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The clinical application of rhBMP-7 for the reconstruction of alveolar cleft☆

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Summary In this study, radiographic assessment was performed to find out the effectiveness of bone regeneration following the application of recombinant human bone morphogenetic protein 7 (rhBMP-7) for the reconstruction of alveolar cleft defects in 11 cases: nine unilateral and two bilateral alveolar clefs. Reconstruction of the alveolar cleft was performed by using 3.5 mg of rhBMP-7 (Osigraft OP1) on a type I collagen carrier. Radiographs were taken 6 months post operation using a Gendex Intraoral Unit with Agfa Dentus M2 Comfort occlusal film. The amount of bony infill was graded on a Kindelan four-point scale. The patients were followed up for an average of 6.6 years. Based on the radiographic analysis, eight out of the nine unilateral alveolar cleft cases received a score of grade I and one patient had a grade II score, using the Kindelan scale. In the two bilateral alveolar clefts, only one side had bone formation. The radiographic appearance showed a normal trabecular pattern similar to the adjacent bone. Thus, rhBMP-7 was radiographically and clinically successful in regenerating the bone at the alveolar cleft which resulted in shortening of the operation time, absence of donor-site morbidity and a shorter hospital stay. The promising results of this preliminary study should encourage a phase II trial to compare bone grafts with BMP for the reconstruction of alveolar defects.

☆ This study was conducted at the University of Glasgow Dental Hospital and School.

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Introduction

Orofacial clefts are one of the most common craniofacial birth deformities with an incidence of 1 in every 600—700 live births in the United Kingdom alone.[1] Bone grafting of the cleft is a well-established technique in the surgical management of cleft lip and palate patients. Debate is ongoing regarding the optimal timing of the procedure.[2] Primary bone grafting is performed simultaneously with lip repair, which is usually done before 2 years of age; however, this failed to produce acceptable and universally favourable outcomes.[3,4] Early secondary bone grafting is performed in patients older than 2 years of age and younger than 5 years of age.[5] During the period of the mixed dentition, secondary bone grafting is frequently performed between the ages of 7 and 12 years.[6—10] The application of both alloplastic[10] and autogenous grafts[4—18] for the reconstruction of alveolar cleft has been studied and compared.[10] Donor-site morbidity is the most common complication associated with autogenous bone graft.[11] The use of bone morphogenetic protein 2 (BMP-2) for the reconstruction of the alveolar defects in eight cases has been studied, the results showed that 65% of bone height was achieved and superior bone quantity was noted in skeletally mature patients.[19,20] The assessment of quantity of bone formation, height and location of bone within the alveolar cleft defect are essential outcome measures.[19,21,22]

The Kindelan score is an objective four-point scale to assess bone formation at the cleft site. The advantage of this scale is its ease of use, and it can be applied even before the eruption of the canine.[23] Satisfactory reliability of the Kindelan scoring system has been reported for the grading of alveolar bone grafting.[24]

This study assesses the feasibility and the reliability of using recombinant human bone morphogenetic protein 7 (rhBMP-7, OP-1) for the reconstruction of alveolar cleft defects. The success being determined both clinically via tooth eruption and subsequent orthodontic treatment as well as radiographically using anterior occlusal radiographs and the Kindelan scale.

Material and methods

This study was conducted as a prospective phase II clinical trial. However, it was closed before the initial recruitment target of 30 could be achieved. In total, 11 patients — nine with unilateral and two cases with bilateral cleft lip and palate — were enrolled in the study. In all the cases, the alveolar cleft was reconstructed with BMP-7 (Osigraft, OP-1, Stryker Biotech, UK). This study was reviewed and approved by the West Glasgow Ethics Committee 1 (EudraCT number: 2005-004392-38, REC reference number 05/S0703/1), the Medicines and Healthcare Products Regulatory Authority (MHRA) (CTA:27410/0001/001-0001, protocol number R050187) and the Research and Development Unit (R&D Reference:R050187). Recruitment for the BMP trial was carried out on consecutive patients who were investigated at a multidisciplinary clinic for the diagnosis and management of cleft lip and palate. The children were asked to fill a child-specific information sheet, and adult versions of the sheet as well as a consent form were given to the parent/guardian at the first appointment. The chief investigator discussed the aims and details of the study with the patients and their parent/guardians. The patients were given enough time to consider and make an informed decision; they were also given the option to withdraw from the study even after signing the consent form.

The patients were managed by a cleft surgical team, and the surgical procedures were performed by a single surgeon. Six of the nine unilateral cleft lip and palate patients (three male and three female patients) underwent presurgical orthodontic arch expansion before reconstruction of the alveolar cleft with rhBMP-7. The alveolar cleft was exposed via a standard buccal gingival mucoperiosteal. The incision was made along the margins of the alveolar cleft vertically toward the crest of the ridge. The incisions were extended within the gingival sulcus on the labial aspect of the adjacent teeth. The incision was then extended to the premolar region, and an oblique backward cut was made toward the vestibule. The labial sulcus incision was extended to the mesial aspect of the central incisor. The mucoperiosteum was elevated off the bony walls of the cleft from the alveolar crest to the nasal floor. Through a palatal ginigival sulcus incision, the adjacent palatal mucoperiosteum was reflected to allow the dissection of the nasal mucosa. This tissue was reflected superiorly to reconstruct the nasal floor. Closure of the nasal layer started from the posterior to the anterior ends using 4-0 resorbable suture. The palatal flaps were advanced medially and sutured together. To achieve a tension-free closure, horizontal scoring of the periosteum at the base of the buccal flap was performed. For each case, a vial of Osigraft® with 3.5 mg of eptotermin alfa (recombinant human osteogenic protein 1(OP-1)) in bovine collagen (a bioresorbable scaffold) was applied at the alveolar defect. A putty additive (Stryker Biotech) containing carboxymethyl cellulose was added to the Osigraft®, and this mixture (Figure 1) was reconstituted with 2—3 ml of sterile 9 mg/ml sodium chloride solution (0.9% w/v) before use. The Osigraft® was mixed with the putty additive and saline to achieve the desired consistency for clinical application (Figure 2). The graft was then packed locally into the cleft region (Figures 3 and 4). The buccal mucoperiosteal flap

Figure 1 Osigraft® and sterile sodium chloride being mixed in a sterile bowl with a sterile spatula.