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Periapical Healing following Endodontic Microsurgery with Collagen Based Bone Filling Material: A Randomized Controlled Clinical Trial

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Protocol:

Subjects are recruited for the study from the patient pool of the Department of Endodontics, School of Dental Medicine, University of Pennsylvania, who are planned for routine treatment of root end surgery. Patients who present to the post-doctoral resident clinic and meet the inclusion criteria are asked to participate in the study. The study includes lesions classes B and C, as described by Kim and Kratchman, J Endod 2006. Teeth designated as Class B present with a small periapical lesion, normal periodontal probing depth, and no mobility. Patients with such teeth often have clinical symptoms, and such cases are ideal for microsurgery. Teeth with Class C designation have a sizeable periapical lesion with a coronal extension of the lesion but without periodontal pocket or mobility.

Randomization is done for single-rooted teeth assigned as either control or test group receiving Foundation bone augmentation material (Morita, Tokyo, Japan). Osteotomy sites in the control group will be closed without placing bone filling material or membrane. For multirooted teeth with noncommunicating osteotomy sites, one osteotomy site is designated as control, and the other site is filled with Foundation bone filling material. Treatments for all patients in control and experimental groups follow the standard of care practices, routinely performed based on surgical guidelines as outlined in Kim and Kratchman, J Endod 2006.

Patients are thoroughly informed about the nature of the surgical procedure and are briefed about potential risks and alternatives by the resident performing the surgery. The performing resident obtains a written consent form for the surgical procedure. The co-investigator briefs the patient about the nature of the study and obtains a separate written consent form for participation in this study. The resident performing the surgery evaluates and treatment plans the case through a clinical and radiographic examination of the involved teeth. Radiographs of the involved tooth and limited-volume cone-beam computed tomography (CBCT) of the defect area are obtained during the consultation as routine protocol for root-end surgery requires. The lesion is assessed for size, location, and proximity to other anatomical structures such as infra-alveolar or mental nerves, sinus cavity, or adjacent roots. On the day of surgery, the resident conducts and completes the surgery as standard protocol requires, including medical history update, local anesthesia administration, flap elevation, and obtaining access to the root tips and the periapical lesion through the removal of bone. Using the surgical microscope, the lesion is examined, 3 mm of the root tip is resected, and the root is stained and inspected for root fracture, missed canals, or isthmus as routinely done during root end surgery. If the fracture line on the root surface is detected, the subject will be excluded from the study. The fractured tooth may be extracted, or the patient will be referred for tooth extraction at a different time after repositioning the flap and suturing. In all other cases, routine surgery will continue with 3 mm of preparation for root-end cavity using ultrasonic tips and filled with bioceramic putty (EndoSequence BC-RRM Fast-Set Putty; Brasseler, Savannah, GA, USA). A post-operative periapical radiograph is taken to verify the position of retrograde filling. The osteotomy site is

then curetted to induce bleeding inside of the surgical site. The co-investigator conducts the randomization of the case. Using a publicly available randomization application, Randomizer for Clinical Trials, single-rooted teeth will be assigned as either control or test group receiving Foundation. For multirooted teeth, the mesial root will be randomized, and the distal root will receive the other treatment. For teeth assigned to receive Foundation, a sterile instrument is used to remove the material from the plastic container and placed in the osteotomy site. In the control group, the osteotomy site is left unfilled, flap repositioned, and sutures placed. Patients are given post-operative instructions and scheduled for follow-up and suture removal 3-5 days after the surgery. PDM chart number, which is patient-specific are accessed only by the provider, PI and co-investigator (for follow-up procedures). Tooth number, gender, age, and list of potential clinical symptoms, the date of surgery (necessary only for a description of the study population for publication) are collected and forwarded to the principal investigator (PI). Several prognostic factors are evaluated such as subject's sex, age, tooth involved, diagnosis, clinical symptoms, lesion classification, treatment rendered before EMS (primary non-surgical root canal treatment, nonsurgical retreatment, previous history of apical surgery). Preoperative CBCT scan is evaluated for the following possible prognostic factors:

1) Presence of cortical plate fenestration. This information was verified clinically during surgery.
2) Thickness of the buccal bone: measured 3 mm coronally from the apex on the B-L view.
3) Lesion size: height, depth and width of the lesion were measured. The value of the largest dimension was recorded as the lesion size.
4) Root angulation: measured between the long axis of the root and a line tangent to the cortical plate at the resection area.

Follow up visits are scheduled, as routinely practiced, every six months following the procedure. At six-month follow-up, periapical radiographs is taken. At 12-month follow-up, digital periapical radiographs and CBCT are obtained. In all follow-up visits, clinical signs and symptoms are evaluated. Molven's success criteria is applied to evaluate healing with periapical radiographs. For outcome assessment, cases will be designated as complete healing, incomplete healing, uncertain or unsatisfactory healing. Healing assessment on CBCT will be classified using modified PENN criteria as complete healing, limited, uncertain, or unsatisfactory healing. In complete healing, there is complete bone repair covering the resected root area, and the periodontal space is reformed with normal width or less than twice the width of the non- involved parts of the root. On the other hand, limited healing is characterized by complete healing in the vicinity of the resected root, but there is a discontinuity of the cortical plate with areas of low density. Low-density areas might also be present asymmetrically around the apex in limited healing or in the former access osteotomy. When the location of the low-density area is symmetrical around the apex or when the thickness is larger than twice the width of periodontal space, healing is classified as uncertain. Lastly, in unsatisfactory healing, the area of low density appears enlarged or unchanged. The co-investigator will be available during the follow-up appointments. All radiographs taken will be coded by case number (derived from the randomization table) and a suffix designating the time the radiograph was taken. Radiographs will be taken at three-time intervals PRE (preoperative, periapical, and CBCT), POP (immediate post-operative, periapical), FU1 (6-month follow-up, periapical), and FU2 (12-month follow-up,

periapical and CBCT). Hence, every single radiograph can be traced accordingly by case number and interval. For example, 002-FU2 equals 12- month follow-up of case number 2. The co-investigator will not evaluate the radiographs herself, since she will be the only one able to reconnect case radiographs with the treatment used. Three calibrated endodontists (Examiner 1, 2, and 3) will evaluate the radiographs, blinded to the treatment used. Reviewers will assess the radiographs in a dark room using the same imaging software and taking standardized breaks. Preoperative and follow up CBCT will be assessed as described above using PENN 3D criteria. Cases with disagreement will be discussed until joint agreement is reached. Results will be recorded on an excel based score sheet and forwarded to the PI. After all radiographs are jointly agreed on by the examiners, without the interference of the PI, the PI will use the final score sheet(s) and rejoin the information obtained from the calibrated radiograph examination with the data from the material randomization table and information on possible clinical symptoms.

Statistical Analysis:

For subjects returning for 1 year follow up, the following statistical tests are completed:

1) Fisher's exact test to evaluate significant association between different healing categories and prognostic factors.
2) Logistic regression models were performed to assess odds of complete healing as a linear combination of prognostic factors.

The osteotomy site was considered as the unit of analysis. A probability of $P < .05$ was assigned as the level of significance.

Multiple imputation analysis was performed for cases lost to follow up using SAS statistical software to evaluate the association between the treatment arm and a particular outcome variable (2D healing, 3D healing, 2D outcome and 3D outcome). Under missing at random assumption (MAR), logistic regression analysis using all the variables from the completed cases was used to impute the missing data. Chi-square test for the independence between the outcome variable and treatment variable is carried out for each imputed data and results are pooled to generate a single p-value.