<u>Protocol Title</u>: The Esthetic Effect of Bio-OSS Collagen® on the Mid-facial Gingival Dimensions When Placed Into Gaps Between 3i® Implants Placed Into Fresh Extraction Sockets and the Labial Plate of Bone

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Background

Dental implants have traditionally been placed in a two stage surgical procedure. Initially, the implant body is placed, followed by three to six months later for the connection of the implant to the abutment. The implant is finally loaded when a prosthetic restoration is affixed to the abutment. Today, evidence exists which reveals that immediately loaded implants may have survival rates that are equal to those of implants loaded after a time delay. Mijiritsky et al. (2009) showed a survival rate of non-functional immediately loaded implants of 95.8%. The amount of dimensional changes of the soft tissues, however, has been poorly documented in the literature. A study by Cardaropoli et al. (2006) evaluated peri-implant tissue alterations in the maxillary anterior region and found 0.6mm apical displacement of labial tissues. However, their approach employed the two stage surgical procedure. Therefore, many questions remain in regard to the clinical success of immediately loaded implants. Following tooth extraction, the alveolar ridge undergoes remodeling of the buccal and lingual walls of the extraction socket, with more pronounced bone loss on the buccal aspect. The placement of an implant into a fresh extraction site does not prevent bone remodeling (Araujo, 2005), and therefore, these ridge alterations must be considered when placing immediate implants, especially in the esthetic zone. After installation of implants into fresh extraction sockets, marginal circumferential defects of varying sizes usually exist.

Whether complete bone fill may occur, regardless of the size of the gap distance between the buccal plate and implant, is still a question to be answered. Botticelli et al. (2004) found that marginal gaps of 3.4 mm can heal with substantial bone formation without the use of barrier membranes or filler materials. Also, a convex surface such as a properly designed provisional restoration provides a template against which soft tissue can heal and remodel (Weinlander, 2010). Ideally, it will allow for adequate bulk of tissue formation and proper emergence profile while meeting esthetic demands and protecting any graft material placed in the gap. Studies have also addressed the effect of gingival biotype on hard and soft issues in immediate extraction implant procedures in the esthetic zone (Kois, 2001, Kan, 2011). Kan (2011) reported apicoocclusal facial gingival tissue stability following immediate implant placement in the maxillary esthetic zone without guided bone regeneration, favorable success rates and peri-implant tissue responses. Although this study reported spontaneous interproximal papilla regeneration, there was however, continued overall facial recession, more so in the thin soft tissue biotype than the thick tissue biotype. Raes at el. (2011) reported successful results and less vertical recession of the facial gingival with a flapless surgical approach during immediate implant placement in thick biotype cases where the bony walls are intact and proper treatment planning with diagnostic tools is executed in appropriate cases. It is a challenge to measure changes in soft tissue width because this dimension is difficult to assess and reproduce. Windlisch et al. (2007) described a new method to measure intra-oral volume changes based upon an optical system which scans the intraoral anatomy with a camera (Schneider, 2003.) In an in vitro study, several datasets of 3-D objects were captured and volumetric differences measured. The results were highly accurate and reproducible. The same method was reported by Strebel et al. (2009) and Schneider et al. (2010) to measure soft tissue changes of the dental papilla, alveolar ridge and buccal mucosa. In a recent study by Thoma et al. (2010), soft tissue

volume gain with a newly developed collagen matrix was evaluated in chronic ridge defects compared to sub-epithelial connective tissue grafts in dogs. Casts were obtained and soft tissue changes were digitally analyzed. The aim of the current study is to evaluate the soft tissue dimensional changes after extraction of teeth in the esthetic zone, when combined with the placement of implants into these fresh extraction sockets. Furthermore, the effect of placing a graft material, Bio-OSS Collagen®, into the gap between the 3i® implant and the labial plate of bone will be evaluated after an immediately loaded provisional restoration is placed.

Study Design

This is a single-blind, randomized, controlled, single-center study:
32 subjects will have an immediate implant placed in the maxillary anterior region (#4-12) after extraction of a hopeless tooth. 16 subjects will be randomly selected to receive Bio-Oss Collagen® (Test group) and 16 subjects will have no graft (Control group) in the gap between the implant and the labial plate of bone.

Hopeless maxillary anterior teeth will be extracted and implants will be placed in a flapless procedure. Implants will be immediately loaded with provisional restorations once determined that the implant is stable. Changes in vertical height and horizontal dimensional changes of the free gingival margins will be evaluated at 3, 6, and 12 months post-immediate implant placement. Both groups are only different by the draft that will be placed at the time of implant placement. Both treatment choices are currently standard of care in immediate implant therapy. Patients will only be include into the study if the extraction socket is intact as outlined below and, therefore, immediate implant placement with or without drafting would be possible. If patients decide not to go ahead with the study, treatment could be performed either way in our clinic. Both methods are standard of care.

Based on the literature (see above and here):

Cornelini R, Cangini F, Covani U, Wilson TG Jr. Immediate restoration of implants placed into fresh extraction sockets for single-tooth replacement: a prospective clinical study. Int J Periodontics Restorative Dent. 2005 Oct;25(5):439-47.

De Rouck T, Collys K, Cosyn J. Immediate single-tooth implants in the anterior maxilla: a 1-year case cohort study on hard and soft tissue response. J Clin Periodontol. 2008 Jul;35(7):649-57. Epub 2008 Apr 16.,

Mijiritsky E, Mardinger O, Mazor Z, Chaushu G. Immediate provisionalization of single-tooth implants in fresh-extraction sites at the maxillary esthetic zone: up to 6 years of follow-up. Implant Dent. 2009 Aug;18(4):326-33.).

Immediate implant placement can be done with or without grafting. An intact socket does not necessarily require grafting. Currently, both procedures (placement with grafting and without grafting) are considered standard of care). One group will receive grafting and the other group

will receive no grafting. Whether the patient can really participate in the study can only be decided after the socket has been evaluated and has been classified as intact (no buccal bone loss, no dehisced bone). Nevertheless, patients will sign study consent before the surgical treatment at the time of initial consultation. If the socket has been compromised during extraction and an immediate implant placement will not be possible, patient will not proceed with study implant therapy and will continue his treatment in the clinic. A standard of care treatment would be to place a delayed implant at a later time point. There is no risk involved in participating in the study since both treatment choices are standard of care.

Statistical Procedures

Our current study aims to analyze dimensional stability after immediate implant placement in fresh extraction sockets. We will simultaneously graft the socket with a synthetic combination bone material and compare it to sockets that will not be grafted. Currently, there are no randomized controlled clinical studies available that compare these two different treatment modalities. However, we will use a randomized controlled study that compared different socket /implant treatments (immediate versus delayed implant placement). They found a difference in buccal/lingual dimensional stability (1.9 in an immediate group versus 3.06 in a delayed group) (Covani et al, 2004). In order to detect a difference of 10% with a power of 80% at a significance level of 0.05 between control and study group, we will need to perform at least 16 procedures per group. Primary efficacy variable is the height and thickness of keratinized tissue at 3,6,12, 24 months post surgery. Post surgery assessment of recession width, color, texture and contour ratings, marginal gingival level, biotype assessment are secondary variables. Summary statistics (mean, SD, median, p25, p75, min, max) will be calculated for all measured variables in each group. Results between both groups will be compared using the Student's t-test for normal distribution and the Mann- Whitney-U test for a non-parametric distribution of values. Categorical values will be compared using the chi-square test. For secondary analyses, we will use appropriate parametric or nonparametric tests to compare group differences.

Confidentiality of Study Data

Confidentiality of Study Data Patients will receive a study number that corresponds the medical record number. Notes and evaluation results during the visits will be recorded electronically or on paper. All paper information will be entered into a Microsoft Excel database for storage and/or stored in a locked cabinet. All consent forms, after being 09/18/2015 signed by the patient and the study documentations will be kept in a locked cabinet in the principal investigator's office. Besides the personnel involved in the study, the following parties may review or copy consent forms, dental records or study documentation: The sponsor and their designees; Agents of the FDA; CUMC and OHRP. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Furthermore, the aggregate results of this study may be used for teaching purposes, at meeting, or in publications, the subject's identity will not be disclosed in these presentations. Electronic data will be stored on encrypted end user devices.

Study Procedures

At the present time, grafting or no grafting at the time of implant placement can be considered standard of care. We will take measurements to compare both groups. How measurements are taken is outlined below:

The surgical technique is described as:

1. Administration of 2000mg Amoxicillin-1 hour prior to surgery. For patients allergic to Amoxicillin, 600mg Clindamycin 1 hour prior to surgery will be substituted.
2. Administration of local anesthesia and impression using alginate will be taken to measure ridge dimensions.
3. Extraction of hopeless tooth will be performed without a flap. Dental extractions are usually done without raising a flap. Only if the tooth is very compromised and the tooth is difficult to access, a flap needs to be raised. Extraction sockets will be evaluated to determine whether it is intact and has no lesion or shows signs of bone loss. This can be done using a periodontal probe. Dental implants will only be placed if the socket is intact.
4. Check for labial plate of bone that is <4mm from the gingival margin.
5. Placement of implant into socket towards palatal wall.
6. Measure:
    a. Thickness of buccal plate 1 mm from crest with special calipers.
    b. Distance from buccal of implant to buccal crest of bone (horizontal gap distance).
    c. Vertical depth of gap on facial aspect of implant
    d. 16 subjects will randomly get Bio-OSS Collagen® packed firmly into gap.
7. Place temporary abutment and fabricated screw-retained provisional.
8. No sutures will be used since no flap was raised. However, if at the surgeon's discretion sutures were indicated, they will be placed. An X-ray will be taken after implant placement. This is standard of care. However, a half arch alginate impression will be taken and attached to the rim that is being used to hold the X-ray film. This way the patient will always bite down in the same way and the X-ray will always be shot in the same angulation.
9. Take 2nd alginate impression:
10. Placement of subject on appropriate analgesic (i.e. Acetominophen with or without codeine #3 or #4, or Motrin 600mg, or Vicodin 500/5/1-2 tabs q6h prn. Rinses with 0.12% Chlorhexidine Gluconate BID for 14 days.
11. Subject will be seen at 1 week post op.
12. Subject will be seen at 3,6 and 12 months. At each of these visits, alginate impressions will be taken and digitally scanned and analyzed. At 6 months, periapical film will be taken and pick-up impression with open tray impression coping.
13. Deliver screw retained final restoration with zirconia framework and pressed lithium disilicate.
14. Take 6th alginate impression. At one year (6 months after delivery of final restoration.) Measure Vertical height of free gingival margin from MGJ Visits 1, 2, 4-6. Measure horizontal dimensional change to tenth of mm using calipers 1mm, 2mm below gingival margin at Visits 1, 2, 4-7.

15. All models created from alginates will be poured with Whip Mix labstone. All models used for fabrication of the final crown will be poured in silky Rock (Whip Mix) or Resin Rock (Whip Mix).
16. Measurements will be done by scanning the facial tissues on each model and then superimposing them on the original one. The difference in height (wKT) and facial-lingual dimension (thickness or tKT) of the free gingival will be evaluated at 3, 6 and 12 months.
17. The cast that was used for the final crown will be evaluated for facial thickness of tissue by measuring one mm and 2mm below the margin of the free gingiva.
18. Images of the implant crown, the surrounding gum tissue and the neighboring teeth will be shown to people outside of the study and they will be asked to rate the color change of the gum tissue.
19. De-identified data will be transferred from Columbia to Jena University. Transfer will be done using an encrypted external device. Data will be stored on a desktop computer at Jena University. The computer is password protected.

Recruitment

Patients will be recruited from patients who present to the Division of Periodontics, Postgraduate Periodontology, College of Dental Medicine, Columbia University for bilateral sinus augmentation and subsequent implant placement. They should be over the age of 18 and meet the eligibility criteria. Subjects are clinical patients and the treating physician will provide the contact information of the study team to subjects.

The treating dentist will make initial patient contact. After evaluating the patients, the patient will be made aware of the study and it will be made clear that participation is completely voluntary. When the patient agrees to participate, the study examiner will verbally inform and consent the patient (listed on consent form). In addition, examiner and subject will sign consent and HIPPA forms. Two copies will be made one for the subject and one copy will be for the study records.

Potential Risks

As with any surgical procedure, complications may occur as part of the surgical protocol. Possible complication related to an implant surgery are:

1. Allergic or other unfavorable reaction to medications
2. Pain and/or swelling
3. Hematoma or bleeding
4. Infection
5. Change in appearance of the teeth or soft tissue (gum tissue)
6. Change in function and chewing comfort
7. Change in sensation on the palate and lip
8. Loss, fracture or loosening of the temporary crown
9. Bone loss around implant

Study Population

Subjects will be selected from the patient population Division of Periodontics, College of Dental Medicine Columbia University School of Dentistry, New York, NY according to stated inclusion and exclusion criteria. A total of 32 subjects with the need for a single tooth maxillary immediate implant (#4-12).

Inclusion Criteria

1. Subject must have read, understood and signed an informed consent form.
2. Subjects must be willing and able to follow study procedures and instructions.
3. Subjects must have labial plate of bone present after extraction no more than 4 mm from the free gingival margin.
4. Subjects must require one maxillary anterior implant.
5. Subjects must be older than 18 years.