Study Protocol and Statistical Analysis Plan

Official title: **Combination of platelet-rich fibrin and calcium sulfate in socket augmentation: A randomized clinical study**

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Study protocol

This study was a randomized clinical trial conducted from March 2015 to November 2016. Ethical approval was obtained from the Ethics Committee, Faculty of Dentistry, University of Malaya, Kuala Lumpur [DF RD 1621/0076 (L)]. All patients were recruited from the outpatient department and oral and maxillofacial surgery department. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. All patients who fulfilled the inclusion criteria were included in the study. They received a detailed explanation of the treatment and gave their written informed consent.

The inclusion criteria for the study was maxillary premolar teeth requiring extraction with neighboring mesial and distal sound/restored teeth, alveolar bone level (measured from periapical radiographs) more than 50% of the root length and age ranges from 25-55 years. The exclusion criteria was bony fenestration of the socket wall confirmed from CBCT scan, acute signs of infection, periodontally compromised teeth, absence of buccal plates, any systemic disease which may hinder the healing process e.g., diabetes, hypertension, bleeding disorders like thrombocytopenia, thalassemia, asthma, patients on long term steroids, osteoporosis, smokers, pregnant and lactating women and history of malignancy or radiotherapy and chemotherapy.

All patients were randomly allocated to either PRF-CS (test) or PRF-xenograft (MinerOss® X syringe, Bio Horizons, Alabama, United States) (PRF-X) (control) group using coin-toss method. The sample size for this study was calculated using *t* tests of means difference between two independent groups, based on a power of 80% and a detectable difference between the two comparative groups of 0.05 where the mean differences for socket depth were 13.73 mm and 9.50 mm with standard deviations of 3.00 and 3.08 respectively (17). The sample size was calculated as 10 subjects (5 subjects in each group).

Pre-surgical preparation

A day before extraction, clinical photographs and impressions of the jaw were performed. An acrylic stent (A) (to serve as a fixed reference point) for each patient was prepared using light cured material. A cone beam computerized tomography (CBCT) scan was performed for the planned extraction site using Kodak 9000C® (Carestream, United States) software. The selected scanning parameters were 70 kV; 10 mA; voxel size = 76µm; acquisition time = 10.8s. The parameters measured from the CBCT scan at baseline were mesial bone height (M_BH), distal bone height (D_BH), socket bone height (SH), buccal bone height (B_BH), palatal bone height (P_BH), horizontal bone width (W) and volume of bone. MIMICS® software (Materialise NV, Belgium, version 16.0) was used for the analysis of bone volume at baseline and at 5 months post-extraction. To measure the soft tissue profile changes from stone casts, another occlusal acrylic stent (stent B) was fabricated using light cure acrylic. Grooves were prepared to serve as fixed points for the periodontal probe. The parameters measured for clinical measurements were mesial soft tissue height (M_SH), distal soft tissue height (D_SH), buccal soft tissue height (B_SH), and palatal soft tissue height (P_SH).

Extraction procedures

Prior to extraction, 20ml of venous blood was collected in two sterile vacutainer tubes. The venous blood was quickly spun in the centrifugation machine (Process for PRF DUO® Centrifuge, France) at 1300 rpm for 8 mins and kept separate for 3-5 mins. After the completion of centrifugation, the fibrin clot was picked up using a tweezer while a pair of sterile scissors was used to separate the Red blood cell layer. Finally, the fibrin clot from 1 tube was placed in the PRF box (PRF processing, Nice, France) to form the PRF membrane whereas the fibrin clot from second tube was compressed to form the PRF plug.

After atraumatic tooth extraction, the extraction socket was carefully curetted and irrigated with normal saline. In the control group, xenograft (MinerOss®X) (size 250-1000μ, 0.5cc) was mixed with PRF membrane (cut into pieces) and placed inside the socket. In the test group, calcium sulfate (CS) was mixed with PRF membrane (cut into pieces) and placed inside the socket. The graft materials were placed up to the level of crest of the extraction socket before being covered with the PRF plug. Simple interrupted sutures (black silk 4-0, Ethilon® Mersilk, Cornelia, Georgia) were applied on the mesial, middle and distal area. An antibiotic, Amoxicillin 500mg (capsule) every 8h for 5 days and an analgesic, Paracetamol 1g (tablet) every 8h for 3 days were then prescribed. The patients were advised to rinse with 0.12% chlorhexidine mouth rinse twice daily for a week. Patients were recalled after a week for suture removal followed by another recall 5 months post-extraction for CBCT scans and planning of implant placement.

Statistical analysis

Descriptive statistics were achieved for data analysis (SPSS 22, IBM, USA). Mean with standard deviations were reported to demonstrate average bone resorption and percentage of changes (PoC). Since the assumptions of the normal distributions were fulfilled, parametric test was used to calculate the linear radiographic changes and for volumetric changes. The paired sample *t* test was performed to calculate the changes obtained within each group (intragroup) from baseline to 5 months. An independent samples *t* test was used for independent groups to assess the difference between the treatment groups. Because of the unmet criteria of normal distribution, non-parametric test was used for clinical measurements and median values with interquartile range were used to calculate the *P* values. The Wilcoxon signed rank test was used to equate the median values in clinical parameters (M_SH, D_SH, B_SH and P_SH) at baseline and at 5 months within each group (intragroup). For intergroup changes from baseline and 5 months, the Mann-Whitney *U* test was used. Level of significance was set to 0.05.