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Cleft Lip and Palate

Microstructured beta-tricalcium phosphate for alveolar cleft repair: a two-centre study

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Abstract. The current standard of care in alveolar cleft repair is timing the procedure in the mixed dentition stage and making use of autologous bone to restore the maxillary defect. Using a synthetic bone substitute bypasses the risk of donor site morbidity and reduces the operation time. In this study, the outcome of alveolar cleft repair using microporous beta-tricalcium phosphate (β-TCP) was investigated in patients with unilateral cleft lip and palate. Twenty patients were enrolled prospectively in this study, divided between two centres. Continuity of the alveolar process, recurrence of oronasal fistulas, and eruption of teeth into the repaired cleft were evaluated at 1 year postoperative. Also, cone beam computed tomography scans were analyzed using a volume-based semi-automatic segmentation protocol. No adverse events were reported. The mean residual bone volume in the repaired cleft at 1 year postoperative was 65%. There was no recurrence of oronasal fistula. Furthermore, 90% of the teeth adjacent to the cleft erupted spontaneously and all patients showed a continuous alveolar process. Secondary alveolar grafting using microporous β-TCP can safely be used in the clinical situation. Residual calcified tissue, canine eruption, and complication rates at the recipient site are comparable to those with autologous grafts.

Key words: alveolar cleft; beta-tricalcium phosphate; 3D imaging; cone beam computed tomography; cleft lip; cleft palate; bone substitutes.

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Repair of the alveolar cleft in patients with cleft lip and palate serves a number of goals. It provides a continuous maxillary arch in which the erupting dentition can be aligned, remedies persistent oronasal fistulas, and also stabilizes the maxillary complex and provides support to the alar base and adjacent soft tissue structures. The current gold standard for alveolar cleft repair is the use of autologous bone harvested from the iliac crest or the mandibular symphysis[1–3]. Although they have proved to be effective and have shown a high percentage of success, these grafting procedures carry the risk of comorbidity such as postoperative pain, hypersensitivity, paresthesia, infection, apical root damage, and visible scarring[4–12]. The use of a synthetic bone substitute circumvents this risk of donor site morbidity and reduces the operation time.

Over the past decades, a number of biomaterials have been tested clinically as alternatives to autologous bone grafting in alveolar cleft repair. The most promising results so far have been obtained using recombinant human bone morphogenetic protein 2 (rhBMP-2)[13,14]. However, following the reporting of serious adverse events in maxillofacial surgery applications, its use has lost popularity in recent years[15].

The authors' study group has previously researched the use of microstructured beta-tricalcium phosphate (β-TCP) as a bone substitute for alveolar cleft repair in vitro[16], in vivo[17,18] and also in a human pilot study[19]. The aim of this study was to evaluate the use of microstructured β-TCP in a prospective two-centre clinical trial.

Materials and methods

Patients

A total of 20 patients with a unilateral alveolar cleft were prospectively enrolled in the study at university hospitals in Bergen, Norway (Haukeland University Hospital) and Utrecht, the Netherlands (Utrecht University Medical Centre); 10 patients were enrolled at each hospital. Permission to carry out this study was granted by the medical ethics committees of Utrecht University Medical Centre and Haukeland University Hospital. All patients underwent early secondary alveolar cleft closure. Surgery was performed when radiological data showed at least 50% development of the root of the canine adjacent to the cleft (or in selected cases the lateral incisor, depending on the opinion of the orthodontist).

If needed, deciduous teeth located around the alveolar cleft were removed at least 8 weeks preoperatively to facilitate watertight closure of the mucoperiosteal layers. If this could not be achieved, the patient was excluded from the study[20]. The mean age of the patients at the time of surgery and the sex distribution are shown in Table 1.

All patients were grafted with microstructured β-TCP (OsOpia; Regedent, Zurich, Switzerland), 10 in Bergen and 10 in Utrecht. One surgeon in Bergen (HV) and one surgeon in Utrecht (RK) performed the alveolar cleft grafting surgeries.

Bone substitute

The calcium phosphate-based scaffold used in this study is a biphasic calcium phosphate with a hydroxyapatite fraction of <10% and a tricalcium phosphate fraction of >90% (OsOpia; Regedent, Zurich, Switzerland). Since the hydroxyapatite fraction is less than 10%, the scaffold is referred to in this article as β-TCP. The scaffold has a porosity of 70% and a granule size of 250–1000 μm. Due to its unique microarchitecture and macroarchitecture, both osteoconductive and osteoinductive properties are attributed to this bone substitute[16]. Furthermore, in vivo studies have shown near complete resorption of the scaffold, which is essential in order to facilitate the eruption of the lateral incisor or canine into the grafted region[17,18].

Surgery

Reconstruction for alveolar cleft was performed under general anaesthesia with naso-endotracheal intubation. Antibiotic prophylaxis was prescribed for 3 days (clindamycin 10 mg/kg/day; Hameln Pharmaceuticals, Hameln, Germany). The surgical procedure involved the creation of three mucoperiosteal layers (nasal, buccal, and palatal). Nasal and palatal layers were prepared and closed with resorbable sutures (3–0 Vicryl and 4–0 Ethicon; Ethicon, Brussels, Belgium). Following closure of the nasal and palatal layers, the cleft defect was filled with microstructured β-TCP. The graft was covered with the buccal layer and closed with resorbable sutures (3–0 Vicryl and 4–0 Ethicon).

Data acquisition

Cone beam computed tomography scans of the maxillary region were acquired preoperatively and at 1 year postoperative. In Utrecht, the i-Cat 3D imaging system was used (Imaging Sciences International, Hatfield, PA, USA). Scans were performed at 120 kV and 3- to 8-mA pulse mode. The field of view was 13 × 6 cm, scan time was 8.9 seconds, and voxel size was 0.4 mm. In Bergen, the 3D Accuitomo system was used (Morita, Irvine, CA, USA). These scans were executed at 85 kV and 9 mA, with a field of view of 4 × 4 cm, scan time of 9 seconds, and voxel size of 0.08 mm. The preoperative and 1-year postoperative datasets were superimposed using a recently described semi-automatic segmentation protocol[20], and the residual volumes of calcified material were calculated. As the Bergen scans were executed with a significantly smaller horizontal and vertical field of view, it was not possible to match the preoperative and postoperative scans according to the protocol. These scans were manually matched using the Image Fusion module in iPlan Cranial (BrainLab AG, Feldkirchen, Germany) and subsequently segmented using the Smart Brush module in BrainLab Elements.

Results

Surgery for all 20 patients was uneventful and there were no postoperative complications. Loss of a very small amount of granules was only rarely seen. No wound dehiscence, postoperative infection, or significant loss of granules occurred.

At 1 year postoperative, no residual oronasal fistulas were present. All patients had a continuous alveolar process on the affected side. The canine adjacent to the alveolar cleft did not erupt spontaneously in two patients, one in Bergen and one in Utrecht. Orthodontic therapy with fixed appliances was started at 3 months postoperative and was without complications. Teeth adjacent to the cleft were readily movable through the grafted region (Fig. 1). The percentages of residual calcified tissue were normally distributed (as confirmed by Shapiro–Wilk test: $P = 0.839$) for the Bergen group, the Utrecht group, and both groups combined. At 1 year postoperative, the mean percentage of residual calcified material at the site of the repaired alveolar cleft defect was 61% (standard deviation 14%) for the Bergen group and 69% (standard deviation 12%) for the Utrecht group. The mean residual calcified material for both groups combined was 65% (standard deviation 14%) (Fig. 2, Table 2).

Table 1. Age and sex distribution of the Utrecht and Bergen groups, and the two groups combined.

	Bergen group	Utrecht group	Groups combined
Number of patients	10	10	20
Mean age at surgery	8.3 years	9.6 years	8.9 years
Sex distribution	8 M, 2 F	6 M, 4 F	14 M, 6 F

M, male; F, female.

Discussion

The average residual calcified tissue volume of 65% in the 20 operated patients in this study is comparable to the 61.6% reported at 1 year after filling the alveolar cleft with autologous chin bone grafts using the same surgical procedure,

Fig. 1. Light photographs showing canine eruption into the repaired alveolar cleft grafted with β-TCP, followed by orthodontic therapy for up to 2 years postoperative: (A) preoperative situation, (B) 3 months after surgery, (C) 12 months after surgery, (D) 24 months after surgery. Note the absence of the lateral incisor adjacent to the cleft and the deciduous canine that is kept in place temporarily due to aplasia of the left first premolar.

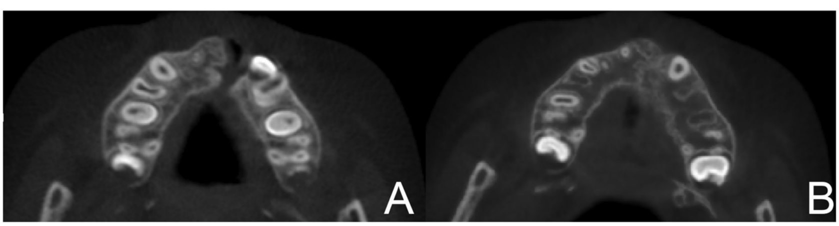

Fig. 2. Axial cone beam computed tomography images of a patient with a unilateral complete alveolar cleft repaired with β-TCP: (A) preoperative situation; (B) 1 year postoperative situation.

surgical timing, and segmentation protocol in a previous study[20].

As described in earlier studies, the largest part of resorption took place in the cranial part of the graft[19]. This resorption may be related to poor functional loading of the scaffold in the region of the piriform aperture, because paranasal muscular function is of lower quality on the cleft side.

Since histological examination of the reconstructed alveolar bone is not possible, we have to rely on radiological and clinical evidence to prove the presence of bone in the reconstructed alveolar cleft. The calcified tissue, as measured in the reconstructed alveolar cleft, is supposed to be nearly 100% bone. Histopathological examinations performed in previous goat model studies on alveolar cleft grafts showed an almost 100% conversion of the grafted β-TCP after 6 months[17]. Furthermore, newly formed corticocancellous bone can be discerned on radiological examination at ≥1 year following alveolar cleft reconstruction. In addition, since a dental follicle can only erupt when vital bone is present, eruption can be seen as evidence for bony transformation of the scaffold. In 18 out of the 20 patient cases in this study, the canine or lateral incisor (depending on orthodontic indication) adjacent to the cleft erupted completely through the scaffold. This 90% eruption of the canine or lateral incisor through the alveolar cleft concurs with the percentage of 87.5% described by Vellone et al. for 24 patients who underwent secondary alveolar bone grafting with autologous iliac crest bone grafts[21].

The advantage of the application of a bone substitute is that no comorbidity arises. In a retrospective study performed in Utrecht, cleft patients reconstructed with β-TCP ($n = 31$) were compared to cleft patients reconstructed with autologous chin bone ($n = 45$). Pain was scored 1 day postoperatively using a visual analogue scale (VAS) ranging from 0 to 10. The number of days in the hospital was also registered. Both the VAS at 1 day postoperative and the duration of hospital stay were dramatically lower in the group of patients treated with β-TCP (unpublished data).

No cost-effectiveness analysis was performed in this study. The price of a single vial of 1 ml of β-TCP is approximately 70 Euros, and only one vial is needed in almost all procedures. Obviously, the cost difference when using β-TCP instead of an autologous bone graft will depend on the clinic where the procedure is performed. In Utrecht, chin bone grafts are harvested by a resident and this takes up to 20 minutes of extra operating time. In

Table 2. Postoperative outcome parameters 1 year after alveolar cleft closure.

	Bergen group	Utrecht group	Groups combined
Residual calcified tissue	61% (SD 14%)	69% (SD 12%)	65% (SD 14%)
Spontaneous eruption of canine/lateral incisor	9 (90%)	9 (90%)	18 (90%)
Continuous alveolar process	10 (100%)	10 (100%)	20 (100%)
Residual oronasal fistula	None	None	None

SD, standard deviation.

Bergen, iliac crest bone is harvested simultaneously with the alveolar cleft closure procedure by another surgeon or resident. Although it takes the same amount of time, a second surgeon is needed in the surgical theatre.

The importance of watertight closure, in order to prevent the bone substitute from leaking and to avoid infection, is indisputable. The same applies to the presence of deciduous teeth; an alveolar cleft that is not cleared of the deciduous dentition is more prone to these adverse effects, as was shown in the previous pilot study. Care must be taken not to overfill the defect and to leave no granules at the cemento-enamel junction of the teeth adjacent to the cleft, since these factors will keep the closure from being watertight.

The method of analysis for measuring the regeneration of a bone defect in a growing skeleton with permanent teeth erupting, however accurate, is rather cumbersome and takes a lot of time. This is readily possible for research purposes, but is impractical for general use.

In conclusion, secondary alveolar grafting using microporous β-TCP can safely be used in the clinical situation. Residual calcified tissue, canine eruption, and complication rates at the recipient site are comparable to those with autologous grafts. Furthermore, it is an inexpensive procedure that, in comparison to autologous bone grafting, reduces postoperative pain, hospital stay, and operating time.

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Competing interests

None.

Ethical approval

Ethical approval for this study was given by the Medical Ethics Committee of the Utrecht University Medical Centre (reference number 09-129/K) and the Medical Ethics Committee of the Haukeland University Hospital (protocol number 2013/732).

Patient consent

Not required.

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