



Three-Dimensional Changes of Maxilla after Secondary Alveolar Cleft Repair: Differences Between rhBMP-2 and Autologous Iliac Crest Bone Grafting

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Background: Recombinant human bone morphogenetic protein (rhBMP)-2 has been used as an alternative to autologous bone transferring, a standard method of treatment. However, its potential adverse effect on anterior maxillary arch is unknown. Thus, the purpose of this study was to quantify sagittal and transversal changes of anterior maxilla after secondary alveolar cleft repair using traditional iliac crest bone grafting versus rhBMP-2.

Methods: Twelve unilateral complete cleft lip and palate patients were randomly divided into 2 groups. In group 1, patients underwent traditional iliac crest bone grafting transferring ($n = 4$), and in group 2, patients underwent alveolar cleft reconstruction using collagen matrix with lyophilized rhBMP-2 ($n = 8$). Computed tomography (CT) imaging was performed preoperatively and at 1 year postoperatively, using a previously standardized protocol. A three-dimensional (3D) CT cephalometric analysis of the linear and angular measurements of the sagittal and transverse maxilla planes was performed to assess intra- and intergroup maxillary changes.

Results: Intra- and intergroup comparisons of the pre- and postoperative 3D CT cephalometric linear and angular measurements of the sagittal and transverse maxilla planes showed no significant (all $P > 0.05$) differences among all studied variables.

Conclusions: There were no significant anterior maxilla changes after maxillary cleft repair either using iliac crest bone grafting or rhBMP-2. (*Plast Reconstr Surg Glob Open* 2015;3:e451; doi: 10.1097/GOX.0000000000000417; Published online 14 July 2015.)

Autologous bone grafting has been considered the standard method for reconstruction of cleft maxillary alveolus.¹ Secondary alveolar

cleft repair with autologous bone grafting promotes reestablishment of dental arch continuity, stabilization of maxillary complex, and prevention of maxillary arch collapse after presurgical orthopedic maxilla expansion.¹ However, donor-site morbidity remains a drawback¹ that has driven development of new strategies, such as recombinant human bone morphogenetic protein (rhBMP)-2 based therapy.²⁻¹² Maxillary alveolar repair with rhBMP-2 in cleft patients immediately before cuspid or lateral incisor root descend seems to be a promising therapy, allowing tooth eruption and orthodontic movement,

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and showing the same overall success rate when compared with traditional iliac crest bone grafting.²⁻¹¹ However, there is still resistance for its widespread use, probably because of a lack of data regarding objective analyses of potential complications, including possible harmful effects of rhBMP-2-based therapy in the anterior maxilla.

In the literature, surgical induced scars by cleft lip and palate repair have been designated as responsible for negative effects on maxillofacial morphology.¹³⁻¹⁵ As previous¹⁶⁻³¹ investigations showed aberrant healing events including intense inflammatory reaction, seroma formation, and pronounced swelling after different surgical repairs with rhBMP-2, we hypothesized that maxillary cleft repair with rhBMP-2 can impose anterior maxillary displacements because of significant inflammatory reaction and scar formation when compared with the traditional autologous alveolar cleft repair.

Thus, the purpose of this study was to quantify three-dimensional (3D) sagittal and transversal changes of anterior maxilla of unilateral complete cleft lip and palate patients who underwent secondary alveolar cleft repair using traditional iliac crest bone grafting versus rhBMP-2.

METHODS

A retrospective study of 18 consecutive nonsyndromic unilateral complete cleft lip and palate patients, who underwent alveolar cleft repair between 9 and 12 years of age, was conducted at a single Brazilian Craniofacial Surgery Unit between 2010 and 2012. The collection of these data started in 2010, resulting in previous publications.^{2,9}

All patients previously underwent a primary rhinocheiloplasty³² between 3 and 6 months of age and underwent palate repair at 1 year of age. Before secondary alveolar cleft repair, all subjects underwent preoperative orthodontic expansion of maxillary segments and had symmetrical arch forms and were randomly assigned to group 1 (traditional iliac crest bone grafting transferring) or group 2 (repair using collagen matrix with lyophilized rhBMP-2). No revision of lip was performed during secondary alveolar cleft repair. Only patients ($n = 6$) who did not have adequate computed tomographic (CT) documentation, previous eruption of the canine, former alveolar surgeries, and/or incomplete follow-up were excluded from the study. Additionally, complications, such as pronounced swelling, infections, and wound dehiscence leading to bone graft loss or rhBMP-2 exposure were recorded.

All subjects were enrolled upon a consent form signed by their parents, in accordance with the Helsinki Declaration of 1975, as amended in 1983. A local institutional research ethics board approval was obtained for this study.

Surgical Procedures

The same senior surgeon (N.A.) performed all surgical interventions in a standard fashion. Key information included below, and additional details were previously described by our group.^{2,3}

Iliac crest bone graft (group 1) and collagen matrix with lyophilized rhBMP-2 (group 2) were placed in the maxillary alveolar defect, after wide exposure of the cleft area. In group 1, through a 3-cm incision, a cortical bone trap door was raised and hinged on the inner edge of the iliac crest, and sufficient chips of cancellous bone (20–40 mL) were then removed. In group 2, rhBMP-2 was reconstituted with distilled water and impregnated the supplied absorbable collagen sponge (Infuse Bone Graft kit; Medtronic, Memphis, Tenn.) for 20 minutes according to the manufacturer's guidelines. The rhBMP-2 impregnated collagen matrix was then cut into several small parts that were used to fill in the alveolar cleft defect as necessary; approximately 3.2–4.2 mg of rhBMP-2 was used. Finally, a lateral mucoperiosteal flap was advanced to cover the cleft and then sutured to the medial flap and palatal flaps.

Skeletal Landmarks and Linear and Angular Measurements

Three bilateral and 6 median bony landmarks and 3 craniofacial planes were defined according to previously published data^{33,34}: *a point/subspinale* (A), the most posterior point on the anterior contour of the upper alveolar process; *anterior nasal spine* (ANS), the apex of the anterior nasal spine; *B point/supramentale* (B), the most posterior point on the anterior contour of the lower alveolar process; *nasion* (N), situated at the frontonasal suture; *cleft* (C) and *non-cleft* (N') *orbitale* (OrC and OrN'), the most inferior point on the inferior orbital margin; *C and N' porion* (PoC and PoN'), the most superior point on the external auditory meatus; *pogonion* (Pog), the most anterior point on the mandibular symphysis; *sella* (S), the point in the center of the sella turcica; *C and N' processus zygomaticus* (ProcZC and ProcZN'), the most inferior and lateral point of the processus zygomaticus; *frankfort horizontal* (H) *plane*, both OrC and OrN' points and the PoN' point; *reference vertical* (V) *plane*, parallel to perpendicular plane to both Or points, passing through the S point; *N-Pog plane*, perpendicular plane to the sagittal plane that went through both N and Pog points (Figs. 1, 2). After de-

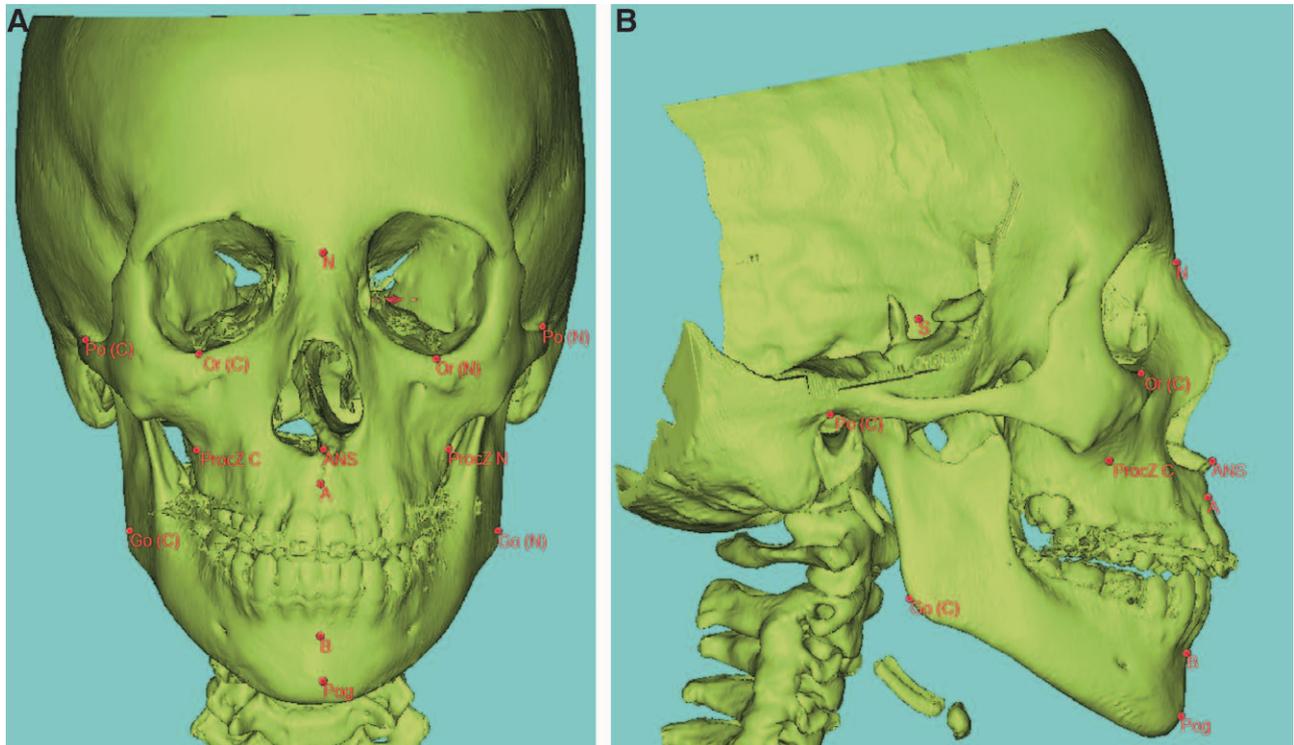


Fig. 1. Craniofacial CT imaging [frontal (A) and right lateral views (B)] of a unilateral complete cleft lip and palate patient processed by Mimics illustrating cephalometric bone anatomical landmarks adopted to quantify anterior maxillary changes (Table 1).

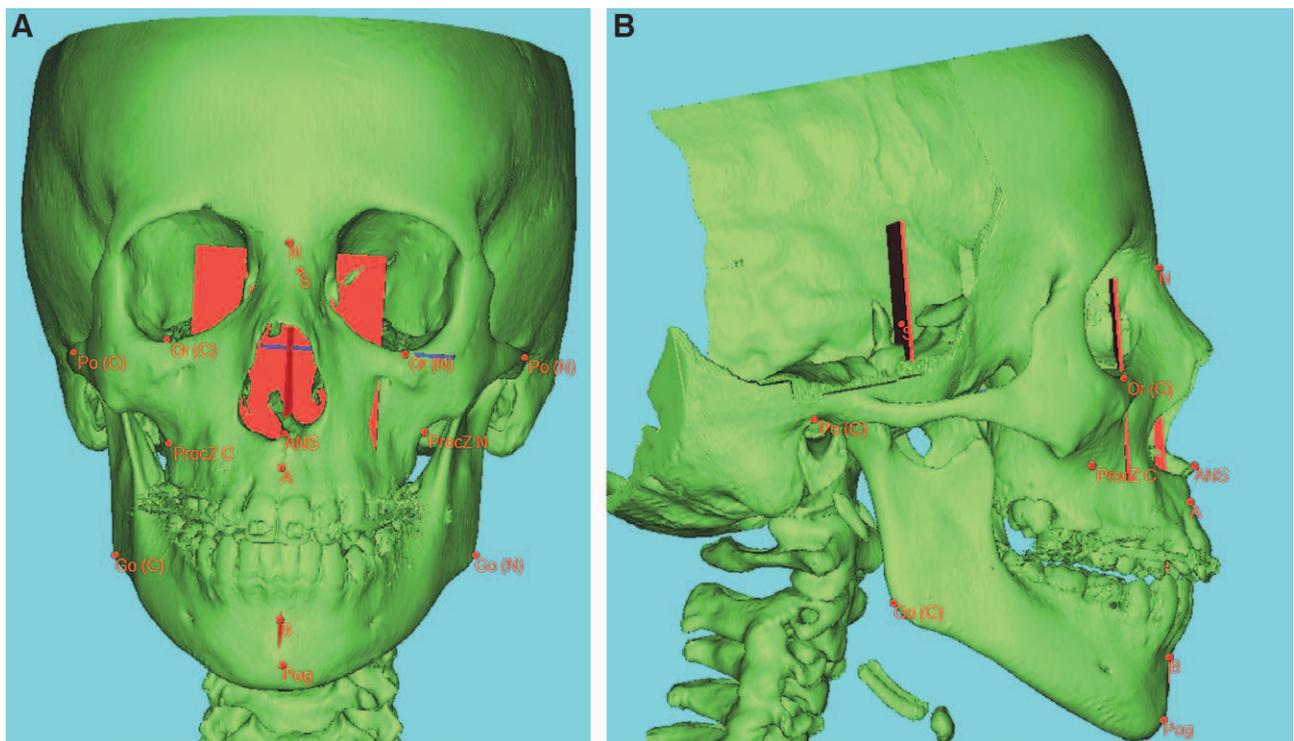


Fig. 2. Craniofacial computed tomography imaging [frontal (A) and right lateral views (B)] of a unilateral complete cleft lip and palate patient processed by Mimics illustrating cephalometric reference planes adopted to quantify anterior maxillary changes.

fining these landmarks, 11 inter-landmark measurements were calculated to show the displacements in the maxilla from both the sagittal and transversal aspects: 6 (ANS/H, N/H, N/V, A/N-Pog, ANS/V, and ProcZC/ProcZN') linear (mm) and 5 (A-N-B, S-N-A, S-N-B, ProcZC-A-ProcZN', and ProcZC-ANS-ProcZN') angular (degrees) measurements. Two ratios of bilateral linear measurements (A/ProcZC//A/ProcZN' and ANS/ProcZC//ANS/ProcZN') were also performed (Table 1).

Three-Dimensional Computed Tomography Cephalometric Analysis

Multislice CT scans of the craniofacial region were performed preoperatively (1 month to 1 week before alveolar cleft repair) and postoperatively (12 months after alveolar cleft repair) for evaluation of anterior maxilla changes. Patients' data were obtained using 1-mm cut, and images were reconstructed. All data were saved as a Digital Imaging and Communication in Medicine file and were then relabeled and randomly reordered to blind the rater.

The data were then transferred to a workstation (Windows 7; Microsoft Corporation, Redmond, Wash.) and analyzed using Mimics medical imaging software (Mimics v10.01; Materialise, Leuven, Belgium), which is a Digital Imaging and Communication in Medicine viewer program previously tested for interbony landmark measurements.³⁵⁻³⁸ Three-dimensional CT images were reconstructed by selecting the simulation module in the bone window. For all cephalometric measurements, the position of images was standardized based on the 3 cutting planes.

A 3D CT cephalometric analysis of the linear and angular measurements of the sagittal and transverse

maxilla planes was performed from frontal and lateral views by 1 investigator in a blinded fashion, who had no prior knowledge about the groups and did not participate in the realization of CT scans and alveolar cleft repair. All measurements were made in triplicate, and the mean of values was used for statistical analysis.^{33,35}

Statistical Analysis

In the descriptive analysis, data were summarized as means ± standard errors. Intragroup and intergroup (preoperative versus postoperative linear and angular measurements) comparisons were performed with the aid of the Wilcoxon, Mann-Whitney, and confidence interval for mean tests. All analyses were performed using the software program Statistical Package for Social Science (SPSS version 17.0 for Windows, Chicago, Ill.). Values were considered significant for a confidence interval of 95% ($P < 0.05$), and tailed analysis was used as a supplement in the presence of statistical difference.

RESULTS

A total of 12 (66.67%) unilateral complete cleft lip and palate patients (6 females and 6 males, with an average age of 10.24 years) met the inclusion criteria. Four (33.33%) patients underwent alveolar iliac crest bone grafting (group 1), and 8 (66.67%) patients underwent alveolar cleft repair with resorbable collagen matrix with rhBMP-2 (group 2). Six (33.33%) patients were excluded because of incomplete CT data after alveolar cleft repair. No complications were seen in these series of patients.

Intra- and intergroup comparisons of the pre- and postoperative 3D CT cephalometric analysis of

Table 1. Linear and Angular Interbony Landmark Measurements Used to Quantify Anterior Maxilla Changes from Both the Sagittal and Transversal Aspects

Measurements	Definitions
Linear items (mm)	
ANS/H	Distance from the ANS point to the H plane
N/H	Distance from the N point to the H plane
N/V	Distance from the N point to the V plane
A/N-Pog	Distance from the A point to the N-Pog plane
ANS/V	Distance from the ANS point to the V plane
ProcZC/ProcZN'	Distance from the ProcZC point to the ProcZN'
Angular items (degree)	
A-N-B	Angle between 3 points (A, N, and B)
S-N-A	Angle between 3 points (S, N, and A)
S-N-B	Angle between 3 points (S, N, and B)
ProcZC-A-ProcZN'	Angle between 3 points (ProcZC, A, and ProcZN')
ProcZC-ANS-ProcZN'	Angle between 3 points (ProcZC, ANS, and ProcZN')
Ratio items	
A/ProcZC//A/ProcZN'	Distance from the A point to the ProcZC point divided by distance from the A point to the ProcZN' point
ANS/ProcZC//ANS/ProcZN'	Distance from the ANS point to the ProcZC point divided by distance from the ANS point to the ProcZN' point

/ indicates linear distance between; - indicates connection between the ends of an angular measurement; // indicates the ratio between.

the linear and angular measurements of the sagittal and transverse maxilla planes showed no significant differences (all $P > 0.05$; Table 2).

DISCUSSION

Maxillary cleft repair with rhBMP-2 has demonstrated efficacy based on bone volume and overall costs analyses.²⁻¹¹ Although data using rhBMP-2 for reconstruction of primary alveolar cleft have shown reduction in the amount of secondary surgery by inducing native bone in the maxillary arch and cleft nasal floor and simultaneously avoiding donor site morbidity,¹⁰ we as others³⁹ believe that any primary alveolar repair either with autologous bone or any bone substitute (including rhBMP-2) may lead to a severe maxillary collapse with midfacial growth disturbance, as recently demonstrated.^{11,40} Thus, our surgical protocol avoided any gingival undermining for reconstruction of alveolar osseous defect at the time of lip or palate repair, postponing it to the age of 9–12 years. So, for this particular treatment timing, a bone substitute that can potentially present similar benefits of autologous bone without the inherent donor site morbidity is warranted.^{3,9}

Previous studies^{2,12} using rhBMP-2 at the stage of mixed dentition showed sufficient bone volume in the alveolar cleft similar to autologous bone therapy. One of the caveats of these previous data^{2,12} was the lack of assessment of potential negative local effects,

although pronounced swelling has been described.^{2,12} As in orthopedic/spine literature,⁴¹ complications and adverse effects associated with rhBMP-2-based therapy should be investigated with similar vigor rather than its efficacy. Therefore, this study was specifically designed to assess anterior maxilla changes in unilateral complete cleft lip and palate patients who underwent alveolar cleft repair using either rhBMP-2 or autologous bone grafting (criterion standard surgical option) at the time of canine eruption. Because maxillary segments in patients with complete cleft lip and palate are unstable at this age, it is possible that any therapy using rhBMP-2 can cause negative local effects, such as maxillary arch collapse with complete teeth misalignment by severely narrowing the anterior portion of the palatal shelves, owing to a severe inflammatory reaction—similar to the phenomenon previously described in different surgical settings.¹⁶⁻³¹ A severe narrowing of the anterior palatal shelves can cause a disaster in the rehabilitation process of cleft patients requiring additional operations and years of orthodontia and potentially outweigh its benefits. Although this subject is extremely relevant, there is no 3D CT cephalometric study devoted to objectively identify transversal and sagittal anterior maxillary changes after using rhBMP-2, which could possibly determinate significant drawbacks and delays of the rehabilitation process, ruling out the possibility of its routine use.

Table 2. Intragroup and Intergroup (Preoperative Versus Postoperative Measurements) Comparative Analysis

Linear and Angular Measurements	Group 1 (Iliac Crest Bone Graft)			Group 2 (rhBMP-2)			Intergroup Comparative Analysis	
	Pre	Post	<i>P</i> Value*	Pre	Post	<i>P</i> Value*	Pre (<i>P</i> Value)	Post (<i>P</i> Value)
Sagittal								
ANS/H (mm)	21.30±7.01	18.39±4.79	0.273	17.28±2.38	18.29±2.45	0.225	0.497	0.865
N/H (mm)	25.82±6.65	28.63±1.95	0.144	28.76±1.67	29.24±2.01	0.401	0.610	0.610
N/V (mm)	61.35±3.83	63.06±1.94	0.465	64.25±5.57	65.24±4.67	0.069	0.671	0.308
A/N-Pog (mm)	4.16±3.16	2.85±3.64	0.144	2.13±1.23	2.59±1.42	0.674	0.174	0.734
ANS/V (mm)	58.56±11.54	64.30±3.89	0.465	67.29±6.51	67.99±6.85	0.123	0.174	0.497
A-N-B (degree)	5.54±2.82	4.12±2.92	0.144	3.73±2.15	3.90±2.10	0.674	0.396	0.865
S-N-A (degree)	78.90±2.56	78.70±2.82	0.144	81.16±3.49	80.05±4.03	0.208	0.234	0.734
S-N-B (degree)	76.44±1.76	76.58±1.35	0.715	78.46±3.29	77.98±4.14	0.674	0.308	0.734
Transversal								
A/ProcZ C//A/ ProcZ N	1.03±0.218	0.95±0.11	0.465	1.00±0.134	1.05±0.24	0.889	1.000	0.734
ANS/ProcZ C// ANS/ProcZ N	1.07±0.123	1.10±0.18	1.000	1.07±0.146	1.12±0.24	0.779	0.734	0.865
ProcZ C/ ProcZ N (mm)	50.5±3.6	51.8±3.4	0.068	54.9±6.9	55.2±6.8	0.779	0.234	0.308
ProcZ C-A-ProcZ N (degree)	105.7±4.7	104.4±2.5	0.465	105.8±8.2	104.5±6.3	0.528	0.865	0.734
ProcZ C-ANS-ProcZ N (degree)	104.2±12.7	102.8±9.4	0.465	101.3±8.0	100.8±8.3	0.484	0.734	0.734

Data are presented as mean ± standard deviation.

All linear and angular interbody landmark measurements were defined in Table 1.

Pre, preoperative; Post, postoperative; / indicates linear distance between; - indicates connection between the ends of an angular measurement; // indicates the ratio between.

*Intragroup pre- versus postoperative comparisons.

Interestingly, our data showed that pre- and post-operative linear and angular dimensions of rhBMP-2 group were similar to the autologous iliac bone graft group. Although inflammatory reaction caused by rhBMP-2^{6,16–31} seems to be higher than autologous bone, our data have shown that it did not cause a negative impact on sagittal and transversal dimensions of the anterior maxilla at 1 year after alveolar cleft repair. As the peak of bone formation using rhBMP-2 is at 1 year after its insertion,² it is likely that its volume will not be reduced at a longer follow-up period, and the maxillary arch will not be restricted or collapsed in an extended time frame. Further long-term follow-up investigation should test this hypothesis.

Our primary hypothesis has proven to be wrong, because rhBMP-2-based therapy did not impose anterior maxillary displacements significantly different from autogenous bone. Thus, previous experiences from the surgical team, accessibility, technical difficulties, overall costs, and different complication rates may support the final therapeutic decision.⁹

We adopted a previously published^{2,3,5,9} dose of rhBMP-2 that has shown to be effective in the induction of bone formation in the alveolar cleft. Thus, although our data have revealed no adverse effect on sagittal and transversal dimensions of the anterior maxilla, our results could not be generalized to an eventual higher dose of rhBMP-2 used to fill the alveolar cleft. In fact, previous researches^{16–18} demonstrated an inverse relationship between bone formation/maturation and rhBMP-2 dose and frequency and severity of adverse events increasing with rising rhBMP-2 dose.^{16–18} Therefore, as it is likely that a higher dose of rhBMP-2 may cause an adverse effect on anterior maxillary dimensions, further analyses are required to prove this hypothesis.

Different methods (eg, direct or indirect cast measurements and two-dimensional and 3D cephalometric analyses) have been used to assess maxillary changes after surgical repair of cleft patients.^{13–15,40} We adopted 3D CT cephalometric technique to solve two-dimensional cephalometric-related problems^{13–15} and to obtain a 3D relationship between the standardized maxilla bone anatomical landmarks and craniofacial planes, rather than only casts-based data.⁴⁰ For this, all linear and angular maxillary measurements were standardized, based on bone landmarks and reference planes previously described.^{33,34} In addition, all data were objectively obtained by 1 blinded investigator using 3D CT imaging processed by a previous validated computer-assisted software program.^{35–38}

A limitation of this study is that we did not adopt all existing bone anatomical landmarks for craniofacial/maxilla morphology assessment, and therefore, additional research should expand our findings by

including additional linear and angular measurements. In addition, we also recognize that further 3D CT analyses (eg, maxillary volume) can contribute to our study. Another caveat is the lack of bone quality assessment. Although we indirectly assumed that the bone quality was sufficient to maintain canine/lateral incisor eruption and adequate stability for orthodontic treatment, as previously described,^{2,3,9} objective bone quality histomorphometric analysis using rhBMP-2-based therapy in alveolar cleft reconstruction should be investigated.

Another caveat of our study is the inequality of patients between groups. Although the number of patients evaluated is similar to recent studies⁴² that also assessed alternative bone substitute in alveolar cleft repair and an equal number of patients was primarily allocated between our groups, only half of the bone graft group underwent CT scan examination, decreasing the sample size in this particular group, but following the recommendation of the local institutional research ethics board. An additional limitation was the lack of longitudinal data that could follow-up skeletally immature patients throughout the last phase of facial growth spurt to identify a potential long-term adverse effect of rhBMP-2. The sagittal cephalometric measurement adopted here has also been used in maxillary growth studies.^{14,15} However, as sagittal facial skeleton growth of cleft patients has been evaluated at longer follow-up periods (eg, 3, 5, 10, and more years of follow-up),^{14,15} further investigation is needed to determine the potential effects of the rhBMP-2 on midface growth of cleft patients after maxillary cleft repair. In fact, we performed all cephalometric measurements at 1 year after the secondary alveolar cleft repair to allow either bone induction or bone integration to its cleft bed and because this time interval (1 year) seems to be an ideal period to assess the anterior maxilla changes by avoiding the insertion of facial growth variable into analysis.

CONCLUSION

This study demonstrated that there are no significant 3D CT sagittal and transversal changes of anterior maxilla 1 year after maxillary cleft reconstruction either with autologous iliac crest bone graft or rhBMP-2.

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