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Comparison between autogenous iliac bone and freeze-dried bone allograft for repair of alveolar clefts in the presence of plasma rich in growth factors: A randomized clinical trial

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ABSTRACT

Purpose: This study aimed to compare the effectiveness of alveolar cleft repair using iliac bone and freeze-dried bone allograft (FDBA) in the presence of plasma rich in growth factors (PRGF).
Materials and methods: Patients with unilateral alveolar cleft (n = 32) were randomly allocated to either the iliac plus PRGF group or the FDBA plus PRGF group. CBCT images were obtained before and 6 months after the surgery to assess the regenerated bone volume. Paired t-tests and two-way analysis of variance (ANOVA) were applied to analyze the data using SPSS 16.0 software.
Results: The patients' mean age was 15 ± 5.7 years (range = 8–27). In the iliac plus PRGF group, the mean volume of cleft before the surgery and the mean regenerated bone volume 6 months after were 1.67 ± 0.66 and 1.14 ± 0.47 cm^3, respectively. The corresponding values were 1.5 ± 0.54 and 0.72 ± 0.23 cm^3 in the FDBA plus PRGF group. The remaining bone to cleft volume ratio was not associated with grafting time (secondary or tertiary) and the original cleft volume. Iliac bone reinforced with PRGF was more successful than FDBA plus PRGF in repairing alveolar cleft ($p = 0.007$).
Conclusion: Due to the poor performance of the allograft, autografts should still be preferred in spite of possible donor site morbidity.

1. Introduction

Alveolar cleft is one of the most prevalent congenital diseases. Its repair is essential for orthodontic treatment, stability and retention of the cleft's adjacent teeth, and optimizing the occlusion of the patients. Autografting has been conventionally considered as the main treatment for alveolar cleft. Regardless of the donor source, cancellous bones are more preferable choices compared to cortical bones (Borstlap et al., 1990). Owing to its appropriate size and high potential for osteogenesis induction, the iliac bone is generally used as the most common donor site (Boyne and Sands, 1976; Bergland et al., 1986). Nevertheless, the success of autografting depends on several factors including the patient's age, cleft width, and functional stresses such as masticatory factors (Oyama et al., 2004). Due to the side effects of autogenous grafts, including extra-surgical intervention on the donor site and donor site morbidity (e.g. paresthesia, hematoma, infection, and probable fractures), surgeons tend to use allografts (i.e., cadaveric bone, freeze-dried allogeneic bone marrow, and demineralized bone matrix) as potential alternatives for autografts (Kraut, 1987). Using allografts eliminates the risk of donor site morbidity while maintaining sufficient supply (MacIsaac et al., 2012). Freeze-dried bone allograft (FDBA) is principally osteoconductive (Hoexter, 1982; Ascencio et al., 2004). Clinical, radiographic, and biological assessments have estimated the success rate of osseous allograft to range between 60% and 90% (Eppley et al., 2005). However, based on cone

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beam computed tomography (CBCT) investigations, the use of the demineralized bone matrix (DBM) did not lead to satisfactory results in alveolar cleft grafting (Madrid et al., 2014). Meanwhile, according to some studies, a combination of allografts and platelet-rich plasma (PRP) enhanced the success rate of sinus and peri-implant grafts and the repair of periodontal osseous lesions (Howes et al., 1988; Ilgenli et al., 2007). Nevertheless, the efficacy and safety of allografts need to be further studied.

A number of growth factors and osteoinductive materials have been recently proposed for the promotion of bone graft success (Marx, 2004). One of these materials is plasma rich in growth factors (PRGF), a type of PRP containing various growth factors. PRGF has received increasing attention due to its simple application and low processing cost compared to several other growth factors. It has been successfully used in oral and maxillofacial grafts and repair of periodontal lesions (Anitua, 2001; Anitua et al., 2009). The application of PRGF in combination with artificial or natural biomaterials has yielded promising results in the handling, adaptation, and acceleration of bone and soft tissue regeneration (Anitua et al., 2007).

The success of alveolar cleft grafting has been measured by different radiographic methods, particularly pre- and post-surgery simple intra-oral and panoramic radiographies (Kindelan et al., 1997; Dempf et al., 2002). While two-dimensional methods can evaluate the height of the regenerated bone, they encounter limitations in volumetric, morphologic, and structural assessments of the new bone. Therefore, the use of CBCT is currently recommended, and volumetric software packages are commonly used to assess the success of alveolar bone grafting.

To the best of our knowledge, no previous studies have evaluated the use of FDBA in combination with PRGF for alveolar cleft repair. Therefore, this study performed volumetric measurements based on pre- and post-surgery CBCT scans to compare the effectiveness of alveolar cleft repair using the application of the iliac bone and FDBA in the presence of PRGF. We hypothesized that combining PRGF with FDBA would increase its effectiveness in repairing alveolar cleft to be comparable to PRGF and iliac.

2. Materials and methods

2.1. Sampling, randomization, and blinding

The target population for this study consisted of patients with non-syndromic, unilateral complete cleft (lip, palate, and alveolar process) who were referred to the Oral and Maxillofacial Department of Shariati Hospital in Tehran, Iran. Considering the 20% difference in the volume of the regenerated bone ($\alpha = 0.05$, $\beta = 0.1$), the sample size was calculated as 16 patients in each group (total number of patients = 32). Based on the age of the participants, two strata, i.e., secondary and tertiary, were defined. Block randomization (using blocks of four) was applied to allocate eight patients from each stratum to each of the two groups (Fig. 1).

All cleft repair operations were conducted by the same surgeon. The researchers who measured the cleft volume on CBCT images (as the outcome) and analyzed the data were blinded to the study groups.

2.2. General description

First, clinical examination was conducted to determine the cleft type, patients' dental age (mixed or permanent dentition), and presence of oronasal fistula. The eligible patients were then interviewed and their demographic characteristics (including name, age, sex, date of birth, and date of referral) were collected using a questionnaire.

Patients with complete unilateral cleft who were referred to the hospital for grafting were randomly allocated to either the iliac plus PRGF group or the FDBA plus PRGF group. Pre-operative CBCT image with minimal field of view (FOV) was obtained from all patients. To follow the long-term results of the intervention and to avoid radiation overdose in children, post-surgery CBCT images were taken after 6 months of follow-up (Madrid et al., 2014; Reddy et al., 2015). After the surgery, orthodontic treatment was provided for all patients with secondary graft in both groups. Although we recommended implant insertion 4 months after the surgery, implant insertion during the 6-month period after the operation was not performed for any of the patients with tertiary graft.

2.3. PRGF preparation process

After the induction of general anesthesia, a 20-cc blood sample was collected by an automatic blood sampling system (Venojet, Terumo Medical Corporation, USA). The sample was poured into four test tubes containing 0.5 cc sodium citrate to prevent clotting. The tubes were slowly shaken and then centrifuged (manufactured in BTI Spain) at 460 *g* for 8 min to separate the blood into three layers including the PRGF, PMGF (plasma moderate in growth factors), and PPGF (plasma poor in growth factors) (Anitua, 2001; Anitua et al., 2009). The layers were then transferred to three separate tubes and preserved in a heat block device at 37 °C. As a result, 2 cc of PRGF, 2 cc of PMGF, and 2–4 cc of PPGF were produced. The obtained PRGF was then combined with either bone or FDBA powder. In addition, to produce the required membrane for the coverage of the graft, the activator was added to PPGF and stored in a heat block at 37 °C for 25–30 min.

2.4. Surgical procedure

The same surgeon performed all alveolar bone grafting surgeries by a buccal advancement flap technique. During this procedure, the buccal flap and palatal flap were first elevated, and the oronasal fistula was dissected. The orifice was then closed, sutured, and directed upward. In the next stage, bone graft was carried out, and the cleft was closed with the advancement of buccal and palatal flaps.

In the iliac plus PRGF group, a 5-cm incision was made to access the donor site bone. Sufficient bone was then removed by a trephine, and corticocancellous bone powder was prepared using a bone mill. Since we intended to match and compare the two groups, iliac bone block was not administered. From the 2 cc activated PRGF, 0.5 cc was immediately sprayed into and around the cleft. The bone powder was mixed with the remainder of the activated PRGF and 2 cc PMGF and allowed to rest for 2–5 min to reach a gelatinous consistency. It was then softly pressed into the cleft cavity to fill it up. Finally, the graft was covered with the gelatinous membrane of PPGF, and the flap was passively sutured without tension. In the FDBA plus PRGF group, the same procedure was followed with FDBA (Cenobone 150–2000 mm), in the form of corticocancellous powder instead of iliac bone powder.

All patients were advised to have a liquid diet for the first 2 weeks after surgery and a soft diet for the next 2 weeks. They were also asked to present at the hospital for monthly follow-up visits.

2.5. Outcome measurements

The main outcome was the volume of the regenerated bone. CBCT images (1-mm axial sections) were obtained from the incisal edge of the upper central incisor to the inferior portion of the pyriform aperture. The patient's head and the CBCT device were adjusted to maintain the axial cuts parallel to the occlusal plane. The baseline volume (V1) was measured on the pre-surgery CBCT