

Reconstruction of the alveolar cleft: can growth factor-aided tissue engineering replace autologous bone grafting? A literature review and systematic review of results obtained with bone morphogenetic protein-2

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Abstract The alveolar cleft in patients with clefts of lip, alveolus and palate (CLAP) is usually reconstructed with an autologous bone graft. Harvesting of autologous bone grafts is associated with more or less donor site morbidity. Donor site morbidity could be eliminated if bone is fabricated by growth factor-aided tissue engineering. The objective of this review was to provide an oversight on the current state of the art in growth factor-aided tissue engineering with regard to reconstruction of the alveolar cleft in CLAP. Medline, Embase and Central databases were searched for articles on bone morphogenetic protein 2 (BMP-2), bone morphogenetic protein 7, transforming growth factor beta, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, vascular endothelial growth factor and platelet-rich plasma for the reconstruction of the alveolar cleft in CLAP. Two-hundred ninety-one unique search results were found. Three articles met our selection criteria. These three selected articles compared BMP-2-aided bone tissue engineering with iliac crest bone grafting by clinical and radiographic examinations. Bone quantity appeared comparable between the two methods in patients treated during the stage of mixed dentition, whereas

bone quantity appeared superior in the BMP-2 group in skeletally mature patients. Favourable results with BMP-2-aided bone tissue engineering have been reported for the reconstruction of the alveolar cleft in CLAP. More studies are necessary to assess the quality of bone. Advantages are shortening of the operation time, absence of donor site morbidity, shorter hospital stay and reduction of overall cost.

Keywords Growth factor · Clefts of lip, alveolus and palate · Bone morphogenetic protein 2 · Bone graft

Background

The incidence of clefts of lip, alveolus and palate (CLAP) varies between races [1]. Mongolians are affected, with incidence of 0.55–2.50 per 1,000 births; Caucasians, 0.69–2.35 per 1,000 births and Negroids, 0.18–0.82 per 1,000 births [1]. Males are more often affected than females [2]. A cleft of the alveolus is present in more than 50% of the cases with CLAP [3].

CLAP is caused by incomplete fusion of the facial prominences during the fourth to tenth week of gestation. Failure of the maxillary prominences to fuse with the intermaxillary prominence results in a cleft of the primary palate. Failure of fusion of the two palatine shelves of the maxillary prominences produces a cleft of the secondary palate. Clefts of the primary palate result in a cleft lip or in a cleft lip and alveolus, clefts of the secondary palate result in a cleft of the palate, and clefts of the primary plus secondary palate result in a cleft of the lip, alveolus and palate or a cleft of the lip and palate [4].

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The aim of reconstruction of the alveolar cleft is to provide continuity and stabilization of the maxillary arch, to close the oronasal fistula, to permit tooth eruption, to provide support of the alar base and to improve nasal symmetry [5]. The alveolar cleft is usually reconstructed in the stage of mixed dentition between 7 and 11 years. Autologous bone graft has been the gold standard of bone replacement for many years because it provides osteogenic cells as well as essential osteoinductive factors needed for bone healing and regeneration. It can be taken from the patient's iliac crest, mandibular symphysis, rib, tibia and calvarium, with each donor site having its specific advantages and disadvantages [6]. Regardless of the site of bone graft harvest, however, there is always more or less donor site morbidity such as postoperative pain, altered sensation, donor site infection and scarring [6, 7]. Growth factor-aided tissue engineering for the reconstruction of the alveolar cleft may eliminate a second surgical site for the harvest of autologous bone and would thus eliminate donor site morbidity [8].

Tissue engineering

The three vital components necessary for the engineering of bone are bone-forming cells, osteoinductive growth hormone and an osteoconductive scaffold. The osteoconductive scaffold provides immediate mechanical support, mimics the bony extracellular matrix and guides the formation of bone in the desired shape and place. The scaffold should be biocompatible and biodegradable. The rate of degradation is ideally inversely proportional to the rate of bone formation. Several synthetic and organic polymers and also ceramics have been proposed as materials to produce scaffolds [9, 10].

The scaffold may also serve as a carrier for the osteoinductive growth hormone. The growth hormone is thus delivered locally and ideally over a sustained period of time. The main role of the growth hormone is to recruit mesenchymal stem cells to the area and make them differentiate into an osteogenic cell lineage [9–11].

Growth factors

Many growth factors are involved in osteogenesis. Bone morphogenetic proteins (BMP-2 and BMP-7), transforming growth factor beta (TGF- β), insulin-like growth factors I and II (IGF I and II), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) have been proposed for use in bone tissue engineering [9, 12, 13].

Bone morphogenetic proteins (BMPs) are a group of proteins known to play a role in osteogenesis and chondro-

genesis. BMPs are also involved in embryonic development and fracture healing. Especially BMP-2 and BMP-7 are known for their osteoinductive qualities [9, 11–13]. TGF- β plays a role in osteogenesis, its actions are diverse and TGF- β is thought to influence the activity of BMPs [9, 12, 13]. IGFs I and II are present in fracture healing sites. IGFs I and II both stimulate type-1 collagen synthesis and decrease collagenase synthesis [9, 12, 13]. PDGF recruits mesenchymal stem cells and promotes angiogenesis [9, 13]. FGF plays a role in maintaining the balance between bone-forming cells and bone-resorbing cells and promotes angiogenesis [9, 12]. VEGF plays a role in angiogenesis, promotes vasodilatation and increases microvascular permeability [9, 12].

Platelet-rich plasma (PRP) contains a wide diversity of growth factors, and therefore, PRP is thought to stimulate bone formation. Growth factors known to be present in PRP are TGF- β , PDGF, IGF, FGF, VEGF, endothelial cell growth factor and epidermal growth factor [14].

Clinical application of growth factors

PRP has been applied for reconstruction of the maxillofacial skeleton with contradictory results [14, 15].

Recombinant human PDGF (rhPDGF) has been approved by the Food and Drug Administration for the repair of periodontal defects. RhPDGF has been studied in combination with β -tricalcium phosphate and in combination with IGF in a gel delivery system for the repair of periodontal defects [16–18].

Recombinant human BMP-2 (rhBMP-2) in combination with a collagen sponge carrier made out of type 1 bovine collagen has been approved by the Food and Drug Administration and is used for specific clinical situations, i.e. interbody spinal fusion, open tibial fractures, sinus augmentation and alveolar ridge augmentation after dental extraction [19, 20].

Recombinant human BMP-7 (rhBMP-7) is used in non-union of long bone fractures and spinal fusion and has been approved by the Food and Drug Administration for these indications. A study has been performed with rhBMP-7 for sinus floor elevation [20, 21].

Literature review

Search

An electronic search was conducted on MEDLINE, EMBASE and CENTRAL databases through PubMed, Embase and Cochrane. The search strategy was aiming towards sensitivity rather than precision. The search

command on each database consisted of two factors: the domain, cleft alveolus, and the determinant, the growth factor, both to be found in title and/or abstract. Searches were conducted for BMP-2, BMP-7, TGF- β , PDGF, IGF, FGF, VEGF and PRP. For each growth factor, synonyms and spelling variants were taken into account.

Method

The search results were checked for doubles. Then, the unique search results were checked against our inclusion and exclusion criteria on basis of title and/or abstract screening. Articles that met the selection criteria on basis of title and/or abstract screening were double checked against the selection criteria by means of full text analysis.

Included were clinical trials and retrospective studies describing the method of reconstruction of the alveolar cleft with growth factor-aided bone tissue engineering in CLAP patients. The exclusion criteria were: use of autologous bone graft, including bone marrow aspirate; previous attempt to reconstruct the alveolar cleft; absence of radiographic quantification of bone in the reconstructed cleft; language of the full text article other than English.

Search results

The search yielded 41 results for BMP-2, 12 results for BMP-7, 73 results for TGF- β , 25 results for PDGF, 32 results for IGF, 96 results for FGF, 21 results for VEGF and 21 results for PRP. After checking for doubles, 34 unique results were left for BMP-2, 10 for BMP-7, 71 for TGF- β , 22 for PDGF, 31 for IGF, 86 for FGF, 19 for VEGF and 18 for PRP.

Title and/or abstract screening

Six studies on BMP-2 and seven studies on PRP met the inclusion criteria. One of these BMP-2 studies was excluded because the full text article was only available in Chinese. Six of the PRP studies were excluded because an autologous bone graft was used in combination with PRP. Five BMP-2 studies and one PRP study were admitted for full text analysis. The results of the title and/or abstract screening are displayed in Table 1.

Full text analysis

Three articles were excluded on basis of the full text screening. The article by Chin et al. [22] on BMP-2 was excluded because besides CLAP, facial clefts were reconstructed and because of absence of radiographic quantification of bone in the reconstructed cleft. The article by Fallucco et al. [23] on BMP-2 was excluded because of

Table 1 The search results and result of title and abstract screening

Search	Unique results	Met inclusion criteria	Excluded	For full text analysis
BMP-2	34	6	1	5
BMP-7	10	0	0	0
TGF- β	71	0	0	0
PDGF	22	0	0	0
IGF	31	0	0	0
FGF	86	0	0	0
VEGF	19	0	0	0
PRP	18	7	6	1

absence of radiographic quantification of bone in the reconstructed cleft. The article by Hibi et al. [24] on PRP was excluded because bone marrow aspirate was used.

Finally, three articles were accepted for the review (Table 2). These three articles were on the reconstruction of the alveolar cleft with the use of BMP-2 in the experimental group and with autologous bone graft in the control group.

In all three articles, unilateral clefts only were included. Prior alveolar surgery was an exclusion criterion for patients in Alonso et al. [25] and Dickinson et al. [26]. No mention of prior alveolar surgery was made by Herford et al. [27].

In the three studies, the kit of Infuse[®] Bone Graft (Medtronic, Sofamor Danek, Memphis, TN) was used. This kit contains an absorbable sponge consisting of type 1 bovine collagen and is impregnated with rhBMP-2. In the three studies, reconstruction of the alveolar cleft in the control group was performed with autologous cancellous bone of the iliac crest.

Mean alveolar cleft size prior to surgery was 0.975 cm³ in the BMP-2 group versus 1.052 cm³ in the control group in Alonso et al. [25], 5.6 cm³ versus 5.1 cm³ in Dickinson et al. [26] and 10.55 cm³ versus 17.86 cm³ in Herford et al. [27].

In the studies by Alonso et al. [25] and Dickinson et al. [26], all patients received preoperative orthodontic expansion of the maxillary segments. No mention of preoperative treatment was made by Herford et al. [27].

Timing of the reconstruction of the alveolar cleft varied between the three studies; Alonso et al. [25] and Herford et al. [27] reconstructed the alveolar clefts during the stage of mixed dentition, whereas Dickinson et al. [26] reconstructed the clefts in skeletally mature patients.

Computed tomography (CT) was used to evaluate bone formation and to measure the quantity of bone formation: Alonso et al. [25] performed a CT at 6 and at 12 months postoperatively, Dickinson et al. [26] performed a CT at 6 months postoperatively and Herford et al. [27] performed a CT at 4 months postoperatively. Dickinson et al. [26]

Table 2 The selected articles

Authors	Title	Published in	Year
Alonso et al. [25]	Evaluation of maxillary alveolar reconstruction using a resorbable collagen sponge with recombinant human bone morphogenetic protein 2 in cleft lip and palate patients	Tissue Eng Part C Methods	2010
Dickinson et al. [26]	Reduced morbidity and improved healing with bone morphogenetic protein-2 in older patients with alveolar cleft defects	Plast Reconstr Surg	2008
Herford et al. [27]	Bone morphogenetic protein-induced repair of the premaxillary cleft	J Oral Maxillofac Surg	2007

assessed the quantity of bone formation also on an Orthopantomogram and on periapical films.

Length of follow-up differed between the three studies. Herford et al. [27] reviewed the patients after 4 months, whereas Alonso et al. [25] and Dickinson et al. [26] reviewed the patients after 1 year. Alonso et al. [25] and Dickinson et al. [26] assessed the morbidity of the surgical procedures during the first year, whereas Herford et al. [27] did not mention postoperative morbidity, nor complications.

The studies by Alonso et al. [25] and Dickinson et al. [26] are randomised controlled trials, whilst the study by Herford et al. [27] is a controlled retrospective review; hence, the level of evidence is lower for Herford et al. [27]. Table 3 shows a summary of the study design of the three articles.

Results

Success of the reconstruction of the alveolar cleft is determined by the amount of bone formation in the cleft, bone height of the alveolar ridge and the position of the bone in the cleft. Bone in the supra-apical area supports the alar base. Bone in the alveolar area provides continuity to the alveolar ridge and gives support to the teeth adjacent to and in the cleft. Secondly, bone quality and functionality are of importance. Parameters for bone quality and

functionality are successful eruption of teeth in the reconstructed cleft, periodontal status of teeth adjacent to and in the reconstructed cleft, successful orthodontic movement of teeth into the reconstructed cleft and successful osseointegration of dental implants in the reconstructed cleft. Complications and adverse events should also be taken into account.

Bone quantity

Dickinson et al. [26] reported more bone formation in the cleft in the rhBMP-2 group (95%) compared to the control group (63%). Alonso et al. [25] and Herford et al. [27] reported slightly less bone formation in the cleft in the rhBMP-2 group compared to the control group, although the differences (5.8% and 7%) seem not significant. Alonso et al. [25] further measured more bone after 12 months compared to after 6 months. In the study by Herford et al. [27], two patients in the rhBMP-2 group showed significantly less bone formation in the cleft than the other patients; the authors explain this by possible wound breakdown of the nasal mucosal layer.

Bone height was measured by Alonso et al. [25] and by Dickinson et al. [26]. Alonso et al. [25] reported lower bone height in the rhBMP-2 group (10.2 mm) than in the control group (13.9 mm), whereas Dickinson et al. [26] reported

Table 3 Analysis of selected articles

	Alonso et al. [25]	Dickinson et al. [26]	Herford et al. [27]
Total number of patients	16	21	12
rhBMP-2 group	8	9	10
Type of alveolar cleft	Unilateral only	Unilateral only	Unilateral only
Timing of intervention	Mixed dentition	Skeletally mature	Mixed dentition
Carrier used for rhBMP-2	Absorbable collagen sponge	Absorbable collagen sponge	Absorbable collagen sponge
Control group graft	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone	Particulate iliac crest cancellous bone
Method for measuring outcome	CT, coronal CT slices	CT ^a , 3D CT reconstructions ^a , OPG, periapical films	CT
Follow-up	12 months	12 months	4 months
Type of study	Randomised controlled trial	Randomised controlled trial	Retrospective controlled review

^a Although follow-up was 12 months, CT scans were performed at 6 months postoperatively by Dickinson et al. [26]

Table 4 Bone quantity results

		Alonso et al. [25] ^a	Dickinson et al. [26]	Herford et al. [27]
Bone volume	rhBMP2 group	74.4%	95%	71.1%
	Control group	80.2%	63%	78.1%
Bone height	rhBMP2 group	10.2 mm (non-cleft side, 15.7 mm)	85% (vs. roots of adjacent teeth) ^b	
	Control group	13.9 mm (non-cleft side, 16.1 mm)	70% (vs. roots of adjacent teeth) ^b	

^a Results given for Alonso et al. [25] are those of the CT scans performed at 12 months postoperatively

^b Dickinson et al. [26] presented bone height on a scale from 0–4, 0 representing 0%; one, 25%; two, 50%; three, 75% and four, 100% bone height; the average score on this scale in the article was converted to a percentage for this table

higher bone height in the rhBMP-2 group (85%) than in the control group (70%).

The position of the bone in the cleft was described by Alonso et al. [25]; in the rhBMP-2 group, most bone was deposited in the supra-apical area of the cleft, whereas in the control group, most bone was seen in the alveolar area.

The reported bone formation and bone height in the cleft are displayed in Table 4.

Bone quality

Alonso et al. [25] reported that tooth eruption occurred without complications in both the rhBMP-2 group and the control group. Dickinson et al. [26] inserted dental implants in 2 out of 9 patients in the rhBMP-2 group and in 1 out of 12 patients in the control group. These implants all showed successful osseointegration. Other information on bone quality, i.e. orthodontic movement of teeth into the cleft area or periodontal status, was not provided.

Complications and adverse events

Alonso et al. [25] observed local postoperative swelling in 37.5% of the patients in the rhBMP-2 group and significant donor site pain in 87.5% of the patients in the control group. Dickinson et al. [26] reported that the control group showed significant donor site pain, more wound healing problems, longer hospital stay and greater overall cost of the procedure (Table 5).

Table 5 Complications and adverse events

	Alonso et al. [25]	Dickinson et al. [26]	Herford et al. [27]
rhBMP-2 group	37.5% local postoperative swelling	1 patient, prolonged healing	Postoperative swelling 2 patients with less than 25% bone formation
Control group	87.5% donor site pain	5 patients, partial loss of graft 1 patient, near complete loss of graft 3 patients, persistent oronasal fistula at 6 weeks postoperative donor site pain	

Discussion

The main advantage of growth factor-aided tissue engineering is the avoidance of a second surgical site needed for the harvest of autologous bone. This results in shortening of the operation time, absence of donor site morbidity, shorter hospital stay and reduction of overall cost.

Promising results with growth factor-aided tissue engineering techniques have been obtained in several fields. However, for the reconstruction of the alveolar cleft in CLAP, only three studies were found that assessed growth factor-aided bone tissue engineering techniques and met our selection criteria. We found no studies on BMP-7, TGF-β, PDGF, IGF, FGF, VEGF or PRP that met our selection criteria. The three studies that met our selection criteria all assessed BMP-2-aided bone tissue engineering. These three studies used the same bone tissue engineering kit (Infuse® Bone Graft) for the reconstruction of clefts in the experimental group and autologous cancellous bone of the iliac crest in the control group. It is remarkable that only studies with BMP-2 were published and that these studies all used the same product produced by the same company. The similarities with regard to study design and the growth factor used make comparison of the studies feasible. On the other hand, the patient numbers in the three studies are small, and there was some variation in the timing of the procedure: in two studies, the alveolar clefts were reconstructed during the stage of mixed dentition [25, 27], whereas in the other study, clefts were reconstructed in skeletally mature patients [26]. The volume of the alveolar

cleft prior to surgery also varied between the three studies, namely Herford et al. [27] reported a much greater volume of the preoperative cleft. This may be explained by the use of preoperative orthodontic expansion of the maxillary segments by Alonso et al. [25] and Dickinson et al. [26]. As to the difference in volume of the cleft between Alonso et al. [25] and Dickinson et al. [26], the different timing of the procedure should again be taken into account. Nevertheless, the results clearly indicate that rhBMP-2 delivered in an absorbable collagen sponge carrier can create a bony bridge in alveolar cleft patients with sufficient volumes of bone, comparable with the amount achieved in iliac crest cancellous bone grafting. An interesting finding by Alonso et al. [25] was the progressive formation of alveolar bone: there appeared to be more bone after 12 months compared to after 6 months in the BMP-2 group. This finding may indicate that evaluation after 4 months, as in the study by Herford et al. [27], is perhaps too quick to assess the final result of the treatment. If this is true, evaluation at a later stage may show more favourable results.

A specifically interesting subset of patients are skeletally mature patients as these patients showed better results in the BMP-2 group in terms of bone quantity, less complications and less adverse events compared to patients who received cancellous bone of the iliac crest [26]. Inferior outcome in patients treated with bone grafting after the stage of mixed dentition, i.e. after the eruption of the permanent canines, has been reported previously [28–30]. Perhaps, this subset of patients can benefit even more from the application of BMP-2.

It is thought that osteogenesis is a complex process that requires certain combinations of growth factors on specific moments during bone formation. Therefore, it was surprising that the use of just one growth factor in combination with an osteoconductive scaffold led to bone formation. A possible explanation is that BMP-2 stands at or near the top of a cascade of growth factors needed for bone formation and that through biological feedback mechanisms, the right combination of growth factors is attained.

The alveolar bone is a unique bone structure. Besides providing mechanical strength to skeletal system and support for the surrounding soft tissues, the alveolar bone also gives support to teeth and allows tooth eruption, orthodontic movement of teeth into the reconstructed cleft, and, if indicated, osseointegration of dental implants. Unfortunately, quality of bone formation in this respect was not assessed in any of the three studies. Future studies are required to address these issues.

Conclusion

The three studies that met our selection criteria all assessed BMP-2-aided bone tissue engineering. We found no studies

on BMP-7, TGF- β , PDGF, IGF, FGF, VEGF or PRP that met our selection criteria.

The application of BMP-2 on an absorbable sponge consisting of type 1 bovine collagen for the reconstruction of the alveolar cleft in CLAP is a very promising technique. Favourable results with BMP-2 have been obtained in terms of quantity of bone formation. The application of BMP-2 results in shortening of the operation time, absence of donor site morbidity, shorter hospital stay and reduction of overall cost.

Recommendation

Larger and well-designed randomised controlled trials are needed to compare the results from BMP-2-aided bone tissue engineering with the results of autologous bone grafts in alveolar bone grafting. In these trials, bone formation should be assessed during at least 12 months. For the assessment of quantity of bone formation, height of bone and location of bone in the cleft defect should be specified. For the assessment of quality of bone, tooth eruption should be evaluated as well as periodontal status of teeth adjacent to and in the former cleft area, success of orthodontic movement of teeth into the former cleft area and osseointegration of dental implants.

Conflicts of interest The authors declare that they have no conflict of interest. We have no financial relationship with the manufacturer of the Infuse[®] Bone Graft or with companies otherwise involved with this product. We have not contacted any company with regard to this article.

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