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Micro-structured calcium phosphate ceramic for donor site repair after harvesting chin bone for grafting alveolar clefts in children

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ABSTRACT

Objectives: The purpose of this study was to evaluate the use of synthetic bone graft material as a filling material at the mandibular symphysis donor site of autologous bone in children.
Materials and methods: A blinded patient group comprised 20 patients with unilateral (UCLP) or bilateral (BCLP) cleft of lip and palate, all with an indication for alveolar cleft repair. The study took the form of a prospective randomized clinical trial. We used lateral cephalograms for the measurement of the symphyseal donor area defect both peroperatively and at 12 months postoperatively. The data obtained were digitalized and the treatment outcome expressed in numbers. Comparisons with a previous study were made. Histology of biopsies and CT scans were used for visualising bone formation.
Results: This study demonstrates that the micro-structured, resorbable calcium phosphate ceramic provides good regeneration properties for the repair of a critical size bony defect in children. One year postoperatively, the measurements taken from lateral cephalograms show that there is scarcely any visible residual defect. Histological investigations of the bone biopsies show solid, induced bone formation and almost complete resorption of the micro-structured calcium phosphate.
Conclusions: The findings of this study (novel in children) indicate that micro-structured resorbable calcium phosphate is an excellent alternative to autologous bone. The digital findings showed a restored donor site defect significantly indicating the efficacy (i.e. osteoconductivity and resorbability) of this bone substitute. The biopsy histology demonstrated the overall presence of newly formed vital bone and the resorption of the bone substitute. Its use for grafting the alveolar cleft is currently researched and it may become the new standard.
Clinical relevance: As co-morbidity and prolonged operation time at the donor operation site are inherent to the alveolar cleft repair procedure, the use of the described bone substitute is winning progress.

1. Introduction

The frequency of occurrence of various forms of congenital facial clefts varies throughout the world and between different ethnic groups, local areas and time span (Gundlach and Maus, 2006). In Europe, the occurrence of clefts of lip, alveolus and palate (CLP) among Caucasians has been reported to be somewhere between 0.69 and 2.35 per 1000 births (Andrä et al., 1988). One of the major interventions in the treatment of patients with unilateral (UCLP) or bilateral (BCLP) cleft of lip, alveolus and palate is closure of the alveolar cleft. The importance of this procedure lies not only in the closure of the alveolar cleft in order to allow the eruption of the surrounding teeth and in enabling orthodontic transfer in the grafted bone, but in addition the soft-tissue profile of lip and ala nasi is also improved by the bone correction (Park et al., 2013) and the dental treatment which follows orthodontic treatment. This is of great social importance in every culture in the world. Transplantation of autologous bone is still the gold standard in alveolar cleft repair strategy (Eppley and Sadove, 2000). Using the chin as standard donor site is routine practice in most cleft centres for cleft surgery repair in the Netherlands and well accepted with low objective and subjective morbidity (Freihofer and Kuijpers-Jagtman, 1989; Borstlap et al., 1990; Hoppenreijs et al., 1992; Freihofer et al., 1993; Booij et al., 2005; Raghoebar et al., 2007;

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Weibull et al., 2009; Weijs et al., 2010). Tooth injuries after harvesting bone from the mandibular symphysis have been reported. In 2005 Booij et al. mentioned an endodontic problem that had developed in three lower incisors. Raghoebar et al. in 2007 found subjective changes in sensibility but no noteworthy complaints or discomfort reported by the patients. Weibull in 2009 mentioned an injury percentage of 1% and stated: "it did in general not affect the patient in daily life". Notwithstanding this low morbidity, the patients (and their parents) have to be informed about the risk of objective and subjective disturbances of the sensibility in the chin donor region and the risk of dental pulp necrosis (Booij et al., 2005). In the Netherlands we have observed almost no adverse effects of the chin graft method. Since it began to be used routinely use in 1995 surgeons have built up a thorough experience in harvesting chin bone for repair of unilateral and even bilateral alveolar clefts (Raghoebar et al., 2001; Al-Ani and Nambiar, 2012).

One problem continues to be inherent to harvesting autologous bone: wherever in the body the bone is harvested, it is accompanied to a greater or lesser extent by co-morbidity (Rawashdeh and Telfah, 2008). The question is: can this be avoided?

A resorbable bone substitute is a potential answer to this question. These substitutes have changed from replacement material to resorbable osteoinductive biomaterials (Kolk et al., 2012). Bone substitution with the application of autologous platelet-rich plasma is also considered (Metzler et al., 2012). Transplantation of autologous dental material has been described (Aizenbud et al., 2013).

The bone substitute that we used is a micro-structured resorbable calcium phosphate that has been tested in animal experiments and has been shown to be equally as effective as autologous bone (De Ruiter et al., 2011). The application of bone substitute only, i.e. with no autologous bone and/or cell material or bone morphogenetic proteins (BMP's), for the repair of alveolar clefts in children is new. We wanted to exclude the risk of complications accompanying the use of artificial grafting material for filling clefts in CLP patients. To this end we chose to first investigate micro-structured resorbable calcium phosphate as a filling material in the chin, the Utrecht donor site of autologous bone for repair of the alveolar cleft (Koole et al., 1989) and the only clinically available defect in our patients.

The critical size defect (CSD) in a child's mandible was never determined and probably never will be. CSD's were originally defined as "the smallest size intraosseous wound in a particular bone and species of animal that will not heal spontaneously during the lifetime of the animal (Schmitz and Hollinger, 1986). However Cooper et al. (2010) stated '*After a review of the existing literature and a critique of the clinical applicability of the models studied, it is suggested that the use of the term "critical-sized-defect" be discontinued*'. The defects following chin bone harvest for alveolar bone closure are obviously not beyond this size. In a previous study (Dik et al., 2010) we have shown that these defects heal spontaneously '*leaving a residual defect* (compared with the original) *of about 14%*'.

1.1. Aim

The aim of this study was to evaluate the safe clinical use of a newly developed calcium phosphate based micro-structured and resorbable bone substitute in children. We used it as a filling material in the autologous chin bone donor site in young patients with a cleft of lip, alveolus and palate (UCLP and BCLP). It was also important to determine the degree of dimensional stability of the micro-structured resorbable calcium phosphate granules used in bone formation and the process of bone graft resorption and remodelling.

2. Material and methods

2.1. Patients

This study was carried out in accordance with the principles expressed in the Declaration of Helsinki. Permission for this study was obtained from the Medical Ethical Committee of the University Medical Centre, Utrecht, The Netherlands (Protocol nr. 06-210).

Before the operation, parents and children were given extensive information about this experimental study. In order to avoid being influenced by the researchers, the parents and children were given the opportunity to speak to an independent but informed physician and to ask any questions they may have had. Patient information forms were developed especially for this study. Patients were included in the study after written informed consent had been obtained. The blinded patient group comprised 20 UCLP and BCLP patients, all with an indication for alveolar cleft repair. The group was sorted by sex and type of cleft (Table 1) and average age at the time of repair surgery (Table 2).

2.2. Material (bone substitute)

The synthetic bone graft material is comprised of 1–2 mm sized micro-structured calcium phosphate particles that contain >90% tricalcium phosphate and <10% hydroxyapatite (RevisiOs BV, The Netherlands) (Fig. 1).

It is a resorbable material for clinical application in bone regenerative surgery. The micro-structured surface of the material renders the material osteoinductive as demonstrated in various preclinical models (Habibovic et al., 2005, 2006; Yuan et al., 2010), without the addition of bone growth factors or other bone inducing agents or cells. These materials have superior ability to accelerate bone healing, compared to non-osteoinductive ceramics.

2.3. Methods

2.3.1. Surgical method

Alveolar cleft repair surgery comprised repair by means of a bone transplant using autologous bone taken from the mandibular symphysis. The bone-harvesting site was then filled with the micro-structured calcium phosphate. The buccal cortical surface of the mandibular symphysis was approached by a horizontal incision in the vestibule of the lower lip in the intercanine region. After making a submucosal flap, an incision was made through the mental muscles on each side and down to the bone. After elevating the muco-periosteal flap the mental nerve was localized bilaterally. Using the position of the apices of the incisors and the germs or roots of the permanent canines as seen on preoperative radiograph, the outline of the bone graft was marked with a fissure burr. The monocortical bone graft was cut out with a reciprocal saw, irrigated

Table 1
Number and gender.

	Male	Female	Total
UCLP	7	5	12
BCLP	6	2	8
Total	13	7	20

Table 2
Average age at time of cleft repair surgery.

	Male	Female
UCLP	11 years 1 month	11 years 2 months
BCLP	12 years 2 months	10 years 9 months