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Alveolar Cleft Reconstruction Using Morphogenetic Protein (rhBMP-2): A Systematic Review and Meta-Analysis

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Abstract

Objective: This study aimed to review the existing evidence regarding reconstruction of the alveolar cleft using recombinant human bone morphogenetic protein-2 (rhBMP-2) in terms of bone volume and bone height.

Design: Systematic review and meta-analysis.

Patients—Participants: A systematic search was done. Randomized and nonrandomized clinical trials, where rhBMP-2 was used in the reconstruction of human alveolar cleft were included.

Interventions: Reconstruction of alveolar cleft with rhBMP-2.

Main Outcome Measures: Average bone volume formation and average bone height formation in the alveolar cleft. Mean difference was calculated and pooled by meta-analysis.

Results: Of 709 identified articles, 5 studies met the inclusion criteria. The average bone volume formation was higher in the rhBMP-2 group than in the control group (61.11% vs 59.12%). The average bone height formation was higher in the control group compared to the rhBMP-2 group (75.4% vs 61.5%). The risk of bias in the selected articles was high. The meta-analysis showed that rhBMP-2 treatment may benefit bone formation compared to iliac crest graft (low certainty evidence; mean difference: −208.76; 95% confidence interval: −253.59 to −163.93; $-I^2 = 0\%$).

Conclusions: The results obtained in primary articles are promising but have a high risk of bias and have low quality of evidence; therefore, it is necessary to conduct controlled clinical trials with a greater number of patients to recommend the use of rhBMP-2 in the treatment of the alveolar cleft. PROSPERO registration number: CRD42018077741.

Keywords

alveolar cleft, alveolar bone grafting, rhBMP-2, bone morphogenetic protein, systematic review, meta-analysis

Introduction

Alveolar clefts correspond to the space between the maxillary segments anterior to the incisive foramen in patients with cleft lip and palate (Santiago et al., 2014). The goals of alveolar cleft reconstruction are to provide support for the erupting dentition and facilitate orthodontic tooth movement, obtain continuity of the maxillary arch, eliminate residual oronasal fistula, improve phonation, provide support for the base of the nose, and perhaps, allow for placement of a future dental implant (Aurouze et al., 2000; Tai et al., 2000; Bajaj et al., 2003).

There is still controversy regarding the ideal bone graft in alveolar cleft reconstruction (Guo et al., 2011). Iliac crest

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autologous graft is mostly used due to their osteogenic capacity, and the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) is an excellent treatment alternative due to its osteoinductive capacity (Wehrhan et al., 2013); however, the main advantage of rhBMP-2 is that it does not require a donor site (Van Hout et al., 2011; Seifeldin, 2016). Other benefits of using rhBMP are reduction in surgery time, elimination of potential complications at the donor site, reduction in hospitalization time, and reduction of total costs (Rengachary, 2002; Wikesjo et al., 2007; Dickinson et al., 2008; Davies and Ochs, 2010; Carreira, et al., 2014; Mehta et al., 2018).

The objective of this study was to review existing evidence regarding the reconstruction of alveolar cleft by rhBMP-2 in humans, in terms of bone volume and bone height.

Materials and Methods

A systematic review was conducted in accordance with the Cochrane Handbook for the Systematic Review of Interventions (Higgins et al., 2011) and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2009). The protocol number in PROSPERO is CRD42018077741 (https://www.crd.york.ac.uk/prospero).

The inclusion criteria were randomized and nonrandomized clinical trials in English or Spanish, where rhBMP-2 was used in the reconstruction of uni- or bilateral alveolar clefts in humans, using any kind of scaffold. Articles were included where bone formation was evaluated using 3-dimensional (3D) imaging studies and articles where bone quality was evaluated using histology and/or histomorphometry. Exclusion criteria were all studies that were not clinical trials; that include patients with previous gingivoperiosteoplasty, patients without a cleft, or patients with facial clefts other than cleft lip palate; and articles in which bone formation was evaluated with conventional 2-dimensional radiographs and animal studies were also excluded.

The following databases were used: Medline, EMBASE, Central Cochrane, LILACS, Cinahl, and SCOPUS in November 2017. The details of the search strategy used are given in Table 1.

All articles obtained from databases were identified, and duplicate articles were eliminated. Articles were selected by title and abstract, and then by full text according to the eligibility criteria using Covidence online software, with 2 researchers (F.U. and J.P.A.) independently. If there was a discrepancy, the opinion of a third independent investigator was requested (C.Z.).

The data extracted were study type, level of evidence, number of patients treated with rhBMP-2 and with iliac crest, average age, type of alveolar cleft, control group, rhBMP-2 scaffold, rhBMP-2 dose, follow-up, bone volume, and bone height formation (BHF).

Two investigators (F.U. and J.P.A.) independently analyzed the risk of bias of the selected articles using Covidence online software (http://www.covidence.org/home) employing the Cochrane risk of bias assessment tool (Higgins et al., 2011), and in the event of a discrepancy, the opinion of a third independent evaluator (C.Z.) was requested. This tool evaluates random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting of results, and other sources of bias. Each domain is classified as low risk of bias, high risk of bias, or unclear risk of bias.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the overall quality of evidence from articles associated with each result, and a "Summary of Findings" table was created using GRADEpro GDT software (http://gdt.guidelinedevelopment.org). The GRADE approach appraises the quality of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The overall risk of bias, inconsistency in results, indirectness of evidence, imprecision, and possible publication risk of the included studies was assessed (Langendam et al., 2013). Depending on the seriousness, the quality of the evidence can be downgraded 1 or 2 levels for each aspect. We classified the quality of evidence for each one of the primary outcomes as high, moderate, low, or very low.

The main outcomes were bone volume formation (BVF) in the alveolar cleft at 6 months and BHF in the alveolar cleft at 6 and 12 months measured by 3D imaging. The BVF was calculated from the mean preoperative bone defect volume (mm^3) minus the mean postoperative bone defect volume (mm^3). The BHF was calculated from the mean postoperative height formation (mm) in the cleft. We pooled studies that compared rhBMP-2 with iliac crest graft. Results were reported as continuous data with a mean difference (MD), and forest plot was constructed showing the summary and estimated 95% confidence intervals (CIs) estimated in the meta-analyses, together with results from individual studies. Heterogeneity between studies was calculated using the I^2 statistic, with I^2 less than 50% graded as not important or moderate, representing no significant interstudy heterogeneity (Moher et al., 2009; Langendam et al., 2013). Review Manager 5.3 (Cochrane IMS, Copenhagen, Denmark) software was used.

Results

A total of 709 articles were found during database search of which 307 were duplicate articles and eliminated, leaving 402 articles for review. After title and abstract review, 391 articles were excluded, with the most common reason for exclusion being that the alveolar cleft was not used as a graft site or animal studies. Eleven articles were selected for full-text review, of which 4 articles were excluded for being retrospective and 2 articles for being written in Chinese. Finally, 5 articles were included (Figure 1).

Five primary articles published between 2008 and 2017 were found. All studies were randomized clinical trials except one (Liang et al., 2017), which was classified by the author as a prospective cohort study; however, due to the characteristics of the work, we classified it as a nonrandomized clinical trial. The

Table 1. Search Strategy Used in Each Database.[a]

MEDLINE	((((((((((maxillary) OR alveolar)) AND ((((((bone graft*) OR cleft*) OR cleft reconstruction) OR defect*) OR malform*) OR cleft defect))) OR ((cleft lip and palate))) OR premaxillary cleft) OR "Alveolar Bone Grafting"[Mesh]) OR "Cleft Lip"[Mesh]) OR "Cleft Palate"[Mesh])) AND ((((Bone morphogenetic protein 2) OR Recombinant human morphogenetic protein-2) OR rhBMP-2) OR "Bone Morphogenetic Protein 2"[Mesh])) AND ((((((bone) AND ((((healing) OR fill) OR height) OR graft healing))) OR volumetric assessment) OR "Alveolar Ridge Augmentation"[Mesh]) OR "Bone Regeneration"[Mesh])	176
EMBASE	((((alveolar) OR (maxillary)) AND ((bone AND graft*) OR (cleft*) OR (cleft AND reconstruction) OR (defect*) OR (malform*) OR (cleft AND defect))) OR (cleft AND lip AND palate) OR (premaxillary AND cleft) OR ('alveolar bone grafting'/exp) OR ('cleft lip'/exp) OR ('cleft palate'/exp)) AND ((bone AND morphogenetic AND protein AND 2) OR (recombinant AND human AND morphogenetic AND 'protein 2') OR ('rhbmp 2') OR ('bone morphogenetic protein 2'/exp)) AND (((bone) AND ((healing) OR (fill) OR (height) OR (graft AND healing))) OR (volumetric AND assessment) OR ('alveolar ridge augmentation'/exp) OR ('bone regeneration'/exp)) AND [embase]/lim	145
Cochrane Central	((((((((((maxillary: ti, ab, kw) OR alveolar: ti, ab, kw)) AND ((((((bone graft*: ti, ab, kw OR cleft*: ti, ab, kw) OR cleft reconstruction: ti, ab, kw) OR defect*: ti, ab, kw) OR malform*: ti, ab, kw) OR cleft defect: ti, ab, kw))) OR ((cleft lip and palate: ti, ab, kw))) OR premaxillary cleft: ti, ab, kw) OR "MeSH descriptor: [Alveolar Bone Grafting]") OR "MeSH descriptor: [Cleft Lip]") OR "MeSH descriptor: [Cleft Palate]")) AND ((((Bone morphogenetic protein 2: ti, ab, kw) OR Recombinant human morphogenetic protein-2: ti, ab, kw) OR rhBMP-2: ti, ab, kw) OR "MeSH descriptor: [Bone Morphogenetic Protein 2]")) AND ((((((bone: ti, ab, kw) AND ((((healing: ti, ab, kw) OR fill: ti, ab, kw) OR height: ti, ab, kw) OR graft healing: ti, ab, kw))) OR volumetric assessment: ti, ab, kw) OR "MeSH descriptor: [Alveolar Ridge Augmentation]") OR "MeSH descriptor: [Bone Regeneration]")	28
LILACS	((((((((((TW: maxillary) OR TW: alveolar)) AND ((((((TW:"bone graft$") OR TW: cleft$) OR TW:"cleft reconstruction") OR TW: defect$) OR TW: malform$) OR TW:"cleft defect"))) OR ((TW: cleft lip and palate))) OR TW: premaxillary cleft) OR MH:"Alveolar Bone Grafting") OR MH:"Cleft Lip") OR MH:"Cleft Palate")) AND ((((TW:"Bone morphogenetic protein 2") OR TW:"Recombinant human morphogenetic protein-2") OR TW: rhBMP-2) OR MH:"Bone Morphogenetic Protein 2")) AND ((((((TW: bone) AND ((((TW: healing) OR TW: fill) OR TW: height) OR TW:"graft healing")))) OR TW:"volumetric assessment") OR MH:"Alveolar Ridge Augmentation") OR MH:"Bone Regeneration")	25
CINAHL	((((((((((AB maxillary) OR AB alveolar)) AND ((((((AB bone graft*) OR AB cleft*) OR AB cleft reconstruction) OR AB defect*) OR AB malform*) OR TX:"cleft defect"))) OR ((AB cleft lip and palate))) OR AB premaxillary cleft) OR MH "Cleft Lip") OR MH "Cleft Palate")) AND ((((AB Bone morphogenetic protein 2) OR AB Recombinant human morphogenetic protein-2) OR AB rhBMP-2) OR MH "Bone Morphogenetic Proteins")) AND ((((((AB bone) AND ((((AB healing) OR AB fill) OR AB height) OR AB graft healing))) OR AB volumetric assessment) OR MH "Bone Regeneration")	30
SCOPUS	((((TITLE-ABS-KEY (alveolar)) OR (TITLE-ABS-KEY (maxillary))) AND ((TITLE-ABS-KEY (bone AND graft*)) OR (TITLE-ABS-KEY (cleft*)) OR (TITLE-ABS-KEY (cleft AND reconstruction)) OR (TITLE-ABS-KEY (defect*)) OR (TITLE-ABS-KEY (malform*)) OR (TITLE-ABS-KEY (cleft AND defect)))) OR (TITLE-ABS-KEY (cleft AND lip AND palate)) OR (TITLE-ABS-KEY (premaxillary AND cleft)) OR (TITLE-ABS-KEY (alveolar AND bone AND grafting))) AND ((TITLE-ABS-KEY (bone AND morphogenetic AND protein 2)) OR (TITLE-ABS-KEY (recombinant AND human AND morphogenetic AND protein-2)) OR (TITLE-ABS-KEY (rhbmp-2))) AND (((TITLE-ABS-KEY (bone)) AND ((TITLE-ABS-KEY (healing)) OR (TITLE-ABS-KEY (fill)) OR (TITLE-ABS-KEY (height)) OR (TITLE-ABS-KEY (graft AND healing)))) OR (TITLE-ABS-KEY (volumetric AND assessment)) OR (TITLE-ABS-KEY (alveolar AND ridge AND augmentation)) OR (TITLE-ABS-KEY (bone AND regeneration)))	305

Abbreviation: rhBMP, recombinant human bone morphogenetic protein-2.
[a]Total 709.

number of patients treated with rhBMP-2 varied between 2 and 21, with an average of 9.2 patients.

The age of patients averaged 11.43 $\pm$ 2.81 years. A primary article included unilateral and bilateral alveolar clefts; still, grafts for bilateral patients were carried out in 2 surgical sessions (Liang et al., 2017). In all articles, rhBMP-2 alveolar clefts reconstruction was compared to iliac crest grafts. The scaffold used with rhBMP-2 in the cleft was collagen sponge alone, collagen sponge with demineralized bone tissue, and hyaluronic acid–based hydrogel. The rhBMP-2 dose used varied between 250 μg and 4.2 mg.

Follow-up was carried out on average at 12.6 months with a minimum of 6 months and a maximum of 21 months. The imaging survey method was computerized tomography in all studies; in one study, conventional occlusal X-rays were also used. No assessment of bone quality was made in any study (Table 2).

Bone Filling

Relationship between BFV and preoperative bone defect volume was expressed as a percentage. The average preoperative volume of alveolar clefts treated with rhBMP-2 and iliac crest was 1827.24 $\pm$ 2157.09 mm^3 and 1796 $\pm$ 1908.4 mm^3, respectively. One study has a higher average age of patients compared to other articles (16.15 years); thus, the clefts are larger in size compared to the rest of the studies (Dickinson et al., 2008). If we do not consider this article in the analysis,

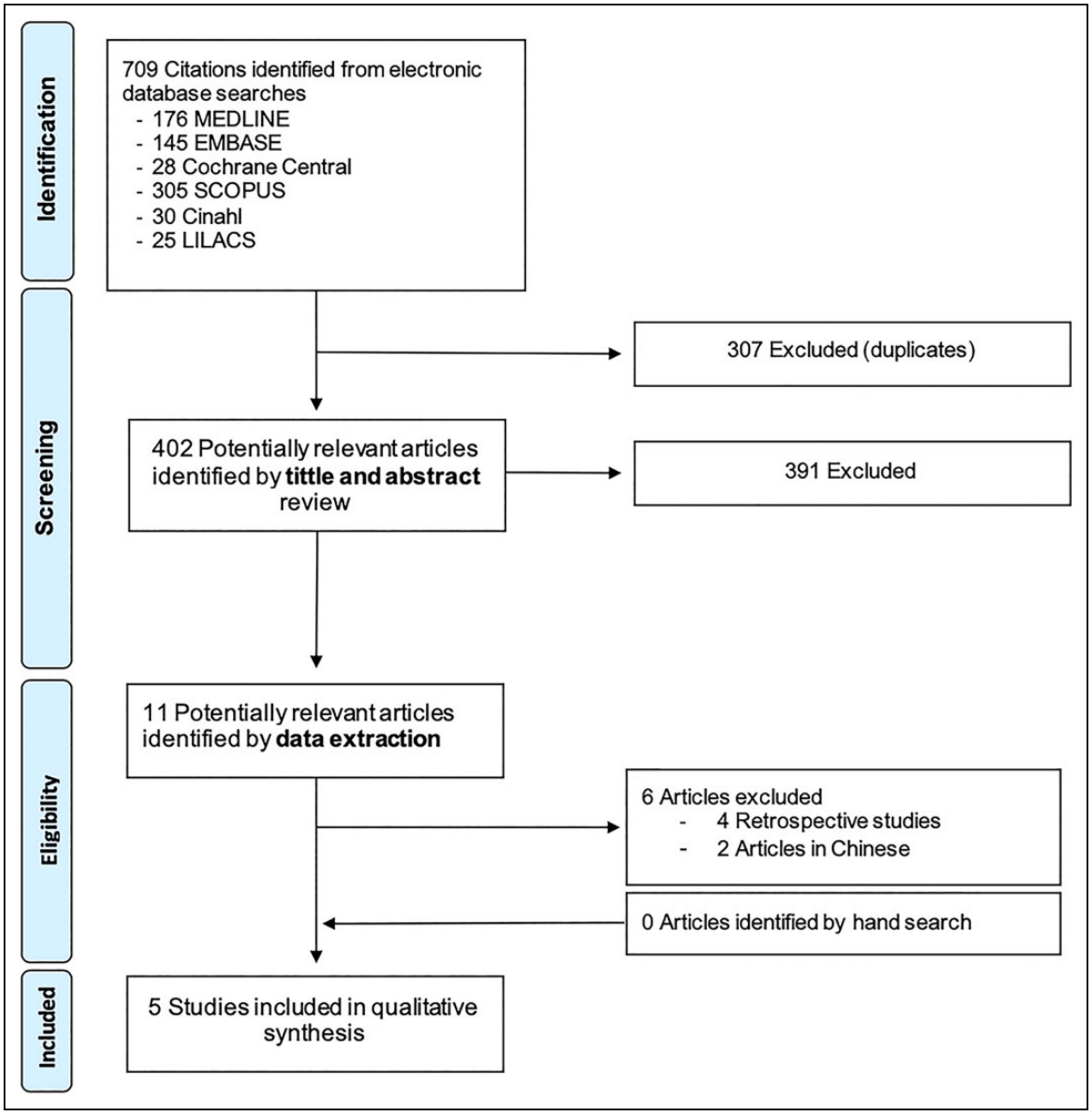

Figure 1. Flow diagram.

the preoperative average volume drops considerably to 884 ± 522.82 mm^3 in the rhBMP-2 group and 970 ± 554.62 mm^3 in the control group. Average bone filling in clefts with rhBMP-2 and iliac crest was 61.11% ± 24.6% and 59.12% ± 18.59%, respectively.

Bone Height

The relationship between BHF and the preoperative height of the cleft is expressed as percentage. Bone height was measured in 2 articles (Alonso et al., 2010; Canan et al., 2012) with a preoperative average of 14.65 ± 1.48 mm in the rhBMP-2 group and 15.5 ± 0.85 mm in the control group. The bone formation percentage at 12 months was 61.5% ± 4.95% in the rhBMP-2 group and 75.4% ± 15.84% in the control group (Table 3).

All studies had at least 1 domain classified as having a high risk of bias. The domains of random sequence generation and allocation concealment were classified as of high risk in one article because the patients' relatives were allowed to choose between an iliac crest bone graft and rhBMP-2 (Liang et al., 2017). In the rest of the studies, the domains were classified as unclear risk. These articles describe sequence generation in a random way; however, in the article, this generation method is not described, and it is also not mentioned whether the sequence was concealed.

Blinding the participants and personnel was not carried out in any of the studies. This was due to the fact that the procedure did not permit carrying out blinding, since in one group the iliac

Table 2. Main Characteristics of the Included Studies.

Characteristic	Liang et al., 2017	Neovius et al., 2013	Dickinson et al., 2008	Alonso et al., 2010	Canan et al., 2012
Study type	Nonrandomized clinical trial	Randomized clinical trial	Randomized clinical trial	Randomized clinical trial	Randomized clinical trial
Level of evidence	2b	2b	2b	2b	2b
n	35	7	21	16	18
Number of patients rhBMP-2 group	21	2	9	8	6
Number of patients iliac crest group	14	3	12	8	6
Mean age	11.9 years	9.92 years	16.15 years	9.5 years	9.67 years
Type of alveolar cleft	Unilateral and bilateral	Unilateral only	Unilateral only	Unilateral only	Unilateral only
Control group graft	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone and periosteoplasty
rhBMP-2 scaffold	Absorbable collagen sponge and demineralized bone matrix	Hyaluronan based hydrogel	Absorbable collagen sponge	Absorbable collagen sponge	Absorbable collagen sponge
rhBMP-2 dose	2.1 mg	250 μg/mL	1.5 mg/mL	3.2 and 4.2 mg	3.2 and 4.2 mg
Follow-up, months	21	6	12	12	12
Outcome measuring method	3 months: Occlusal Rx; 6-9 months: CBCT	CT scan	CBCT	CBCT	CBCT
Results	3 months occlusal Rx: 67% of patients in experimental group and 56% of patients in control group had complete bone fill. 6-9 months CBCT: Bone filling in experimental group 31.6% and 32.5% in control group. No significant difference.	Bone filling: 46% Experimental group and 48% control group. No significant difference.	Bone filling: 95% experimental group and 63% in control group. Significant difference between groups.	Bone filling: 74% experimental group and 80.2% in control group. No significant difference. Bone height: 65% experimental group and 86.6% control group. There was significant difference between groups.	Bone filling: 75.1% experimental group and 78% in iliac crest group. Bone height: 58% experimental group and 64.2% in iliac crest group. No significant difference between groups.

Abbreviations: CT, computed tomography; CBCT, cone-beam computed tomography; rhBMP-2, bone morphogenetic protein-2.

crest graft is collected and in the other group no collection takes place. In 2 articles, blinding of outcome assessment was classified as low risk, since the operator who evaluated the imaging results did not know to which group any particular patient belonged (Dickinson et al., 2008; Alonso et al., 2010). In the rest of the studies, it was not stated whether the evaluators of the images were blinded or not.

Evaluating incomplete results data, we assessed that the number of patients included in the article were also included in the results. No study reported loss of patients. All articles were evaluated with a low risk of bias. In the selective reporting of results, none of the articles had a study protocol previously recorded, so we cannot know if there were additional results that were not published. Nevertheless, the variables described in materials and methods were reported as results in all of the studies; therefore, they were classified as having low risk of bias. In other bias, the difference between groups and cointerventions was evaluated. One of the exclusion criteria for the review was previous alveolar surgeries. All articles statistically demonstrated that there was no significant difference between the treatment groups with the exception of 1 article (Neovius et al., 2013) in which the patient characteristics were described, but it was not determined whether there was a significant difference between the groups (Figure 2).

Three of 5 articles reported sufficient data for the postoperative evaluation of bone formation in the alveolar cleft at

Table 3. Outcomes of the Selected Studies.

Bone Filling				
	Mean Volume Defect Preop, mm^3	Mean Volume Defect Postop 6 months, mm^3	Bone Filling Percentage, %	
rhBMP-2	1.827.24 ± 2.157.09	391.46 ± 247.1	61.11 ± 24.6	
Iliac Crest	1.796.05 ± 1.908.4	710.76 ± 730.64	59.12 ± 18.59	
Bone Height				
	Mean Bone Height Preop, mm	Mean Bone Height Postop 6 Months, mm	Mean Bone Height Postop 12 Months, mm	Percentage (12 Months)
rhBMP-2	14.65 ± 1.48	8.2 ± 0.42	9 ±1.7	61.5 ± 4.95
Iliac crest	15.5 ± 0.85	11.5 ± 2.83	11.7 ± 3.11	75.4 ± 15.84

Abbreviation: rhBMP-2, bone morphogenetic protein-2.

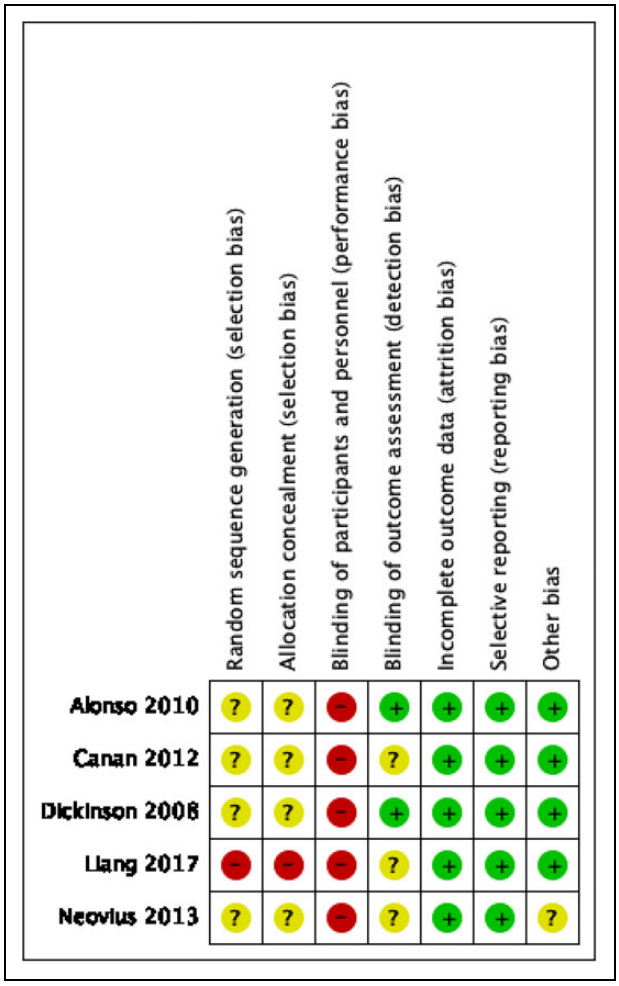

Figure 2. Assessment of risk of bias in the included studies.

6 months. One article was not included because the age of patients was higher than that of the other included articles, and as a result, preoperative cleft volume was greater than those in the rest of the articles (Dickinson et al., 2008). Another article was also not included due to a lack of data; the author was contacted, but it was not possible to obtain all of the data (Liang et al., 2017). In alveolar cleft bone formation analysis, 3 studies were compared. Greater bone formation was observed in the rhBMP-2 group compared to the iliac crest treatment group (MD: −208.76; 95% CI: −253.59 to −163.93; $I^2 = 0\%$; Figure 3). No meta-analysis of the bone height result could be conducted, since not all data were available.

The quality of evidence of the 3 articles included in the meta-analysis was evaluated according to the GRADE criteria. These articles were randomized clinical trials; therefore, they were classified as high-quality evidence. However, methodological issues limited the quality of evidence. The risk of bias was evaluated as serious, downgrading the evidence by one level, since the articles had a high risk of bias associated with selection, performance, and detection. Inconsistency was considered not serious, since clinical and methodological variation was low. Indirectness of results was also considered not serious, since evidence included in the review appropriately answers the question in terms of population, intervention, comparison, and results studied. Imprecision was rated as serious, downgrading the evidence by 1 level because the included studies had a small number of patients. The difference in results between the experimental and the control groups is small, and as a result, the number of patients included in the studies should have been higher. Publication bias was rated as not serious. Finally, the level of evidence was rated as low, in other words, rhBMP-2 may improve bone regeneration in the alveolar cleft (Figure 4).

Although the meta-analysis showed greater bone formation in the group treated with rhBMP-2, these results must be interpreted with caution, since the articles contain low-quality evidence.

Discussion

This review is the first to perform a risk of bias assessment to develop a meta-analysis and evaluation of the quality of evidence from clinical trials that used rhBMP-2 in alveolar cleft reconstruction at the time when the search was done. It is crucial to evaluate the risk of bias, since the presence of selection, performance, detection, attrition, and/or reporting biases may lead to an over- or underestimation of rhBMP-2 effect in alveolar cleft and may engender misleading conclusions as well

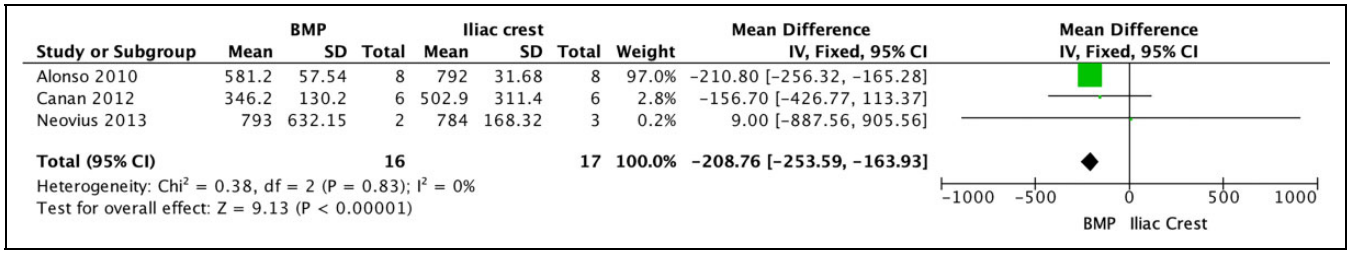

Figure 3. Forest plot of pooled mean bone filling in alveolar cleft (mm^3).

RhBMP-2 compared to iliac crest for bone regeneration in alveolar cleft

Patient or population: Alveolar cleft in unilateral cleft lip and palate patients.
Setting: Cleft lip and palate centers in hospitals or universities.
Intervention: rhBMP-2
Comparison: iliac crest

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with iliac crest	Risk difference with rhBMP-2
Bone filling (mm3) assessed with: CBCT follow up: mean 6 months	33 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	-	The mean bone filling (mm3) was **692,97** mm3	MD **208.76 mm3 lower** (253.59 lower to 163.93 lower)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. We downgraded the evidence by one level because of risk of bias. The studies lack of blinding of participants and personnel who was performing the surgery. The blinding of outcome assessment was performed in one study.
b. We downgraded the evidence by one level because of imprecision. The studies include a low number of patients. The difference between the outcomes is low, the number of patients should be higher.

Figure 4. GRADE Quality Evidence. GRADE indicates grading of recommendations assessment, development and evaluation; rhBMP-2, recombinant human bone morphogenetic protein-2.

as influence the quality of evidence. In our search, 4 systematic reviews were found. In 2011, Cochrane (Guo et al., 2011) carried out a review of secondary alveolar bone grafts in cleft patients, and only 2 articles were selected (Segura-Castillo et al., 2005; Dickinson et al., 2008). Both the studies were small, with 21 and 27 patients, and both were classified with a high risk of bias. Another author performed a systematic review evaluating whether tissue engineering can replace

autologous grafts (Van Hout et al., 2011). Three articles were selected comparing iliac crest grafts with rhBMP-2 using a small number of patients (16, 21, and 12 patients). No evaluation of risk of bias was carried out. More favorable results were observed using rhBMP-2; however, the authors recommend to perform more studies to obtain more accurate results. In 2014, a systematic review of tissue engineering strategies in the reconstruction of alveolar clefts was carried out. Sixteen articles were selected, which had great diversity in terms of data acquisition, cleft size, images acquired, and follow-up times. There was no evaluation of the risk of bias (Janssen et al., 2014). Another systematic review of regenerative medicine in the treatment of alveolar clefts was done in 2015, where all of the included articles had a high risk of bias (Khojasteh et al., 2015).

In none of the systematic reviews was it possible to perform a meta-analysis of the results nor was the evidence quality evaluated. The latter is key since although the results of primary studies may indicate a result if the quality of evidence is low or very low, it is not a reliable result (Ryan and Hill, 2016).

The age at which alveolar cleft treatment is performed is crucial, and the best results are obtained before the eruption of permanent canines between 8 and 12 years (Eppley and Sadove, 2000; Hogan et al., 2003; Macisaac et al., 2012); during permanent dentition, the results are less predictable (Collins et al., 1998; Horswell and Henderson, 2003). The age of patients in primary articles averages 11.43 $\pm$ 2.81; however, when the article that includes adult patients is eliminated (Dickinson et al., 2008), the average age decreases to 10.25 $\pm$ 1.12 years, suggesting that our results are representative of the best age for the execution of this surgery.

As it relates to the volume of the included alveolar clefts, these were highly diverse with the preoperative defect volume average of 1.811.64 $\pm$ 1.920.14 mm^3; however, once again excluding the article that includes adult patients (Dickinson et al., 2008), the average decreases to 927.06 $\pm$ 501.08 mm^3. Alveolar clefts with greater volume, as in adult patients, may have less bone regeneration, since the irrigation in the central part of the graft is reduced compared to a smaller cleft. None of the studies define what a critical size defect is for reconstruction with rhBMP. It is interesting to discuss the effect of the volume of the critical size defect in the bone formation with rhBMP or iliac crest. The MD between the groups, from Dickinson's study, was in favor of the iliac crest bone graft (MD: 2100.00 [1865.29-2334.71]). According to this analysis, in wide clefts, it would be more appropriate to use iliac crest bone graft than rhBMP. This statement should be interpreted with caution, since it is only one article with a limited number of patients.

Regarding cleft type, only unilateral alveolar clefts were included. Reconstruction behavior of unilateral and bilateral clefts may be different, since they have differences in its stability and irrigation. As a result, although reconstruction of bilateral patients is carried out in 2 surgical sessions, local conditions are different. The graft resorption is low in unilateral patients, since 70% of the graft remains, but in bilateral patients, only 45% of the graft remains (Van der Meij et al., 2001).

The osteoinductive function of rhBMP depends directly on dosage. Low doses generate cartilage and a lesser amount of bone tissue; however, higher concentrations generate a greater amount of bone and may arise from membranous ossification (Li and Woozney, 2001; Davies and Ochs, 2010; Carreira, et al., 2014). As a result, the concentration of rhBMP at the graft site is more important than the total dose administered (Boyne et al., 2005; Davies and Ochs, 2010). The range of doses used is very broad (250 μg/mL to 4.2 mg), since the article that used hydrogel uses a very small dose of rhBMP-2 because one of the objectives of using this scaffold is precisely to reduce the dosage (Gentile et al., 2014). If we do not take this article into consideration, the doses used was 1.5 to 4.2 mg of rhBMP-2. None of the studies specify the dose–response curve in relation to the cleft volume or the size of the absorbable collagen sponge used.

The rhBMP scaffold is crucial, since the concentration of rhBMP available for osteoinduction depends on it (Li and Woozney, 2001). RhBMP-2 is lost due to diffusion, irrigation, or suction; therefore, it is necessary to contain the rhBMP-2 in a scaffold holding so that it can act on the surgical site (Rengachary, 2002). An ideal scaffold must be biocompatible, biodegradable, stable in sterilization processes, resistant to stress, compression, and easy to handle (Rezvani et al., 2016). Absorbable collagen sponge is the most used scaffold; however, it has the main disadvantage of low mechanical resistance (Gentile et al., 2014; Mostafa et al., 2015).

Follow-up in primary articles was performed between 6 and 21 months, which may also create some doubts. Evaluation of bone formation is recommended between 4 and 6 months, a time period when integrated bone implant installation must be carried out, since at the 21-month follow-up, the neoformed bone tissue is remodeled and reabsorbed if it is not underfunctioning.

In the same way, the ideal imaging method is cone beam computed tomography as it is more objective and reproducible than the use of conventional X-rays (Shirota et al., 2010; de Moura et al., 2016). In all included studies, bone volume evaluation was performed in the same way. All studies reported a bone formation volume that was the same or higher in the experimental group compared to the control group.

Conclusion

Available evidence regarding the use of rhBMP-2 as an alternative treatment in the reconstruction of the alveolar cleft in humans, in terms of volume and bone height, is limited. Although results obtained in primary articles are promising, it must be understood that these have a high risk of bias and low-quality evidence. Therefore, it is necessary to carry out controlled clinical trials with a greater number of patients with 3D imaging measurements of bone formation at 6, 12, and 18 months in order to be able to recommend or not recommend the use of rhBMP-2 in the treatment of alveolar clefts. Also, it would be interesting to perform a subgroup analysis according to the cleft volume.

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Supplemental Material

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