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Early Results on the Efficacy of Demineralized Bone Matrix, Bone Morphogenic Protein, and Freeze-dried Bone Chips in Alveolar Cleft Repair

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Background: Conventional treatment for alveolar cleft repair is done using autologous iliac crest alveolar bone graft (ABG). However, this method may not be ideal in all patients. Analysis of the efficacy of a mixture of demineralized bone matrix (DBX), bone morphogenic protein (rhBMP-2), and freeze-dried bone chips (FDBC) as an alternative for alveolar cleft repair was performed.

Methods: Consecutive patients from August 2019 to June 2022 undergoing early alveolar cleft repair, concomitant hard palate and alveolar cleft repair, secondary alveolar cleft repair, and regrafting from a previously failed ABG were analyzed. Computed tomography scans were performed to evaluate graft take at least 6 months postoperatively. Images were reviewed and scored. Alveolar graft height and graft thickness were recorded. A standardized scoring system was developed, with a score of 0 representing no graft take and 3 representing best possible graft take.

Results: Fifty-five consecutive alveolar clefts (43 patients) were identified as having undergone ABG and satisfied all the other inclusion criteria. Of these, 29 underwent first time ABG and 26 underwent redo ABG. The mean graft height and graft thickness recorded for all clefts was 2.2 and 2.0, respectively.

Conclusions: Early results evaluating the efficacy of ABG using DBX, rhBMP-2, and FDBC show feasibility in regard to both graft height and thickness when using a maxillary computed tomography scan to measure the bone graft take. These results suggest that DBX, rhBMP-2, and FDBC may act as a versatile bone graft material in cleft care, although further studies are needed to determine long-term outcomes.
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INTRODUCTION

The most common facial congenital malformation, cleft lip with or without cleft palate, affects crucial pediatric patient functioning. Incomplete fusion of the medial nasal prominence and maxillary prominence leads to alveolar clefting in 0.18 to 2.50 out of every 1000 live births, with 75% of all cleft lip and cleft palate accompanied by alveolar bone defects.[1,2] Cleft lip with or without cleft palate repair remains in constant evolution, with the optimal timing and method of reconstruction reevaluated as a means to improve functional outcomes.

Conventionally, the lip is repaired at 3–6 months, with the two most commonly used methods being variations of rotation-advancement repair and subunit repair.[3,4] Cleft palate repair usually consists of closure of the nasal and oral mucosa of both soft and hard palate without bony reconstitution around the age of 1 year. This timing allows for the development of normal speech and prevents compensatory sounds. Finally, the alveolar cleft is repaired at the age of 6–8 years with concomitant alveolar bone grafting (ABG).[5] In an attempt to improve outcomes, our institution has implemented a cleft repair protocol that involves the repair of the soft palate only at the age of 1 year. At the age of 2 years, the hard palate is repaired along with concomitant closure of the alveolar cleft. Bone grafting of both structures is done at this time with the goal to restore the bony anatomy of both the hard palate and alveolus. This mitigates observed shortcomings with the conventional cleft repair protocol including maxillary

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arch collapse while promoting synchronous growth of the maxilla and providing alveolar bone stock to allow proper eruption of permanent teeth.[6]

Current standard repair of the alveolar cleft involves closure of the soft tissue envelope with autologous iliac crest bone grafting (ICBG).[7] However, autologous bone grafting may be less than ideal in those undergoing concomitant alveolar cleft closure at a younger age, as children from 2–3 years old have minimal cancellous bone stores. Initially, a combination of demineralized bone matrix (DBX) and bone morphogenic protein (rhBMP-2) was used.[8,9] However, our experience revealed increased resorption of the bone graft material on routine follow-up imaging, leading us to modify our protocol to include freeze-dried bone chips (FDBC) to the DBX-rhBMP-2 mixture. This modification demonstrated consistent bony consolidation in the alveolar cleft. Consequently, we began offering this grafting modality to patients undergoing ABG with the goal of improving operative time, decreasing donor site morbidity, and decreasing postoperative pain.

Analysis of the efficacy of DBX, rhBMP-2, and FDBC for alveolar cleft repair in all patients who underwent early alveolar cleft repair, concomitant hard palate and alveolar cleft repair, secondary alveolar cleft repair, and regrafting from a failed ICBG was performed. A maxillary CT scan was used to measure the bone graft take. A simple and easily reproducible grading system has been developed to quantify both the graft height (GH) and graft thickness (GT).

METHODS

Study Participants

In August 2019, our institution began using DBX, rhBMP-2, and FDBC for early alveolar cleft repair (in patients with cleft lip and cleft alveolus only), early concomitant hard palate and alveolar cleft repair with ABG (in patients with complete cleft lip and palate), and secondary ABG repairs (primary alveolar grafting after 6 years of age) or redo ABG repairs. A retrospective chart review was conducted to identify patients who underwent concomitant hard palate and alveolar cleft repair with ABG and secondary ABG using DBX, rhBMP-2, and FDBC from August 2019 to June 2022 by a single surgeon (BG). Patients and/or patient guardians were counseled on the relative risks and benefits of each modality, including secondary and redo ABG with iliac bone grafting, secondary and redo ABG with DBX, rhBMP-2, and FDBC and early ABG with or without concomitant hard palate repair with DBX, rhBMP-2, and FDBC. A shared decision-making paradigm was used, and informed consent was obtained. At our institution, we have implemented a standardized computed tomography (CT) protocol 6 months postoperatively to evaluate graft take. Participants were excluded if CT image was not available. Patient characteristics, including age at surgery, sex, laterality, presence of co-morbid syndromes, and mean time from operative repair to CT imaging, were collected and analyzed. This study was approved by the institutional review board (IRB_00131670).

Takeaways

Question: The study aimed to analyze the efficacy of DBX, rhBMP-2, and FDBC for alveolar cleft repair in patients who underwent concomitant hard palate and alveolar cleft repair and secondary alveolar cleft repair.

Findings: Early results evaluating the efficacy of alveolar bone grafting using DBX, rhBMP-2, and FDBC suggest feasibility in regard to graft height and thickness in those who underwent concomitant ABG and secondary ABG.

Meaning: DBX, rhBMP-2, FDBC may act as a versatile substitute to autologous bone grafting in alveolar cleft repair.

Operative Technique

For patients undergoing ABG with concomitant hard palate repair, the hard palate is closed using the two-flap Bardach palatoplasty. Oral and nasal mucosal flaps are elevated at the level of the alveolar cleft. Two large oral mucoperiosteal palatal flaps are elevated at the level of the hard palate based on the greater palatine vessels. Vomer flaps are elevated medially, and nasal mucosal flaps are elevated laterally on the cleft sides in continuity with the alveolar nasal mucosal flaps. Watertight nasal alveolar and hard palate mucosal closure is done. If severely malpositioned palatal shelves are encountered, partial bony resection is performed with a Kerrison rongeur to facilitate the nasal mucosal dissection and closure. Furthermore, the removal of malpositioned palatal shelves alleviates nasal obstruction. A small portion of the cortical bone is removed on both sides of the alveolar clefts, using a rongeur to promote bone take at the level of the graft site. A combination of DBX, rhBMP-2, and FDBC in 10:10:80 ratio, respectively, is placed at the level of the alveolar cleft and hard palate over the watertight closed nasal mucosa. The previously raised oral mucosal hard palate and alveolar flaps are advanced and inset to achieve watertight closure over the bone graft. An impression is taken and a custom acrylic splint is then applied over the repair. The splint is kept in place for 6 weeks postoperatively to protect the graft site and incision.[10] The same steps were used restricted to the alveolar structures in those who underwent early, secondary, and redo alveolar bone grafting.

CT Image Scoring

Postoperative CT images were reviewed and scored by three independent reviewers. Alveolar GH and GT were recorded. A standardized scoring system was developed by the authors to easily and reproducibly quantify graft take (Table 1). Alveolar GH was determined in the coronal plane from the nasal floor to the cementoenamel junction, generating a score from 0, indicating gaps in the alveolar process cleft without any bone bridges in the bone graft, to 3, indicating normal height of the alveolar ridge (Fig. 1). Alveolar GT was determined in the axial view by evaluating the thickness of the graft between the labial and palatal surfaces (Fig. 2). A score of 0 indicates inadequate thickness of bone throughout the entire alveolar cleft height, whereas score 3 indicates

Table 1. Scoring System Used to Quantify Graft Take by Measuring Alveolar GH and GT

Score	Criteria
Graft height	
0	Bone gap in the alveolar process cleft without any bone bridges in the alveolar cleft
1	One-third of normal alveolar height anywhere from the nasal floor to cementoenamel junction
2	Two-thirds of the normal alveolar height anywhere from the nasal floor to cementoenamel junction
3	Normal height of alveolar ridge from the nasal floor to cementoenamel junction
Graft thickness	
0	Inadequate thickness of bone throughout the entire alveolar cleft height
1	Adequate thickness of one-third of the normal alveolar height
2	Adequate thickness of two-thirds of the normal alveolar height
3	Adequate thickness of the entire normal alveolar height

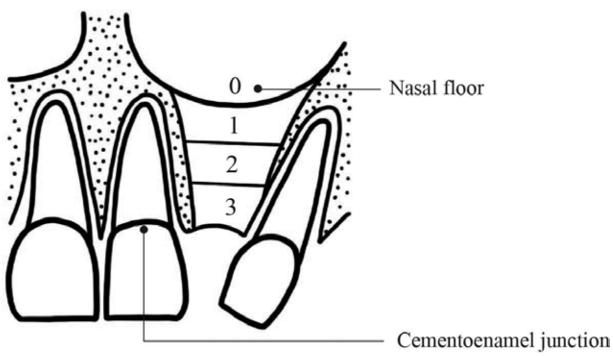

Fig. 1. Illustration demonstrating the scoring system in determining bone GH.

adequate thickness of the entire normal alveolar height. Adequate thickness was defined as at least 80% of the thickness of contralateral normal alveolus, in the case of unilateral clefts or the thickness of the normal appearing alveolus derived from the maxillary process, in bilateral clefts. GH and GT scores of greater than or equal to 2 (at least two-thirds normal alveolar height with 80% thickness throughout this height) were considered clinically sufficient. It was estimated that this amount of the bone would be sufficient to allow for unhindered tooth eruption, orthodontic repositioning, or placement of dental implants.

Analysis

Descriptive statistics were obtained, and cohorts were stratified by type and timing of ABG, age, laterality, sex, and initial versus regrafted ABG. Adobe Illustrator (Adobe Inc, San Jose, Calif.) was used to generate publication quality illustrations and images.

RESULTS

Eighty-three consecutive alveolar clefts were identified as being repaired during the study period. Of the total 83, 55 consecutive alveolar clefts (43 patients) were identified as being treated with a combination of DBX, rhBMP-2, and FDBC as the graft material and also had a postoperative CT scan done 6 months or later after the surgical procedure to allow proper evaluation of the graft take. The cohort was 61% male individuals, with 64% of patients having unilateral and 36% having bilateral clefts. Of these 55 clefts, 29 underwent first time ABG and 26 underwent redo ABG. Among the 29 clefts that underwent first time ABG, six underwent early alveolar cleft repair (age <6 years), 12 underwent early concomitant hard palate and alveolar cleft repair with ABG, and 11 underwent secondary alveolar bone graft. Median age was 5.2 years in the first-time ABG cohort and 10.5 years in the redo ABG cohort. The mean follow-up time to CT after the grafting procedure was 11.5 months. In each group, first time ABG and redo ABG, four patients underwent before grafting buttress cortectomies and transverse palatal expansion. Additional patient characteristics are included in Table 2.

The mean GH and GT recorded for all clefts was 2.2 and 2.0, respectively (Table 3). When breaking down the results based on first time ABG, the mean GH was 2.3 and the mean GT was 2.1. Three of 29 clefts (11%) in this group showed scores below the set threshold and can be considered for regrafting. When these three clefts were not taken in account, the group scores increased to GH 2.4 and GT 2.2. Of note is the subgroup that underwent early (2.1 years old average age) concomitant hard palate and alveolar cleft repair with ABG in the setting of complete cleft (Veau 3 or 4). This subgroup showed the best overall graft take with average GH 2.3 and average GT 2.3. Possible reasons for this are the overall narrower width of the cleft due to younger age; lack of teeth in the cleft (the bone graft is in contact with alveolar bone and not dental tissue); and healthy, nonscarred periosteum available to cover the entire graft on both nasal and oral sides. None of the patients in this subgroup was noted to have significant VPI requiring early surgical correction.

For the group that underwent redo ABG, the cumulative GH was 2.3 and GT was 1.9. Seven of the 26 clefts (26 %) in this group showed graft take with scores below the set threshold and were considered or underwent regrafting. When these seven clefts were not taken in account, the group scores increased to GH 2.5 and GT 2.0. Of note, the majority of patients who received redo ABG had a failed iliac crest alveolar bone graft at the first operation done in a standard fashion (secondary alveolar bone graft only, after the age of 6 years). Only three patients (five clefts) were redo ABGs previously treated with DBX, rhBMP-2, and FDBC as the graft material.

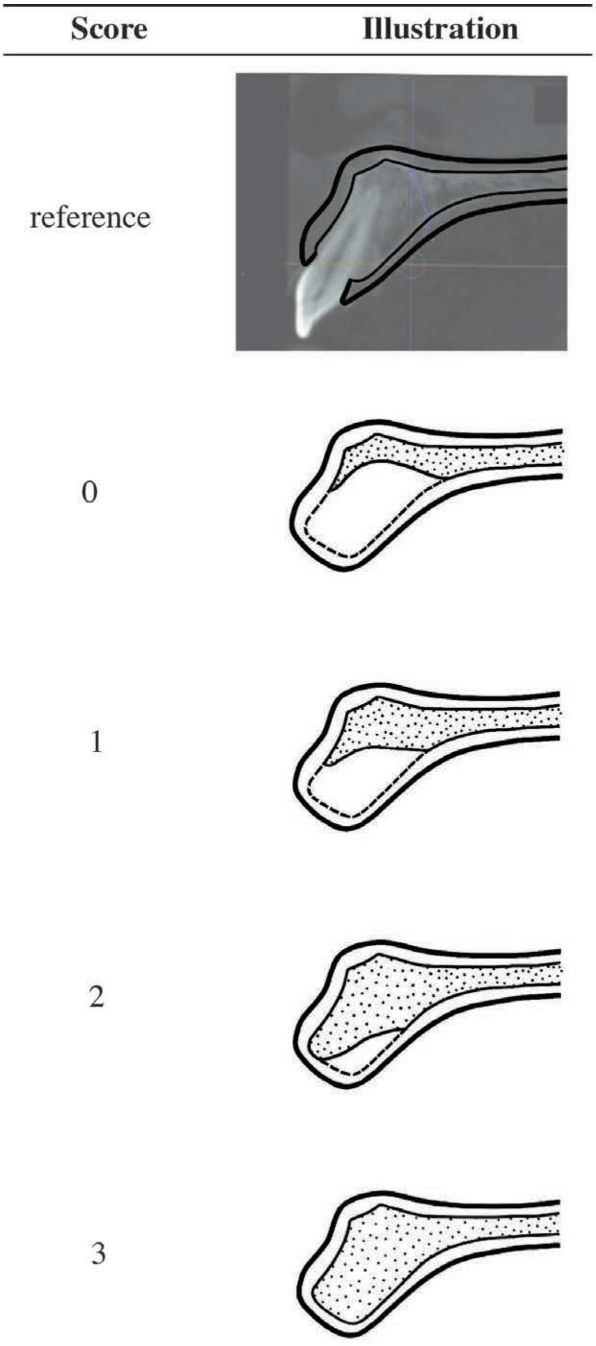

Fig. 2. Illustration demonstrating the scoring system in determining bone GT.

DISCUSSION

Although the necessity of alveolar cleft repair in cleft palate is widely accepted, the optimal timing and method of repair have long been controversial topics. Historically, surgeons in our cleft program performed two-staged palatoplasty with soft palate repair at 1 year of age and hard palate repair at the age of 3–4 years. This was followed by delayed closure of the alveolar cleft with bone grafting around the age of 7 years.[6] Institutional experience suggests that a shortcoming of only closing soft tissue in the hard palate repair led to a high rate of maxillary instability requiring secondary orthognathic correction of transverse maxillary deficiency. To minimize this identified shortcoming and optimize overall outcomes, we progressively modified our protocol over time. Currently this includes infant orthopedics with nasoalveolar molding initiated shortly after birth and lip repair at around the age of 3 months. Soft palate repair is done at the age of 1 year. This is followed by early concomitant repair of the hard palate and alveolar cleft at the age of approximately 2 years, with bone grafting of both structures using DBX, rhBMP-2, and FDBC as graft material.

The adoption of secondary ABG in mixed dentition before the eruption of permanent teeth is largely guided by evidence suggesting that earlier alveolar bone grafting may have detrimental effects on facial growth.[11,12] However, several studies have demonstrated maxillary growth and dental arch morphology comparable between cleft patients when comparing early versus late bone grafting.[13–15] In one study investigating 36 children who underwent early ABG (ages 2–4) versus 56 who underwent late repair, the authors found that early ABG did not negatively affect the dental arch relationship up to 8 years after the primary repair.[15] We have been monitoring our early bone graft patients very closely in regard to the maxillary growth. To this point, of all the patients, only three have been identified with moderate class III malocclusion (<4 mm negative overjet), with none having severe class III malocclusion. Four patients displayed on examination very mild class III malocclusion, with the rest having normal occlusion. In addition, only two patients in the entire group were identified to have small crossbite. The rest of the patients have normal palate width, with no crossbite.

Although alveolar cleft reconstruction has relied heavily on autologous ICBG, advances in allographic bone grafting agents have been shown more recently to be feasible, acting as potential substitutes.[16,17] While these agents alone have been demonstrated to be inferior to autogenic bone grafting when used individually,[18,19] acceptable outcomes have been reported when used in combination with each other or in conjunction with autologous bone grafting.[8,9] Our results suggest the feasibility of grafting using DBX, rhBMP-2, and FDBC in regard to overall graft take in the setting of early alveolar cleft repair, concomitant hard palate and alveolar cleft repair, secondary alveolar cleft repair, and regrafting from a failed ICBG.

The appeal of allographic materials as an alternative to ICBG is the potential for flexibility in timing of alveolar bone grafting. In addition to reducing donor site morbidity, eliminating the need for bone harvest decreases operative time and may reduce operative costs.[20–23] However, the viability of rhBMP-2, DBX, and FDBC as an alternative is contingent upon demonstrating equivalent outcomes to ICBG without introducing new risks to patients. Theoretical risks have been raised around the potential of rhBMP-2 to induce malignant transformation or lead to heterotopic ossification. Although there is no evidence to substantiate these theories when using small doses of

Table 2. Patient Characteristics

	All ABG	First Time ABG				Redo ABG
		All	Early Alveolar Cleft Repair	Early Concomitant Hard Palate and Alveolar Cleft Repair	Secondary Alveolar Bone Graft	
No. patients	43	25	5	10	10	17
No. clefts	55	29	6	12	11	26
Age at surgery (y), median (range)		5.2 (2–16)	3.8 (3–5)	2.2 (1.8–2–8)	9.5 (6–16)	10.5 (3–24)
Male, n (%)*	34 (61%)	18 (62%)	4 (66%)	7 (58%)	7 (63%)	16 (61%)
Laterality, n (%)*						
Unilateral	35 (64%)	21 (72%)	4 (66%)	8 (66%)	9 (91%)	14 (54%)
Bilateral	20 (36%)	8 (27%)	2 (34%)	4 (34%)	2 (9%)	12 (46%)
Mean follow-up to CT (mo)*	11.5	11.6	11	12.9	10.6	11.2

Table 3. Results of all Clefts that Underwent Repair Using DBX, BMP, and FDBC as Graft Material

	All ABG	First-time ABG				Redo ABG
		All	Early Alveolar Cleft Repair	Early Concomitant Hard Palate and Alveolar Cleft Repair	Secondary Alveolar Bone Graft	
Graft height	2.2	2.3	2.3	2.3	2.3	2.3
Graft thickness	2.0	2,1	1.8	2.3	2.1	1.9

Averages of alveolar GH and GT of each subgroup are presented.

rhBMP-2 like those included in cleft repair, the lack of long-term follow-up may be an area of concern. It should be noted that recent meta-analyses addressing malignant potential over the long term found a weak increase in cancer rates in those receiving rhBMP-2, but not to a degree that reached statistical significance.[24,25]

Wide variation exists in the literature in regard to quantifying graft take and total bone fill in alveolar cleft repair. Dental radiographs in conjunction with various radiographic scales (including the Berlgand index, Kindelean index, among others) have been the most widely adopted methods in assessing alveolar bone graft take.[26–31] However, these methods are limited in that they do not allow the assessment of GT and lack the three-dimensional evaluation necessary to adequately quantify bone fill. Additionally, several studies have demonstrated that the use of intraoral radiographs are inadequate for making clinical orthodontic and surgical decisions.[32–34] In 2002, Witherow and colleagues developed the Chelsea scale to take into account the wide clinical variation not covered by the Bergland index, but it still remains limited to two dimensions.[35] Other methods have been described in the literature in an effort to mitigate these limitations. While these techniques are sufficient for quantifying graft take for research purposes, they are methodologically cumbersome and not easily applicable in a clinical setting.[36,37] Our approach of using a maxillary CT scan to measure bone graft take by quantifying GH and GT in the axial and coronal planes was developed to be simple and easily reproducible. The main advantage of the CT scan measurement is the accuracy in quantifying the thickness of the graft that can be grossly overestimated when traditional x-ray techniques are used for measurement (Fig. 3).

The obvious shortcomings of implementing a postoperative CT protocol for all patients undergoing alveolar repair with bone grafting are the cost and convenience of the modality. However, more substantial are the deleterious effects of radiation exposure, of which children are potentially susceptible. Therefore, special precautions could be applied to minimize exposure, including utilization of lower doses of radiation, widening the slices from standard 0.5 mm to 2.0 mm, and limiting the scanned area to the alveolar region to avoid radiosensitive areas.[38]

It is recognized that this study is not without limitations, including those inherent to single-center retrospective studies. Furthermore, variations in cleft width were not accounted for. Additionally, we did not account for the subgroup of patients in the secondary ABG cohort who underwent maxillary buttress cortectomies and transverse palatal expansion before grafting. For those who underwent regrafting of a failed ICBG, we did not account for any useful residual bone graft present at the time of the regrafting procedure. Although acceptable early outcomes have been observed in our cohort, assessment of the results before the completion of facial growth may not reflect the final effects of the treatment. Further longitudinal follow-up is needed in this population to evaluate long-term outcomes of interest, including speech outcomes, the longevity of the primary graft, the effects of early repair on palatal expansion, effects on maxillary growth, and permanent tooth eruption and stability.

CONCLUSIONS

The early results evaluating the efficacy of ABG using DBX, rhBMP-2, and FDBC show feasibility in regard to both GH and GT when using a maxillary CT scan to measure the bone graft take. These results suggest that DBX, rhBMP-2, FDBC may act as a versatile bone graft material in cleft care, although further studies are needed to determine long-term outcomes. In addition, a novel, simple, and easily reproducible grading system used to quantify the GH and GT in this setting has been described here.

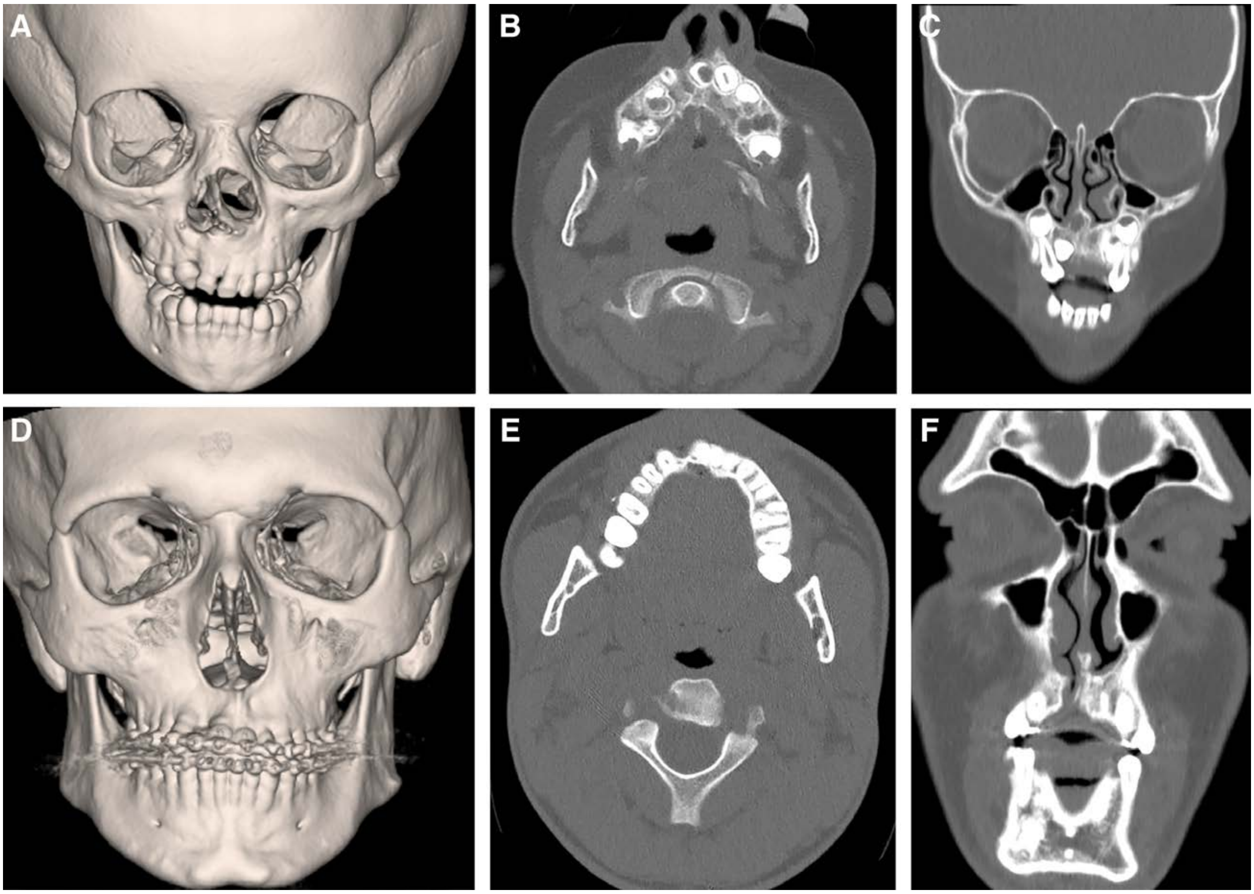

Fig. 3. CT scan done to evaluate GH and GT in patients who underwent repair of the alveolar cleft using DBX, BMP, and FDBC (3D reconstruction, axial view and coronal view). A–C, Demonstration of a patient with good results in both GH (3) and GT (3). D–F, Demonstration of a patient with good results in GH (3) but a poor result in GT (0).

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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