Protocol #: 18-1722
Project Title: Histologic Comparison of Healing After Tooth Extraction with Ridge Preservation Using Two Different Xenografts
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I. Hypotheses and Specific Aims:

1) There will be additional vital bone at 16-20 weeks with Salvin-Oss®.
2) To compare the clinical and histological outcome of using Bio-Oss® or Salvin-Oss® in a tooth extraction ridge preservation model.

II. Background and Significance:

Dental implants have become a predictable and reliable therapy in the replacement of missing teeth. [1-3] Extraction sites that are not grafted for ridge preservation may lose up to 50% of their ridge width the first year after extraction. [4-6] Ridge preservation is a simple procedure that has proven to decrease the loss of ridge width during healing. [7-9] Multiple graft products are on the market, such as allografts, xenografts, and alloplasts. All have been used in ridge preservation techniques in an attempt to maintain the ridge width after the tooth was extracted. For this study we focus on xenografts to preserve alveolar bone after tooth extraction prior to placement of a dental implant.

Xenografts are commonly used materials for bone growth and bone contour augmentation techniques. Xenografts have been shown to have osteoconductive potential, [10] similar to that of the allografts [11], in addition to providing a scaffold for space maintenance. [12] The turnover of the xenograft particles has been shown to be longer than that of allografts[13] which may be beneficial in maintaining the volume of tissue in the area. Prior studies have compared demineralized freeze-dried bone allograft (DFDBA) and freeze-dried bone allograft (FDBA) for

percentage of vital bone[14], however currently there is no study comparing the two most common used xenografts on the market, Bio-Oss® and Salvin-Oss®. The use of xenografts is routine care, and the selection of the specific product is currently based on the cost to obtain the material and provider preference (e.g. personal handling preference). The purpose of the current study is to compareBio-Oss® and Salvin-Oss® in the preservation of alveolar bone after extraction of non-molar teeth. Bio-Oss® is a bovine product while Salvin-Oss® is porcine. Both products that have similar manufacturer stated outcomes. Bio-Oss® has been on the market longer than Salvin-Oss® and is more costly. Both are FDA approved for bone grafting techniques in humans.

The primary objective is to histologically evaluate and compare the percentage of new bone formation in healing extraction sockets of non-molar teeth grafted with Bio-Oss® versus Salvin-Oss®.

The secondary aim is to observe clinical changes in ridge height and ridge width after grafting with these two materials.

III. Preliminary Studies/Progress Report: none

IV. Research Methods

This is a single site, open label, randomized study, comparing two FDA-approved xenografts, Bio-Oss® and Salvin-Oss®.

A. Outcome Measure(s):

1) Histologically measure % vital bone, % residual graft, % of connective tissue

2) Clinically measure:

- **a.** the change of ridge height on the buccal and lingual
- **b.** change of ridge width
- **c.** % change of ridge width

B. Description of Population to be Enrolled:

40 patients, who must be active, non-emergency patients at the University of Colorado School of Dental Medicine Graduate Periodontics Department will be enrolled in this study. Subjects will be included if they are at least 18 years of age, consent to be in the study, planned for non-emergent dental treatment, and ASA Class I or II.

Patients who qualify must require extraction of a single-rooted non-molar tooth and are interested in receiving a dental implant at the site of tooth extraction. Patients must be committed to have the dental implant placed 16-20 weeks after extraction and ridge preservation

Inclusion criteria: 1) adequate restorative space for implant-retained restoration; 2) $\geq$10mm alveolar bone height without impingement on the maxillary sinus or inferior alveolar canal; 3) root location and angulation that would be consistent with the subsequent implant placement. To ensure an adequate depth of socket for harvesting a bone core biopsy without inclusion of native bone all roots should have a minimum of 10mm of radiographic bone support, and have angulation similar to the angulation of the implant to be placed at the site.

Subjects will be excluded if <18 years old, currently pregnant or require antibiotic prophylaxis prior to dental procedures as outlined by the 2017 American Heart Association guidelines, decisional challenged adults, are a current smoker or ASA Class III or IV.

Study Design and Research Methods

Patients will be randomly assigned (1:1) to one of two treatment groups (Bio-Oss® or Salvin-Oss®) at the time of surgery through random selection of sealed envelopes.

The xenograft materials to be studied, Bio-Oss® and Salvin-Oss®, will each be obtained from a single batch. This request for single batch materials will be given to the manufacturer prior to shipment of the bone material.

All bone material will be ground to a particle size ranging from 250-1000um per the manufacturer.

3) Measuring of clinical endpoints (as described below):

- **a.** the change of ridge height on the buccal and lingual
- **b.** change of ridge width
- **c.** % change of ridge width

Surgical procedure (Routine Care, except where indicated as research only):

The identified tooth will be extracted per standard of care in a minimally traumatic manner with either no flap or minimal flap reflection no more than 2mm beyond the alveolar crest, followed by curettage and irrigation of the socket. The socket will be thoroughly examined for defects, such as dehiscences or fenestrations. As previously described by Beck and Mealey[15] a University of North Carolina (UNC) periodontal probe will be used to make the following clinical measurements: the height of the buccal and lingual crest will be measured by using a UNC periodontal probe to connect the midfacial cemento-enamel junctions of the adjacent teeth, and then the vertical distance from that reference line to the crest of bone on the midfacial and midlingual will be measured. Calipers will be used to measure the ridge width as well as buccal plate thickness 2mm from the crest of the ridge at the midfacial aspect to the nearest 0.5mm. All measurements will be performed by one of two examiners that will be calibrated. All surgeries will be performed by periodontal residents under the direct supervision of board-certified attending faculty. The faculty will then select the xenograft product to be used based on the

product identified in the sealed envelope. While the measurements are being completed, the randomly selected graft material (Bio-Oss® or Salvin-Oss®) will be hydrated with sterile water. The socket will be filled to or slightly coronal to the crest of the bone. A resorbable collagen membrane material will be placed over the graft material and will be secured over the socket orifice with non-resorbable sutures (this is the standard of care for site preservation techniques). Flaps will not be reflected unless a minor dehiscence is detected. In cases in which there is a bony dehiscence, small flaps will be reflected just beyond the extend of the dehiscence and a collagen membrane material will be used to cover dehiscence (per standard of care). Only minor dehiscences will be accepted; if the depth of the dehiscence is 50% or greater the depth of the socket, the participant will be excluded from the study. Post-operative instructions will be given to the patient along with post-operative analgesics and antibiotics. Sutures will be removed 2 weeks after ridge preservation procedure (per standard of care).

Patients will return approximately 3 months after the extraction for a cone-beam computerized tomographic scan (CBCT), which is the standard of care for implant placement work up. At the time of implant placement 16-20 weeks after extraction, there will be minimal buccal and lingual flap reflection, and ridge width as well as buccal and lingual height measurements will be made as previously described.

In routine care, the first step in implant placement is creating an osteotomy site with a 2.0mm diameter twist drill and suctioning away the removed bone.
For this study, we will not use a twisted drill, but rather a trephine drill with a 2.0mm internal diameter and a hollow center. This will allow us to save a core biopsy approximately 8mm in length, rather than discarding the drilled-out bone. The core biopsywill then be placed in 10% neutral-buffered formalin. This use of the hollow trephine drill is the only research procedure in this study, and will allow us to obtain bone for histological analysis.

Following collection of the core biopsy material, the osteotomy is enlarged to slightly smaller dimension than the actual implant being placed. The smallest implant diameter on the market is 2.9mm.

Histological samples will be stained with Harris's hematoxylin and counterstained with treosin. Each section will be examined at 20X magnification, with the entire area of the section evaluated. Similar to Wood and Mealey[14], image manipulation software will be used to create individual layers of vital bone, residual graft particles, and CBCT/other. These layers will be converted to a binary (black and white) form, and area by percentage of each of the three layers will be digitally calculated based on number of pixels using image analysis software.

C. Description, Risks and Justification of Procedures and Data Collection Tools:

The UNC periodontal probe and caliper are used routinely in clinical practice to chart periodontal values.
CBCT are used since they deliver lower radiation than medical grade CT scans and are routinely taken as standard of care for implant placement.
The risk of using the hollow drill to obtain a core biopsy is no greater than the risk of using a twisted drill and discarding the drilled our bone material.

D. Potential Scientific Problems:

A potential dropout rate of 30% was anticipated with the number of patients needed for statistical significance.

E. Data Analysis Plan:

Unpaired Student *t* tests will be used for between-group comparison of ridge dimensions and of percentages of newly formed vital bone, residual bone graft particles, and CT/other. Mann-Whitney U tests will be performed to confirm significant findings based on *t* tests. Discrete measure comparisons for treatments will be performed using Fisher exact tests. For all tests, $P<0.05$ will be considered significant. Pearson correlations will be used to assess the relationships between the histologic bone core percentages for the three tissue groups. Spearman correlations will be used to evaluate relationships between the histologic percentages and the clinical ridge dimension changes in each group.

G. Summarize Knowledge to be Gained:

If there is more vital bone at an earlier time point in Salvin-Oss® than Bio-Oss® then a clinician may re-enter the site at an earlier time point for implant placement.

H. References:

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