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Case Report Open Access

First Clinical Application of New Bone Substitute Material to the Alveolar Cleft

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Abstract

Secondary bone grafting of alveolar cleft using autologous particulate cancellous bone from the ilium is an essential treatment for cleft lip/palate patients. However, secondary surgical invasion represents a disadvantage. To avoid this disadvantage, octacalcium phosphate collagen composites (OCP/Col) were developed as a new bone substitute material. Through preclinical studies and clinical application for cyst holes and extraction sockets, OCP/Col demonstrated satisfactory bone repair. In this case report, OCP/Col alone was implanted into a 13-year-old patient with incomplete unilateral cleft lip and alveolus. Postoperative changes of the OCP/Col treated site were evaluated by computed tomography for two years after operation. It was revealed that sufficient bone bridge was formed in the treated alveolar cleft after implantation of OCP/Col without autologous bone grafting. At the bottom of the nasal cavity, preoperative asymmetry was improved. In addition, usual orthodontic treatment was completed 1 year and 10 months postoperatively, and good occlusion was achieved. These results suggest that OCP/Col is clinically applicable as bone regenerative material, representing an alternative to autologous bone grafting.

Keywords: Alveolar bone grafting; Bone substitute material; Octacalcium phosphate collagen composites; Clinical application

Introduction

Autologous bone grafting into the alveolar cleft has become indispensable for occlusion management in cleft lip/palate patients with alveolar cleft since the report by Boyne and Sands [1], and is a part of the routine treatment. Until now, transplantation of autologous iliac bone has been conducted selectively for jaw bone defects in the field of oral surgery [2]. However, secondary surgical invasion to a healthy part of the body is inevitable when accessing a bone donor site, and physical limitations exist to the amount of bone that can be harvested. In addition, although the risk of complications such as paresthesia and hernia exists, the incidence of such complications is low [3,4]. To eliminate such disadvantages, various bone substitute materials have been studied in recent years, but a satisfactory alternative to autologous bone has yet to be developed. Nard et al. [2] searched the literature for articles on non-autologous materials used for alveolar clefts, and they found reports dating back to the mid-1970s, but reports have hit new peaks in recent years. For the preceding four decades, autologous bone grafting has been the gold standard. Groups from Tohoku University first investigated disk-shaped octacalcium phosphate/collagen composites (OCP/Col) as a bone substitute synthesized using both synthetic OCP ($Ca_8H_2(PO_4)_6{\cdot}5H_2O$) [5] and atelocollagen derived from porcine skin [6]. OCP/Col has been applied to various artificial bone defect models in beagle dogs and excellent bone regenerative ability has been reported [7-13]. Also, the first clinical application in humans confirmed the safety of this material [14], and bone regenerative ability in tooth extraction sockets and cystshas since been described [15,16]. Then, it was conducted a multicentre single-group trial (UMIN: 000018192) in a company-initiated clinical trial using OCP/Col for bone defects in the field of oral surgery. As part of this clinical trial, OCP/Col was implanted into the alveolar cleft of patients with unilateral cleft lip and alveolus. This study is the first clinical evaluation of OCP/Col being implanted into the alveolar cleft.

Methods

OCP/Col

As previously reported [5,6] sieved granules of OCP (particle sizes of 300-500 μm) were added to concentrated pepsin-digested atelocollagen isolated from the porcine dermis (NMP collagen PS; Nippon Meat Packers, Tsukuba, Ibaraki, Japan). OCP formed 77% of the weight of the OCP/Col mixture. The OCP/Col mixture was then lyophilized, and a disk was molded (diameter of 9 mm, thickness of 1.5 mm; weight, 12 mg). OCP/Col disks were prepared by a dehydrothermal treatment (150˚C, 24 h) and sterilized by electron beam irradiation (22 kGy) (Figure 1).

Case

Patient: A 13-year and 6-month-old boy with incomplete unilateral cleft lip and alveolus.

History of present illness: This patient was born in April 2002 at 37 weeks' gestational age, by caesarean section as a fraternal twin, and birth weight was 2788 g. From the pediatric department of a certain hospital he was introduced and admitted to our hospital for scrutiny of incomplete cleft lip, and the management of the patient was started. At 3 years and 3 months old (July 2005), cheiloplasty was performed for the vermilion border alone. The patient subsequently underwent regular observation. In January 2013, the patient began standard orthodontic treatment for delayed eruption of the right maxillary

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central incisor, and continued alignment of the permanent anterior dentition. A bone defect was confirmed in the right alveolar cleft from the central portion of the alveolus to the bottom of the nasal cavity by computed tomography. Consequently, it was decided that OCP/Col would be implanted into the alveolar defect. This operation was approved by the Tohoku University Hospital Ethics Committee and was carried out with the consent of both the patient and his legal guardian. As a result, OCP/Col was implanted into the alveolar cleft under general anesthesia in October 2015 as a bone substitute.

General anamnesis: Nothing in particular.

Family history: This patient's young sister (dizygotic twin) showed no cleft abnormalities.

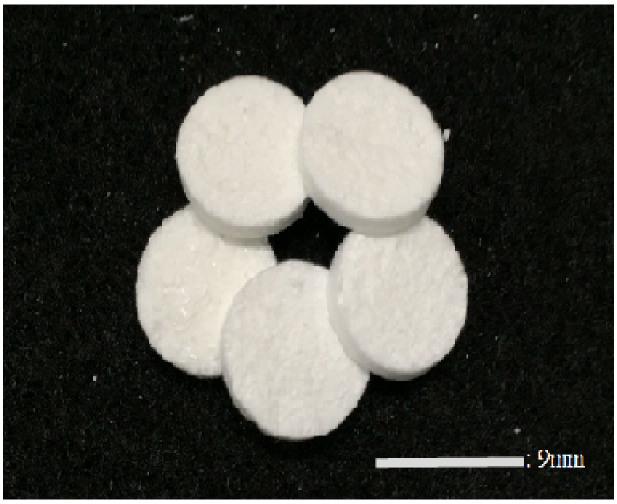

Figure 1: Bone substitute material: octacalcium phosphate collagen composites (OCP/Col).

Preoperative findings in oral cavity

Bilateral maxillary second primary molars and bilateral mandibular first and second primary molars remained intact. The right maxillary lateral incisor was smaller than the left maxillary lateral incisor. Permanent incisors were aligned and occlusal condition was judged good, and naso-oral fistula was not observed (Figures 2a and 2b).

Figure 2a: Intraoral finding.

Figure 2b: Intraoral finding.

Operation and postoperative progress

Under general anesthesia, a recipient bed was formed in accordance with standard bone grafting procedures. From the distal side of the maxillary right canine, a mucosal incision was made along the labial gingival margin of the maxillary left central incisor, and a longitudinal incision was added to the alveolar part of both teeth. The mucosal periosteum of the same part was peeled off from alveolar crests to the nasal cavity side.

The maxillary bone and alveolar bone defect were exposed. Between the maxillary right central and lateral incisors, a mild depression was seen from the labial-side alveolar crest to the central part of the alveolus, but continuous bone was recognized. In addition, the bone defect was confirmed in the direction of the nasal cavity from the vicinity of the root apex of the lateral incisor (Figures 3a).The nasal mucosa of the alveolar cleft was peeled, and the labial-side cortical bone was cut and removed with a round bur to clearly indicate the portion of bone defect and clearly showed the defect of the inner palatal side. Ablated nasal mucosa was trimmed and raised toward the nasal cavity side, then sutured both sides with absorptive thread to make the height the same as the healthy bottom of the nasal cavity. The recipient bed was then completed. The width of the alveolar cleft was 15 mm at the lower edge of the piriform aperture, mesial height was 14 mm, distal height was 5 mm, depth of the bottom of the nasal cavity was 19 mm, and depth of the alveolar portion was 8 mm (Figure 3b).

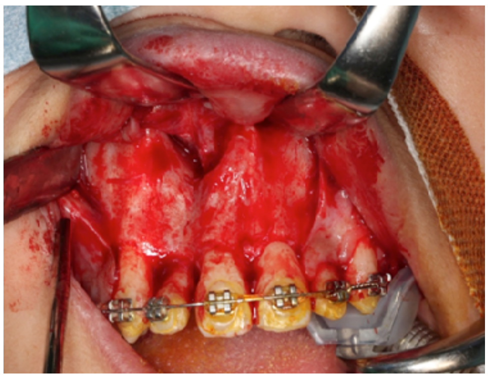

Figure 3a: Intraoperative photograph.

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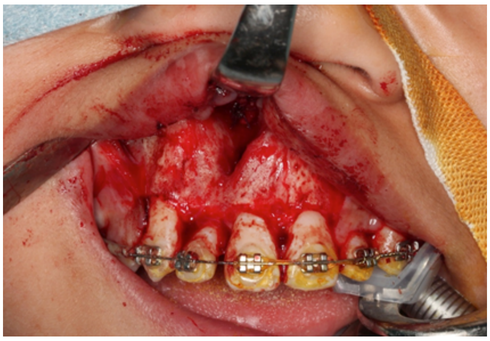

Figure 3b: Intraoperative photograph.

After penetration around the maxillary cortical bone with a round bur, 15 OCP/Col discs were implanted (Figures 3c and 3d).

Figure 3c: Intraoperative photograph.

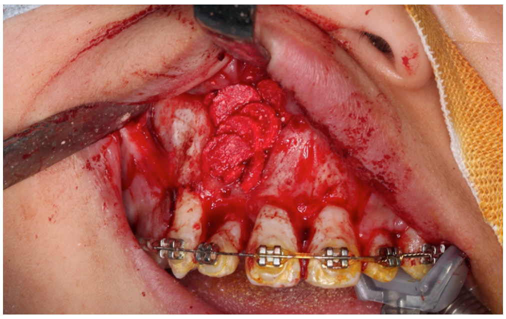

Figure 3d: Intraoperative photograph.

After that, the periosteum inside the mucosal periosteal valve was incised to relax the tissue, the mucoperiosteum was repositioned and sutured with absorbable thread, and the wound was closed. The operation was then completed. Operation time was 54 min and bleeding volume was 20 ml. Although postoperative swelling was evident in the right cheek for several days, no pain was present in the iliac area and no restrictions to motion were seen, so total hospital stay was 10 days (3 days preoperatively, 7 days postoperatively).

Postoperative findings in the oral cavity

After implantation of OCP/Col, multi-bracket appliances were set to the maxillary lateral dentition and the mandibular dentition. Standard orthodontic treatment was completed in August 2017, and good occlusion was formed (Figures 4a and 4b).

Figure 4a: Intraoral finding.

Figure 4b: Intraoral finding.

CT findings

CT was taken parallel to the PO-ANS line with SOMATOM Definition Flash® (Siemens, Germany; tube voltage, 120 kV; tube current, 35 mA), from the height of the anterior teeth to the area of the infraorbital foramen. These were performed preoperatively, and at 1 month, 3 and 6 months, 1 year and 2 years after operation.

Postoperative changes in the alveolar cleft

Postoperative changes in the OCP/Col-implanted area were examined in the following three tomographic planes (Figure 5).

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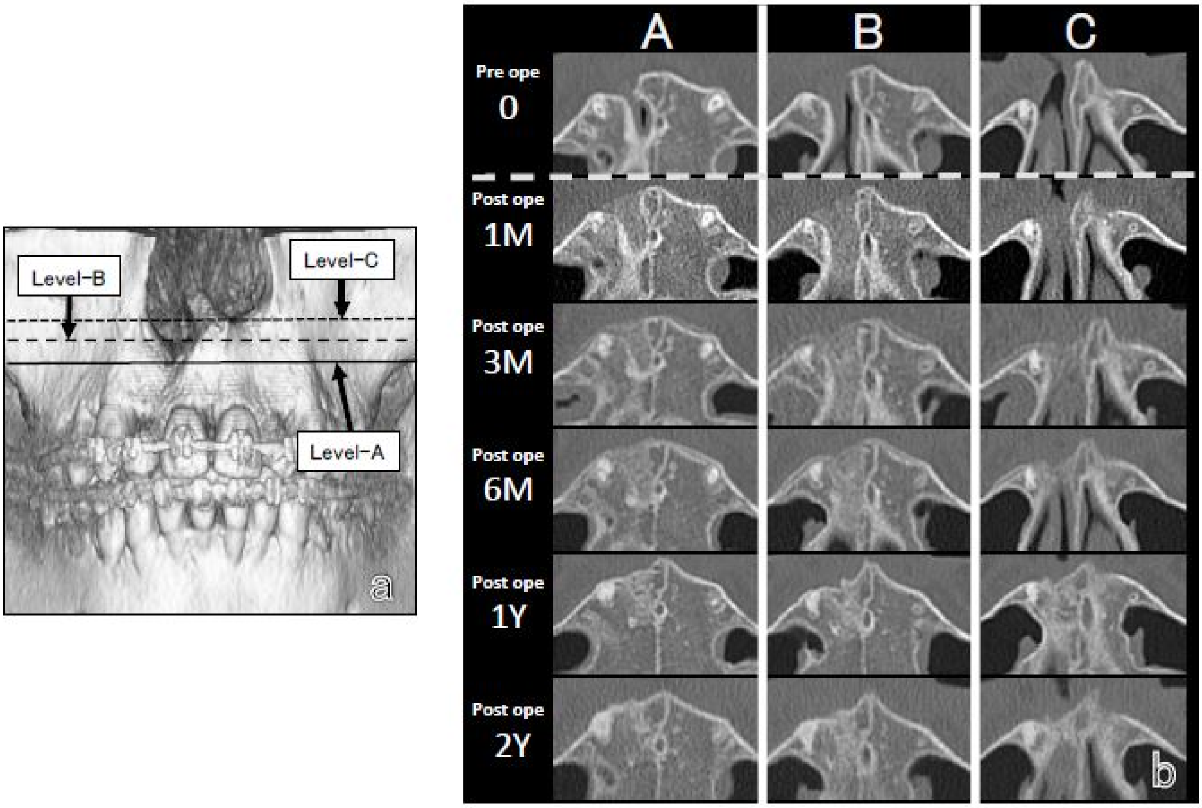

Figure 5: Postoperative change in the alveolar cleft.

The tomographic plane of level A was taken as the height corresponding to the lowest point on the imaging plane where the defect of the alveolar cortical bone could be confirmed before surgery. This was approximately equivalent to the middle of the vertical height from alveolar crests to the bottom of the nasal cavity on the healthy side. Level C was defined as the tomographic plane just before the maxillary bone at the bottom of the nasal cavity on the healthy side lost continuity with the nasal septum. The tomographic plane halfway between Levels A and C was defined as level B.

OCP/Col itself shows little radio-opacity as previously reported [9]. In this case, the OCP/Col-implanted area at each level was indicated by radio-opacity at 1 month after operation. At 3 and 6 months after operation, layered radiopaque areas extended to the mesial-distal part outside the alveolar cleft. These layered areas were distinguished from the original cortical bone surface layer. However, this area became a single radio-opaque layer and had completely merged at 1 year after operation. In addition, from around 6 months after operation, the boundary between the cortical bone of the alveolar cleft and the OCP/Col-implanted area became unclear. Although a region with higher radio-opacity was seen in the first year after operation, the radio-opacity of the same area was reduced and became indistinguishable from surrounding original maxillary bone after 2 years. Finally, asymmetry of the nasal base was improved by the bone bridge at the bottom of the nasal cavity at level C (Figure 5).

Evaluation of the lower edge of the piriform aperture by three-dimensional structured images

At 3 months after OCP/Col implantation, asymmetry was found at the bottom of the nasal cavity on both sides, but this surface was found to be improved by new bone formation at 6 months. The surface condition of the bone became smooth, resembling the healthy side, and the boundary with surrounding maxillary bone became obscure. Finally, asymmetry of the bottom of the nasal cavity improved bilaterally (Figure 6).

CT values were automatically measured using We VIEW Z system version 1.0.0 on the Tohoku University hospital electronic chart. Tomographic images of each level (levels A-C) at 1, 3 and 6 months, 1, and 2 years after implantation of OCP/Col were selected with reference to the preoperative image, and CT values of OCP/Col-implanted areas corresponding to inherent alveolar cleft were evaluated. On images, each measurement was performed three times, and the average value was determined and used. On the other hand, the control CT value was defined as a value obtained by automatically measuring and averaging three times the region having substantially the same width as the congenital alveolar cleft including maxillary cortical bone on the healthy side using the same tomographic image each time. Control CT values on both levels A and B showed the same tendency because of rich cancellous bone components in the maxillary bone. In level C, cortical bone components of the lower edge of the piriform aperture surface were reflected, so CT values were higher than those of levels A and B (Figure 7).

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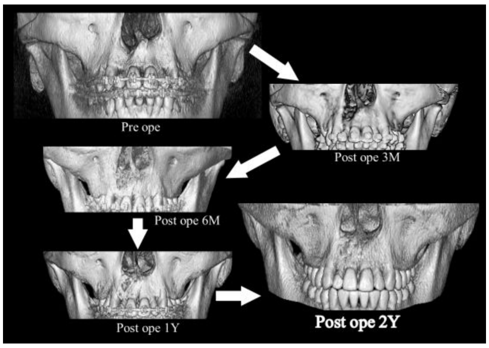
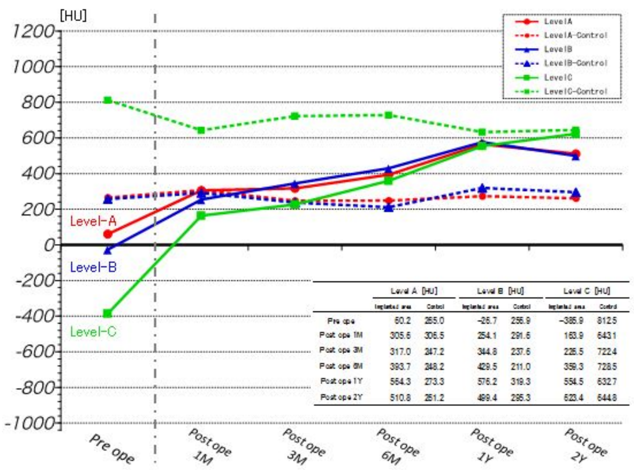


Figure 6: Evaluation at the lower edge of the piriform aperture by three-dimensional structured images.

Changes in CT values for OCP/Col-implanted areas



	Level A [HU]		Level B [HU]		Level C [HU]	
	Implanted area	Control	Implanted area	Control	Implanted area	Control
Pre ope	60.2	265.0	−26.7	256.9	−385.9	812.5
Post ope 1M	305.6	306.5	254.1	291.6	163.9	643.1
Post ope 3M	317.0	247.2	344.8	237.6	226.5	722.4
Post ope 6M	393.7	248.2	429.5	211.0	359.3	728.5
Post ope 1Y	564.3	273.3	576.2	319.3	554.5	632.7
Post ope 2Y	510.8	251.2	499.4	295.3	623.4	644.8

Figure 7: Changes in CT values of OCP/Col-implanted areas.

CT values of the OCP/Col-implanted area tended to increase from 1 month to 1 year after operation at both levels A and B, but had decreased by 2 years after operation. Both levels A and B showed high CT values from 3 months on the implanted side compared to the healthy side. At level C, which contained air before surgery, a negative value was initially seen, showing an upward trend similar to both levels A and B until 1 year postoperatively. However, at 2 years, unlike both levels A and B, level C showed a continuously increasing tendency, becoming comparable to the healthy side.

Discussion

The purpose of bone grafting to the alveolar cleft is to fill the bone defect with "bone" under the oral mucosa and acquire continuity of the separated bone fragments. Using an adequate bone bridge, various therapeutic effects can be obtained. The most important purpose of alveolar bone grafting is to allow alignment of the teeth into the bone bridge like normal dentition. This means that the non-erupted permanent teeth will be induced to erupt in the alveolar bone bridge, and teeth adjacent to the alveolar cleft can be arranged and root axes controlled by orthodontic treatment. Embedding of dental implants is also possible when there are no teeth to arrange. In consideration of these issues, the properties of regenerated hard tissue need to be equivalent to those of natural bone in the closure of alveolar defects with application of bone substitutes. If autologous bone is to be grafted, events that might occur such as tooth eruptive disorder, dysplasia of the teeth and abnormal absorption do not need to be considered.

According to our own results from animal experiments using OCP/Col, the crystal structure of regenerated hard tissue has been confirmed as equivalent to natural bone by X-ray diffraction [7-9]. In addition, in experiments using young beagle dogs, after mandibular molar teeth had been extracted early, OCP/Col disks were implanted into the tooth extraction sockets. As a result, succeeding permanent teeth spontaneously erupted, and eruptive disorder or dysplasia of the teeth did not occur. On the other hand, we reported that succeeding permanent teeth might stay in areas of implantation of β-TCP (Beta-tricalcium phosphate) granule as a control [13]. One important factor is that teeth that have not erupted before operation will erupt spontaneously into the hard tissue formed by the implanted bone substitute, and this is one reason for selection as a bone substitute material for the alveolar cleft.

In this case, bone-like opacity was confirmed on CT in the area of cleft implanted with OCP/Col from 1 month postoperatively. Subsequently, opacity of this area increased over time and formed a bone bridge to the alveolar bone defect.

No change in the bone bridge shape was seen after 1-2 years postoperatively, and stable hard tissue was confirmed. At both Level A and B, the change in CT value after OCP/Col implantation showed a similar tendency. That is, the CT value was higher than that for the healthy-side maxillary bone from 3 months postoperatively, remaining increased until 1 year postoperatively, and always showing a higher value than healthy bone, but a decreasing tendency was seen from 2 years postoperatively.

On the other hand, at Level C, a continuous increasing tendency was seen until 2 years after operation, reaching the same CT value as natural bone on the bottom of the healthy-side nasal cavity, which is rich in cortical bone.

In a previous report [12] on an OCP/Col implantation experiment into artificial alveolar cleft, characteristic cortical and cancellous bone parts were confirmed in the bone bridge. In the human alveolar cleft as in this case, the properties of implanted area are inferred to be similar to physiologically healthy bone, when bone remodeling progresses. Furthermore, in this case, the bone bridge formed by implanting OCP/Col improved left-right asymmetry at the bottom of the nasal cavity. This suggests that downward deflection on the affected side will be corrected and esthetic restoration can be expected.

Various studies on the application of bone regeneration material to alveolar clefts have been reported [17,18]. These have advocated reducing the amount of autologous bone, applying both bone regeneration material and autologous bone to the alveolar cleft. Even in the same oral cavity, various surgical procedures to harvest bone can be necessary. Therefore, this case report is very meaningful because the congenital alveolar cleft was filled with bone tissue with single use of OCP/Col as a bone substitute material, resulting in the acquisition of symmetry for the bottom of the nasal cavity.

The cleft type in this case was mild, with incomplete cleft lip and alveolus, and the range of the bone defect was limited, and teeth adjacent to the alveolar cleft had already erupted. We thus could not confirm induced eruption of adjacent teeth that had not erupted preoperatively into the bone bridge formed by OCP/Col, or the alignment of teeth by orthodontic treatment. However, good bone bridges were found to be formed using OCP/Col alone in this case of cleft lip and alveolus, with improved asymmetry of the bottom of the nasal cavity, allowing occlusal treatment under standard orthodontic treatments. These results confirmed this material as sufficiently clinically applicable.

Conclusion

OCP/Col offers a bone regeneration material that can be used instead of autologous bone, with OCP/Col alone forming a sufficient bone bridge at the alveolar bone defect in a patient with cleft lip and alveolus.

Declarations

Tadashi Kawai received 3 million yen as joint research funds from the Toyobo Co., Ltd. Company. The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Competing interests

All the authors disclose that there are no conflicts of interest relevant to this trial.

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