17 ± 1.23	1.5 mg/mL rhBMP-2 favored to ACS alone and no treatment
			After flap elevation, 1.5 or 0.75 mg/mL rhBMP-2 or ACS alone or nothing was placed in the socket and over the entire treatment site, primary flap closure was obtained		RWC at 25% ESL: group a: 3.27 ± 2.53; group b: 1.76 ± 1.67; group c: 0.82 ± 1.40; group d: 0.57 ± 2.56	1.5 mg/mL rhBMP-2 favored to other groups
Misch (2010), case series	10 patients (10 sites); NA	>50% buccal dehiscence	1.5 mg/mL rhBMP-2/ACS + 20% mineralized cortical/cancellous bone allograft was placed in the socket, and then only rhBMP-2/ACS was placed over the socket to the level of the surrounding gingiva. No flap, no primary closure	CT scans were taken before tooth extraction and 4–6 mo later	Mean RWC (range): –1.07 mm (+0.63 to –2.18 mm)	—
Huh et al (2011), 3-center RCT	72 patients (72 sites); molars and premolars	<50% bone loss	Groups: test: 1.5 mg/mL ErhBMP-2 coated β-TCP/HA; control: β-TCP/HA alone Graft was placed in the socket, without flap elevation and without primary closure of the socket	CT scans were taken just after ridge preservation and 3 mo later	RHC: Test: –0.059 ± 0.960; Control: –1.087 ± 1.413 RWC at 25% ESL: Test: 1.279 ± 1.387; Group: 0.006 ± 1.149	Favored test group Favored test group
Kim et al (2014), 2-center RCT	59 patients (59 sites); bicuspids/ anterior teeth	<50% bone loss	Groups: test: 0.05 mg/mL rhBMP-2/DBM + collagen membrane; control: DBM + collagen membrane After flap elevation, graft was placed in the socket, primary closure was obtained.	CT scans were taken within 4 d and at 4 mo after ridge preservation	RHC: Test: –1.17 ± 0.82; Control: –1.50 ± 1.07 RWC at 1 mm (from the initial lingual wall height): Test: –1.06 ± 1.26; Control: –1.21 ± 1.31	No difference No difference

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Table 1. (Continued)

Study/ Design	Sample Size for This Outcome Measure/ Location	Socket Anatomy	Study Groups and Surgical Protocol	Measurement Method	RWC and RHC	Outcome
Coomes et al (2014), RCT	38 patients (38 sites); all kinds of teeth	≥50% buccal dehiscence	Groups: test: 1.5 mg/mL rhBMP-2/ACS; control: ACS alone Graft was placed in the socket, without flap elevation and without primary closure of the socket	Cone-beam CT scans were taken just after tooth extraction and 5 mo after ridge preservation Baseline ridge width was measured "theoretically" based on the ideal buccolingual dimension	Mean palatal/lingual RHC: Test: –0.39; Control: –0.64 RWC at 3 mm from the initial lingual wall height: Test: –2.07 ± 1.17; Control: –3.40 ± 1.73	No difference Favored test group

Negative values mean bone loss and positive values mean bone gain after treatment.
ErhBMP-2 indicates *E. coli* rhBMP-2; ESL, extraction socket length; NA, not available; RHC, ridge height change; RWC, ridge width change.

although the test group revealed slightly less changes from baseline (–0.06 ± 0.96 vs –1.09 ± 1.41).[34]

In a 2-center RCT, Kim et al[28] did not find any benefit of adding low dose (0.05 mg/mL) rhBMP-2 to demineralized bone matrix (DBM) and collagen membrane in the extraction sockets.

Alveolar Bone Quality

Of 7 included articles, 1 RCT[29] and 3 case series[27,31,33] reported data regarding ridge quality of the newly formed bone after application of rhBMP-2. Fiorellini et al determined the quality of newly formed bone 4 months after application of rhBMP-2/ACS using histologic core biopsy and CT and found no significant difference among the groups. For all specimens, the most common findings were trabecular bone structures and remodeling of woven bone into lamellar bone. Low to moderate numbers of osteoblasts, negligible number of osteoclasts, and low vascularity were observed. Inflammation or residual ACS was not observed in any of the specimens. The newly formed bone was comparable in sockets grafted with different doses of rhBMP-2/ACS (1.5 and 0.75 mg/mL) and control sites.[29]

Patients' Safety, Adverse Events, and Postoperative Complications

Among studies evaluating patient's safety, Fiorellini et al reported antibody against type I bovine collagen in the study groups receiving ACS alone or in combination with rhBMP-2. In some patients, the antibody was still detected at 4-month evaluation.[29] Moreover, Kim et al[28] detected antibody against rhBMP-2 in 1 patient treated with this agent, but this incidence was not observed in the control group.

In a 3-year case series study, Cochran et al reported the adverse events occurred in the patients (n = 6) after ridge preservation treated with rhBMP-2, based on Coding Systems for a Thesaurus of Adverse Reaction Terms (COSTART). The adverse events with the frequency of greater than 1 occurrence during the 3 years were as follows: 6 cases with mouth pain, 1 case with oral erythema, and 1 case of infection.

Table 2. Characteristics of the Studies Evaluating Quality of the Newly Formed Bone

Study/Design	Sample Size for This Outcome Measure	Defect Anatomy	Study Groups and Surgical Protocol	Outcome Measures	Results	Outcome
Cochran (2000), 2-center case series	5 patients (6 samples)	NA	0.43 mg/mL rhBMP-2/ACS	Histologic examination, core bone biopsy 16–30 wk after socket grafting	Highly variable amount of woven bone, low number of osteoblasts, osteoclasts, and capillaries, small number of mononuclear cells, no residual ACS, trabecular bone (1 specimen), and cortical bone with fibrosis (1 specimen)	—
Fiorellini et al (2005), 8-center RCT	57 patients (67 specimen)80 patients (95 sites)	≥50% buccal dehiscence	Groups: a: 1.50 mg/mL rhBMP-2/ACS; b: 0.75 mg/mL rhBMP-2/ACS; c: ACS alone; d: no treatment	1. Histologic analysis from core biopsy at 4 mo	Generally: trabecular structure in 2/3 of cases, thickness of trabeculae was moderate to large, remodeling of woven bone into lamellar bone was the most common observation, and no residual collagen matrix	No difference
				2. Bone density difference (mg/mL) from native bone by CT using a standard density block at baseline and at 4 mo	a: 8.61 mg/mL; b: –22.77 mg/mL; c: 15.78 mg/mL; and d: 16.19 mg/mL	No difference
Misch (2010), case series	10 patients (10 defects)	>50% buccal dehiscence	1.5 mg/mL rhBMP-2/ACS + 20% mineralized cortical/cancellous bone allograft	Tactile sense of practitioner during drilling procedure for implant placement, 4–6 mo after ridge preservation	D2 (2 sites); D3 (7 sites); and D4 (1 site)	—
Wallace (2014), case series	7 patients (10 sites)	Sockets with 4 intact walls	1.5 mg/mL rhBMP-2/ACS	1. Bone density based on HU in CBCT taken 4 mo after ridge preservation (mean ± sd)	510.6 ± 244.7 HU	—
				2. Histomorphometric examination 4 mo after ridge preservation:		
				% New vital bone (mean ± sd)	49.6% ± 10.8%	
				% Marrow or fibrous tissue (mean ± sd)	50.4% ± 10.8%	
				3. Insertion torque	45 ± 6.2	

CBCT indicates cone-beam computed tomography; HU, Hounsfield unit.

Table 3. Characteristic of the Studies Evaluating Patient's Safety, Adverse Events, and Postoperative Complications

Study/Design	Sample Size for This Outcome Measure	Study Period	Study Groups and Socket Graft	Concentration and Dose of rhBMP-2 per Extraction Socket	Outcome Measures	Results
Cochran et al, (2000), 2-center case series	6 patients (7 sites)	3 y	rhBMP-2/ACS	Concentration: 0.43 mg/mL	Oral wound examination just after surgery and at 2 and 5 d and 4, 8, 12, and 16 wk after surgery	Erythema up to 4 and 12 wk after surgery (in 1 patient)
				Mean total dose: 0.27 mg (range: 0.12–0.88 mg)	Patient's vital signs (temperature, respiration, pulse, and blood pressure) during study period	No significant change
					Serum chemistry/UA/CBC with diff at baseline and 2 d and 4 wk after surgery	No significant change
					Serum antibodies (anti-rhBMP-2, anti-bovine collagen type I, and anti-human collagen type I proteins) at baseline, and 5 d, 4, 8, and 16 wk after surgery	No detectable antibody
					Adverse experiences with and without regard to causality during 3 y after surgery based on	8 adverse experiences of grade 1 and 4 adverse experiences of grade 2. No cases with grade 3 or 4.
					WHO toxicity (frequency of occurrence of the overall toxicity), grades 1–4	Body system: digestive (9 cases) and body as a whole (1 case)
					Body system and COSTART term (adverse experiences with a frequency greater than 1 occurrence)	COSTART term: mouth pain (6 cases), erythema (1 case), colitis (2 cases), and infection long after surgery (1 case)
					Implant failure	None
Fiorellini et al (2005), 8-center RCT	80 patients (95 sites)	4 mo	Groups:	Concentrations: 1.50 and 0.75 mg/mL	Oral wound examinations at baseline; 2 and 14 d, and 1, 2, 3, and 4 mo after surgery	A total of 250 adverse events in 78 of the 80 enrolled subjects. The most frequent reports: oral edema (75%), mouth pain (68%), and oral erythema (46%).
			A: 1.50 mg/mL rhBMP-2/ACS	Mean total dose		Greater number of cases of oral edema and erythema in the study treatment groups compared to the no treatment group (data not shown)
			B: 0.75 mg/mL rhBMP-2/ACS	0.9 mg in the 0.75 mg/mL group	Serum chemistry/CBC at 2 d, and 1 mo after surgery	No significant change
			C: ACS alone	1.9 mg in the 1.50 mg/mL group.	Periapical radiographs were taken at baseline and 2, 3, and 4 mo after treatment	No overexuberant bone formation or radiolucent voids

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Table 3. (Continued)

Study/Design	Sample Size for This Outcome Measure	Study Period	Study Groups and Socket Graft	Concentration and Dose of rhBMP-2 per Extraction Socket	Outcome Measures	Results
			D: no treatment		Serum antibodies (anti-rhBMP-2, anti-bovine collagen type I, and anti-human collagen type I proteins) at baseline and 1, 2, and 4 mo after surgery.	No detectable antibodies to rhBMP-2 or to human type I collagen. Antibody to bovine type I collagen at baseline (2 in the group D and 1 in the group A) Transient antibody to bovine type I collagen (returned to baseline level by 4 mo) in 4 patients. Detectable antibody to bovine type I collagen at the 4-mo evaluation in 4 patients.
Misch (2010), case series	10 patients (10 defects)	4–6 mo	rhBMP-2/ACS + 20% mineralized cortical/cancellous bone allograft	Concentration: 1.5 mg/mL Dose: not reported	Oral wounds examination	Four patients experienced moderate swelling of the upper lip and face. The other 6 patients had minimal swelling. Three sites showed mild erythema of the healing soft tissue.
					Implant failure	None
Kim et al (2014), 2-center RCT	66 patients (66 sites)	3 mo	Groups A: rhBMP-2/DBM + collagen membrane (n = 34) B: DBM + collagen membrane (n = 32)	Concentration: 0.05 mg/mL Dose: not reported	Oral wounds examination at baseline and days 2 and 14 and 1 and 3 mo postoperatively, (ie, pain, discomfort, swelling, fever, and wound dehiscence). Serum chemistry/UN/CBC at the screening and final visit Serum antibody (anti-rhBMP-2/DBM) at baseline and 3 mo after surgery	No severe postoperative complication No significant change At baseline: anti-rhBMP-2/DBM was detected in 1 patient in group A and 3 patients in group B At 3-mo examination: 2 patients in group A and no patient in group B developed anti-rhBMP-2/DBM
Coomes et al (2014), RCT	38 patients (38 sites)	5 mo	Groups A: rhBMP-2/ACS B: ACS alone	Concentration: 1.5 mg/mL Dose: not reported	Oral wound examination	Mild erythema and localized swelling in 12% of group A vs 0% of the group B.

CBC with diff indicates complete blood count with differential; COSTART, Coding Systems for a Thesaurus of Adverse Reaction Terms; UN, urine analysis.

Table 4. Quality Assessment and Potential Risk of Bias of Included RCTs, Based on Cochrane Risk Assessment Tool

Criteria	Fiorellini et al (2005)	Huh et al (2011)	Kim et al (2014)	Coomes et al (2014)
Representative of general population	Yes	Yes	Yes	Yes
Allocation concealment method	No	No	Yes	Yes
Examiner masked	Yes	No	No	No
Calibration (intraexaminer/interexaminer)	No	No	No	No
Defined inclusions/exclusions	Yes	Yes	Yes	Yes
Correction for confounding factors	No	No	No	No
Appropriate statistics methods	Yes	Yes	Yes	Yes
All patients accounted for at the end of study	Yes	No	No	No
Analysis accounts for patient losses	NA	No	No	Yes
Estimated potential risk of bias	High	High	High	High

NA indicates not applicable.

Table 5. Quality Assessment of Case Series Studies, Based on Modified Delphi Method

Criterion	Cochrane (2000)	Misch (2010)	Wallace (2014)
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study population			
2. Were the cases collected in more than 1 center?	Yes	No	Unclear
3. Were patients recruited consecutively?	Unclear	Yes	No
4. Were the characteristics of the patients included in the study described?	No	No	Partial
5. Were the eligibility criteria (ie, inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	No	Partial
6. Did patients enter the study at a similar point in the disease?	Unclear	Partial	Unclear
Intervention and cointervention			
7. Was the intervention of interest clearly described?	Yes	Yes	Yes
8. Were additional interventions (cointerventions) clearly described?	Unclear	Unclear	Unclear
Outcome measures			
9. Were the outcome measures clearly defined?	Partial	No	Partial
10. Were the outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Partial
11. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	No
Statistical analysis			
12. Were the statistical tests used to assess the relevant outcomes appropriate?	No	No	No
Results and conclusions			
13. Was follow-up long enough for important events and outcomes to occur?	Partial	Partial	Partial
14. Were losses to follow-up reported?	Yes	Yes	Unclear
15. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	No	No
16. Were the adverse events reported?	Yes	Yes	No
17. Were the conclusions of the study supported by the results?	Partial	Partial	No
Competing interests and sources of support			
18. Were both competing interests and sources of support for the study reported?	Yes	No	Yes
Percentage of "Yes" response to the question	50%	38.8%	16.6%

One study reported the incidence of wound dehiscence at 5th postoperative day in 1 of 6 patients received rhBMP-2/ACS for ridge preservation. Moreover, 1 patient experienced localized erythema, which was remained at 6-month visit.[27] A clinical trial indicated that the incidence of erythema and localized postoperative swelling was greater in the patients received rhBMP-2/ACS compared with that of control group (ACS alone).[30]

DISCUSSION

The aim of this systematic review was to determine the efficacy and safety of rhBMP-2 for alveolar ridge preservation in the extraction sockets. Because of the high heterogeneity among the included trials, meta-analysis was not performed. Within the limits of this review, a main finding was that alveolar ridge preservation with rhBMP-2/ACS slightly reduces alveolar ridge width change in a dose-dependent order. From a clinical point

of view, the benefits of rhBMP-2 for ridge preservation were less significant in terms of ridge height reduction. This finding is in agreement with a recent study that showed ridge preservation fail to prevent vertical resorption of buccal and lingual plates.[35]

At present, possible risk of long-term adverse events associated with rhBMP-2 is unclear because of the lack of long-term trials and small number of patients.

Alveolar Ridge Quantity

Among the 6 studies examined the ridge dimension, 3 RCTs used rhBMP-2 after flap elevation and the other studies used flapless technique. Regardless of flap or flapless technique, the effect of rhBMP-2 on maintenance of ridge width was more apparent when cases with more severe bone loss (≥50% buccal bone dehiscence) were included.[29,30] However, studies on extraction sockets with less than 50% buccal bone dehiscence found less significant differences.[28,34]

It is important to note that alveolar ridge remodeling was an inevitable phenomenon after tooth extraction, and socket grafting with or without rhBMP-2 was not able to prevent this event. However, when the graft was extended over the socket, Fiorellini et al[29] showed alveolar ridge width gain. The same group published another article on the same clinical trial, reporting bone volume changes in extraction sites treated with rhBMP-2/ACS, based on standardized CT examinations and the Simplant program. The mean new bone volume for treatment groups was 0.104 ± 0.063 cm^3 for the untreated group, 0.084 ± 0.044 cm^3 for the group treated with ACS alone, 0.106 ± 0.033 for the group treated with 0.75 mg/mL rhBMP-2/ACS, and 0.192 ± 0.064 for the group treated with 1.5 mg/mL rhBMP-2/ACS.[36]

The potential benefit of rhBMP-2 was less significant, when allograft or alloplastic material instead of collagen sponge was used as the carrier.[28,34] It seems that preservation of alveolar ridge dimension might be more predictable after application of bone substitute material compared with that of collagen sponge.

Among the 4 RCTs presenting data regarding alveolar ridge height, 2 studies did not show any difference between the test and control groups. In the other 2 studies, the mean difference between the test and control groups was reported to be within 1 mm, which may not be clinically significant.

Alveolar Ridge Quality

Adding rhBMP-2 to ACS in the extraction socket did not improve the quality of newly formed bone 4 months after extraction.[29] It appears that in systemic healthy subjects, natural healing potential of the extraction socket is quite sufficient to provide a high-quality bone in the alveolar site, and rhBMP-2 does not have any additional effect on the quality of new bone.

From tissue engineering point of view, there is a concern regarding the bioavailability of rhBMP-2 for inducing bone formation. During natural socket healing process, increased expression of rhBMP-2 is observed during accumulation and proliferation of osteoblast precursors, which is usually after 2 weeks of tooth extraction.[37] However, using radiolabeled rhBMP-2 with ACS in a rabbit model, 32% of the initial dose remained at the osteotomy site at day 7.[38]

Various delivery systems have been evaluated for their efficacy and biocompatibility as the carrier for rhBMP-2. An ideal carrier must retain rhBMP-2 for a certain time to induce bone formation; possess a porous structure for cellular infiltration and proliferation, vascular invasion, and maintain shape against any pressures; and have appropriate mechanical strength so that it can be cut or molded into various shapes to fit to bone reconstruction sites, with no toxicity and not interfering with BMP activity. Meanwhile, it should resorb to not impede the bone formation or not to compromise the physiological and biomechanical properties of bone. DBM, metals, gelatin, hydroxyapatite, tricalcium phosphate, poly D, L-lactic-co-glycolic acid, collagen, polylactide–polyethylene glycol block copolymer have been evaluated as BMP-2 carriers. Among them, ACS is the only FDA-approved carrier for rhBMP-2.[39] Collagen sponge is a bovine type I collagen matrix with high affinity to rhBMP-2. ACS is soak-loaded with rhBMP-2 solution just before surgical implantation.[20] Collagen sponges possess many favorable properties, but they lose physical strength and collapse when blood smeared. Another important drawback is the considerable proteolysis of the collagen matrix during the initial days after surgery, due to the inflammatory phase of surgical wound healing, leading to its elimination by the body.[40] Because of lack of available trials, the benefits of rhBMP-2 delivered on other carriers are not clear. Further studies are needed to find an ideal carrier for rhBMP-2.

Patients' Safety, Adverse Events, and Postoperative Complications

Given the marginal benefits of rhBMP-2 in terms of preserving alveolar ridge dimension, the risks of using of this highly potent tissue-signaling drug must be carefully weighed against potential benefits. There are significant concerns regarding the safety of exogenous rhBMP-2 in human. A recent systematic review supported the protumorigenesis role of high-dose exogenous rhBMP-2.[41] The risk of cancer associated with rhBMP-2 seems to be dose-dependent[40]; however, the exact cutoff point for increased risk of cancer has not been determined yet. The range of mean dose of rhBMP-2 used in the different studies varied from 0.27 to 1.9 mg (Table 3). A multicenter randomized controlled clinical trial on patients who underwent lumbar spinal arthrodesis using 40 mg rhBMP-2 or autogenous bone graft reported that rhBMP-2 was associated with increased risk of new cancer after 2 years.[42]

Currently, the use of rhBMP-2 in tumor area is off-label, prepubertal and skeletally immature patients and in pregnant women or whom intended to become pregnant.[39] Ectopic bone formation has been associated with application of high doses of rhBMP-2.[43] This side effect was not reported in the subjects received rhBMP-2 for alveolar ridge preservation. The number of patients included in the studies was too small to assess risk of adverse events. In addition, the follow-up period was

too short to allow the development of serious adverse events. Hence, the risk of adverse events after application of rhBMP-2 for alveolar ridge preservation is unclear.

Agreement/Disagreement With Other Reviews

In an industry-sponsored systematic review on the application of rhBMP-2 in alveolar ridge augmentation, Freitas et al included 3 studies, including 2 case series (the same population with different follow-up period) and 1 clinical trial. They reported that rhBMP-2 enhanced ridge width and maintained ridge height.[21] Another systematic review by Kelly et al investigated the effect of rhBMP-2 on maxillary sinus floor elevation and ridge augmentation. In the meta-analysis, they pooled data from ridge augmentation (2 RCTs) and alveolar ridge preservation (4 RCTs). Data for ridge width and ridge height were pooled together, as well. The mean difference was found to be 0.56 mm in favor of rhBMP-2.[22] Our findings support the results of a recently published critical assessment of systematic reviews on biologic agents to promote bone formation indicated that due to substantial methodological variability, the findings of the existing systematic reviews should be interpreted with caution.

Conclusion and Clinical Recommendations

Because of large heterogeneity in the study designs, it is not possible to aggregate data in quantitative meta-analysis or make a conclusive decision an application of rhBMP-2 in extraction socket grafting. Available data suggest that in comparison with placebo group, application of higher dose rhBMP-2 loaded on ACS in extraction socket seems to be more effective in preserving the extraction socket width compared with that of lower dose rhBMP-2. Moreover, this effect might be more apparent in cases with more than 50 buccal bone dehiscence. However, this benefit may not be of significant clinical importance. Application of rhBMP-2 in the extraction socket is not able to prevent loss of alveolar ridge height. Hence, the cost benefit of ridge preservation with BMP-2 must be carefully considered.

Based on the findings of this study, some suggestions are recommended for future clinical trials:

1. Long-term well-controlled clinical trials with large sample size must be developed to investigate patients' safety, clinical outcome, and cost-effectiveness of rhBMP-2 in alveolar ridge preservation.
2. Anatomical confounding factors, surgical protocol, and method of measuring the ridge dimension (clinical and radiographic) should be standardized to measure the true effect of rhBMP-2 on alveolar ridge preservation.
3. Different carriers for rhBMP-2 should be compared to find the more appropriate carrier system.

Disclosure

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

Approval

This is a systematic review of previously published RCTs and case series. There is no intervention on either human or animal subjects.

Roles/Contributions by Authors

N. Moslemi: designed and supervised the study, screened the titles and abstracts to be included, contributed to acquisition and interpretation of data, critical revision of manuscript for important intellectual content, and writing the discussion and approval of the final version of manuscript. V. Khoshkam: contributed to analysis and interpretation of data and revised the manuscript for important intellectual content and English vocabulary. S.C. Rafiei: contributed to literature search, screening the titles and abstracts, and writing the background. N. Bahrami: contributed to manuscript drafting. H. A. Roosta: contributed to extracting data, manuscript drafting, formatting references and tables, and manuscript revision for important intellectual content and approval of the final version of the manuscript.

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