

A VOLUMETRIC ANALYSIS OF SOFT AND HARD TISSUE HEALING FOR RIDGE PRESERVATION AND SOCKET SEAL AFTER TOOTH EXTRACTION

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1.0 INTRODUCTION

Anatomical changes and physiological processes taking over tooth extraction were studied in the past (Cryer 1916, Rogers and Applebaum 1941, Pietrokovski and Massler 1967), however since the introduction of dental implants in modern odontology these issues and the prevention of edentulous jaw atrophy have become an important topic. The survival of implants and their ability to provide adequate function and esthetics are strictly correlated with their proper positioning in relation to the alveolar housing, the neighboring teeth and the occluding dentition. It is thus easily understood the tremendous effort that has been used by many researchers and practitioners in reducing this unavoidable modeling and remodeling process.

1.2 ALVEOLAR RIDGE REMODELING

Maxillary and mandibular bony complexes are composed by several anatomical structures with a proper function, composition and physiology: i) basal bone that develops together with the overall skeleton, and forms the body of mandible and maxilla; ii) alveolar process that develops following tooth eruption and contains the tooth alveolus; iii) the bundle bone that lines the alveolar socket, extends coronally forming the crest of the buccal bone, and makes part of the periodontal structure as it encloses the external terminations of periodontal fibres (Sharpey's fibers).

After tooth extraction, bundle bone appears to be the first bone to be absorbed (Boyne 1966, Hsieh, Devlin et al. 1994, Devlin and Sloan 2002) whereas alveolar bone is gradually absorbed throughout life (Carlsson and Persson 1967, Ashman 2000). The remodeling process results in a ridge morphology reduced in vertical height and more palatal in relation to the original tooth position (Cryer 1916, Rogers and Applebaum 1941, Pietrokovski and Massler 1967, Pietrokovski and Massler 1967).

Studies from the Lindhe's group suggest bone resorption to occur in 2 phases (See Figure 1). During the first phase, bundle bone is rapidly resorbed and replaced with woven bone leading to a great reduction in bone height especially in the buccal aspect of the socket, as its crestal portion is comprised solely of bundle bone (Araujo and Lindhe 2005). In-vitro animal studies have demonstrated the osteogenic potential of PDL derived cells (Cho, Matsuda et al. 1992, Ramakrishnan, Lin et al. 1995) although the role of bundle bone in providing cells for the regeneration of new bone has been more recently challenged (Steiner, Francis et al. 2008) as new bone formation appears to initiate from the surrounding alveolar bone cells (Boyne 1966, Hsieh, Devlin et al. 1994, Devlin and Sloan 2002). Lindhe's group reported that the presence or absence of PDL in the extraction

socket does not influence the features of healing after 3 months (Cardaropoli, Araujo et al. 2005). During the second phase, the outer surface of the alveolar bone is remodeled causing an overall horizontal and vertical tissue contraction. The reason for this remodeling process is still not well understood. Disuse atrophy, decreased blood supply, and localized inflammation might play important roles in bone resorption. However, it is now apparent that bone remodeling is a complex process involving structural, functional, and physiologic factors and that surgical trauma from extraction induces microtrauma to surrounding bone, which accelerates bone remodeling (Garetto, Chen et al. 1995).

Resorption rate of the alveolar ridges is faster during the first six months following the extraction (Pietrokovski and Massler 1967, Johnson 1969) and proceeds at an average of 0.5-1.0% per year for the entire life (Carlsson and Persson 1967, Ashman 2000). The height of a healed socket never reaches the coronal level of bone attached to the extracted tooth and horizontal resorption seems to be greater in the molar region compared to the premolar area (Schropp, Kostopoulos et al. 2003, Hammerle, Araujo et al. 2012). Schropp *et al.* estimated two-thirds of the hard and soft tissue changes occur in the first 3 months. The authors reported 50% of crestal width to be lost in a 12-month period (corresponding to 6.1 mm; range 2.7 to 12.2 mm) 2/3 of which (3.8mm; 30%) occurred in the first 12 weeks. When examining the premolar area only a loss of alveolar ridge width of 4.9mm (45%) was reported, of which 3.1mm (28.4%) occurred in the first 12 weeks (Schropp, Wenzel et al. 2003). A recently published systematic review (Tan, Wong et al. 2012) reported a greater horizontal alveolar ridge reduction (29-63%; 3.79 mm) than vertical bone loss (11-22%; 1.24 mm on the buccal, 0.84 mm on mesial and 0.80 on distal sites) at 6 months. In a long-term study, Ashman reported alveolar bone shrinkage of 40-60% in height and width within the first 2-3 years (Ashman 2000, Ashman 2000).

1.3 SOCKET HEALING

Immediately after tooth extraction, the alveolar socket is filled by blood clot that is replaced by granulation tissue within 1 week (see Figure 1) (Amler 1969). In the healing of a skin wound, epithelial cells migrate underneath and are protected by the blood clot. In socket healing instead, the epithelium migrates over the granulation tissue to cover the healing socket (Mangos 1941). This happens because this inflammatory tissue is recognized as a connective tissue by the epithelial cells therefore cellular migration occurs over its surface. This is important when we examine Guided Bone Regeneration applied to socket grafting. Starting from the apical and lateral residual bony walls the granulation tissue is rapidly remodeled to provisional matrix. Mineralizing processes occur leading to the formation of woven bone that eventually is replaced by mature lamellar bone (Trombelli, Farina et al. 2008).

Early human histological investigations reported that extraction sockets are filled with delicate cancellous bone in their apical two thirds at 10 weeks, and are completely filled with bone at 15 weeks (Mangos 1941). Increased radiopacity is demonstrated as soon as 38 days and radiopacity similar to that of the surrounding bone at 105 days (Mangos 1941). These figures might be partially biased as specimens were harvested from cadavers therefore their late age and their systemic condition might have led to delayed wound healing capabilities. On the other side, animal studies demonstrate accelerated healing as 3 weeks old extraction sockets in humans compare with to 9-10 days old sockets in dogs and a 3½ months sockets in humans compares with 8 weeks sockets in dogs (Clafin 1936).

1.4 RATIONALE FOR EXTRACTION SOCKET PRESERVATION

Bone formation in the alveolar socket is a naturally occurring event as long as surrounding alveolar walls remain intact; however the alveolar ridge volumetric contraction may impair proper implant placement. To reduce loss of alveolar bone to acceptable levels, several surgical techniques have been proposed. Reducing the extraction trauma and limiting flap elevation (Fickl, Zuhr et al. 2008) are essential for obtaining success in each of these procedures. Animal studies show mixed results when evaluating differences in ridge remodeling between flapped and non-flapped extraction sockets (Blanco, Nunez et al. 2008, Fickl, Zuhr et al. 2008, Fickl, Zuhr et al. 2008, Araujo and Lindhe 2009, Vignoletti, Matesanz et al. 2012) although it has been hypothesized that by disrupting the thin layer of cells that comprises the osteogenic layer of the adult periosteum, the elevation of a flap might diminish the ability of periosteal cells to regenerate bone while an undisturbed periosteum maintains its osteogenic potential (Melcher 1969, Melcher 1971, Melcher 1976, Araujo and Lindhe 2005). It is possible that flap elevation affects alveolar dimensional alterations only in the short-term (Tan, Wong et al. 2012). In guided bone regeneration 4 methods can be used to increase the rate of bone formation and to augment bone volume: osteoinduction by the use of appropriate growth factors; osteoconduction, where a grafting material serves as a scaffold for new bone growth; distraction osteogenesis, by which a fracture is surgically induced and bone fragments are then slowly pulled apart; and finally, guided tissue regeneration, which allows spaces maintained by barrier membranes to be filled with new bone (Hammerle and Karring 1998). Utilizing these concepts it has been proposed guided bone regeneration with non-resorbable and absorbable membranes, several types of bone grafts with or without use of barrier membranes or the addition of mucogingival treatments and more recently the use of bioactive molecules for the generation of bone in the extraction socket. When analyzing the results of the following described studies it should be kept in mind the goal of the additional service that is provided to the patient, which include:

- To enable installation and stability of a dental implant
- To reduce loss of alveolar bone volume
- To reduce need for additional bone grafting procedures
- To enable the generated tissues to provide implant osseointegration
- To improve the esthetic outcome of the final prosthesis
- To regenerate bone faster allowing earlier implantation and restoration

1.4.1 RIDGE PRESERVATION WITH BONE GRAFT

The clinical advantages of bone fillers in alveolar ridge volume preservation and prevention of additional bone grafting procedure are largely supported by the available literature (Sclar 1999, Iasella, Greenwell et al. 2003, Luczyszyn, Papalexou et al. 2005, Fickl, Zuhre et al. 2008). Minimal ridge remodeling has been observed when using non-resorbable hydroxyapatite crystals covered by a rotated pediculated split thickness palatal flap (Nemcovsky and Serfaty 1996), DFDBA covered with an ePTFE membrane (Brugnami, Then et al. 1996) or even allogenic or xenogenic bone grafts covered with nothing but a collagen plug (Sclar 1999, Wang and Tsao 2007) (Figure 1). Histological evidence demonstrates that bone formation occurs over the surface of the implanted osteoconductive graft particles (Artzi, Tal et al. 2000, Artzi, Tal et al. 2001). At 3 months or later grafted sockets generally demonstrate higher mineralized tissue figures, when considering both new vital bone and remaining graft particles, but the formation of new bone appears to be similar in grafted and non-grafted sites. It can be extrapolated that residual particles occupy part of the volume that would have been occupied by bone marrow if bone grafting were not adopted (Araujo, Linder et al. 2008).

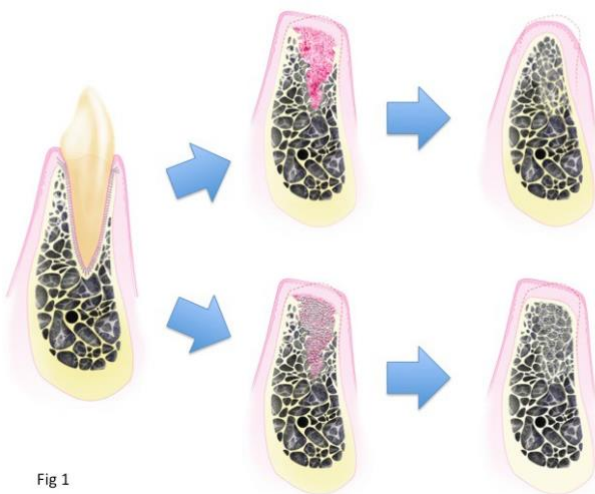


Fig 1

Figure 1. Healing of the extraction socket with and without socket grafting. When socket grafting is not adopted major alveolar ridge resorption occurs. In a first phase, initially the blood clot, subsequently the granulation tissue and later the provisional matrix and the woven bone fill up the alveolus. The bundle bone is completely resorbed causing a reduction in the vertical ridge. In a second phase the buccal wall and the woven bone are remodeled causing the horizontal and further vertical ridge reduction. When socket grafting is adopted, the first phase and vertical bone reduction still occur, however the second phase and the horizontal contraction are reduced.

At earlier healing stages (2 weeks) instead, grafted sockets demonstrate xenograft particles enclosed in connective tissue and coated by multinucleated cells when nongrafted sites already show newly formed woven bone occupying most of the socket (Araujo, Linder et al. 2009). This response is typical of a foreign body reaction which can be elicited by the xenograft and though it is clinically non-immunogenic, non-toxic and chemically inert (Luttikhuisen, Harmsen et al. 2006), it results in a delayed healing response during the earliest stages of socket healing. Many articles reported only a partial resorption of the grafted particles at short and long timepoints (Brugnami, Then et al. 1996, Becker, Clokie et al. 1998, Iasella, Greenwell et al. 2003, Wang and Tsao 2008, Araujo, Linder et al. 2009, Mordenfeld, Hallman et al. 2010, Rasperini, Canullo et al. 2010) arising doubts on the achievement of the osteointegration of implants inserted in augmented sites and on the success of the restorative therapy. Histological animal studies (Fiorellini, Kim et al. 2007, De Santis, Botticelli et al. 2011) evaluated the osteointegration of dental implants following bone regeneration performed with different bone fillers and observed a bone-to-implant contact similar to that of implants placed in pristine bone (40% to 65%). Furthermore clinical studies observed that good primary stability can be reached at implant insertion, that the grafting procedure does not impair early osteointegration (Carmagnola, Adriaens et al. 2003, Molly, Vandromme et al. 2008) and that implants placed in bone regenerated using mineralized grafts are able to sustain loading and provide similar long-term results as those placed in pristine bone (Fiorellini and Nevins 2003).

Mineralized grafting materials may interfere with the earliest stages of socket healing and their elimination may require several years (Araujo, Linder et al. 2008) or they may in fact be nonresorbable even in the long term (Mordenfeld, Hallman et al. 2010). On the other side, their ability to prevent crestal ridge resorption and sustain long-term implant success has been clearly demonstrated (Carmagnola, Adriaens et al. 2003, Fiorellini and Nevins 2003, Molly, Vandromme et al. 2008).

Other advantages in the use of osteoconductive grafting material were reported by a clinical and histological human study of post-extractive defects in posterior maxillary area treated with a xenogenic graft. In this study, Rasperini *et al.* confirmed the space maintaining activity of the implanted material and reported a decreased demand for sinus lift augmentation procedure when the socket preservation procedure was performed (Rasperini, Canullo et al. 2010). Through a computed tomography analysis of maxillary anterior post extractive defects, Nevins *et al.* reported that 79% of grafted sites underwent less than 20% buccal plate loss, while 71% of nongrafted sites demonstrated more than 20% buccal plate loss. An interesting finding of this investigation was that even the experienced surgeons participating to this study were not able to predict the fate of the

buccal plate, therefore the authors suggested socket grafting to be performed at the time of extraction (Nevins, Camelo et al. 2006).

1.4.2 FREE SOFT-TISSUE GRAFT OVER MINERALIZED BONE GRAFT

The placement of free soft-tissue graft to cover the augmented alveolar socket was introduced to minimize the soft tissue shrinkage, optimize aesthetical results of implant restoration and obtain a primary closure that may preserve the graft from bacterial infections and secondary graft failure (Stimmelmayer, Allen et al. 2010, Thalmeier, Hinze et al. 2010). The first attempt to cover the socket graft with an autogenous soft tissue implant was described by Landsberg and Bichacho in 1994 (Landsberg and Bichacho 1994). Nevins *et al.* suggested the use of soft tissue grafts to improve ridge topography after tooth extraction (Nevins and Mellonig 1994) and in combination with immediate implant placement (Landsberg 1997).

In 1999 Tal described the survival of circular connective tissue grafts placed over extraction sockets treated either with DFDBA or Bio-Oss. They found that the survival was not dependent on the adopted graft and that at 1 week 18/42 grafts were vital, 13/42 were partially vital and 11/42 were non-vital. Complete closure of all sockets occurred 4 weeks post extraction. The Authors noted that more often partially vital grafts maintained their vitality over the socket area more than on the graft margins; they concluded that the nourishment could be originated from plasmatic elements in the socket blood clot more than from vessels originating from the periphery of the graft (Tal 1999).

1.4.3 GEISTLICH MUCOGRAFT® SEAL OVER MINERALIZED BONE GRAFT

The use of Geistlich Mucograft® is an alternative to autogenous soft tissue graft. The 3-D collagen matrix can be used for root coverage procedures and/or for gain of keratinized tissue (Nevins, Nevins et al. 2011, Lorenzo, Garcia et al. 2012). Geistlich Mucograft® Seal can be used over mineralized bone graft (BioOss® Collagen) after minimally invasive tooth extraction in order to preserve hard and soft tissue volume for future implant placement (Jung, Philipp et al. 2013). The collagen of Geistlich Mucograft® is processed to favor immediate blood clot stabilization. This leads to early vascularization (Ghanaati, Schlee et al. 2011, Rocchietta, Schupbach et al. 2012), facilitates soft tissue cell ingrowth (Ghanaati, Schlee et al. 2011), and excellent integration of the 3-D matrix within the surrounding tissues (Ghanaati, Schlee et al. 2011, Rocchietta, Schupbach et al. 2012). In a clinical trial, Thoma and collaborators evaluated whether Geistlich Mucograft® Seal could improve early wound healing and esthetics, and decrease wound sensitivity compared to spontaneous healing (Thoma, Sancho-Puchades et al. 2012). The authors reported that the defect area

decreased over time for both treatments and re-epithelization was completed in all subjects by day 15. The defect area was significantly smaller for the Geistlich Mucograft® Seal (mean \pm SD: 19.3 \pm 3.4 mm²) compared with control (21.3 \pm 3.3 mm²) at day 4 ($p < 0.05$), and at day 8 (Geistlich Mucograft® Seal: 11.7 \pm 2.5 mm²; control: 13.6 \pm 2.9 mm²; $p < 0.01$). The color match was more favorable for Geistlich Mucograft® Seal at day 4, 8 and 29 ($p > 0.05$). Somatosensory measurements revealed slightly lower wound sensitivity at day 4 for Geistlich Mucograft® Seal compared with control. Jung and investigators compared the use of Geistlich Mucograft® Seal along with BioOss® Collagen to 3 different socket preservation approaches; 1. BioOss® Collagen along with free gingival graft, 2. β -tricalcium-phosphate-particles with polylactid coating (β -TCP), and 3. Spontaneous healing (control). Results demonstrated that the application of BioOss® Collagen, covered with Geistlich Mucograft® Seal or Free gingival graft, resulted in less vertical and horizontal changes of the alveolar ridge as compared with controls 6 months after extraction (Jung, Philipp et al. 2013).

2.0 AIMS

Aim 1: To evaluate the clinical and radiographic changes following socket graft + use of collagen dressing or 3D-collagen matrix between baseline and month-6.

Aim 2: To evaluate the volume changes on soft tissue following socket graft + use of collagen dressing or 3D-collagen matrix between baseline and month-6, and wound healing assessment.

3.0 STUDY DESIGN

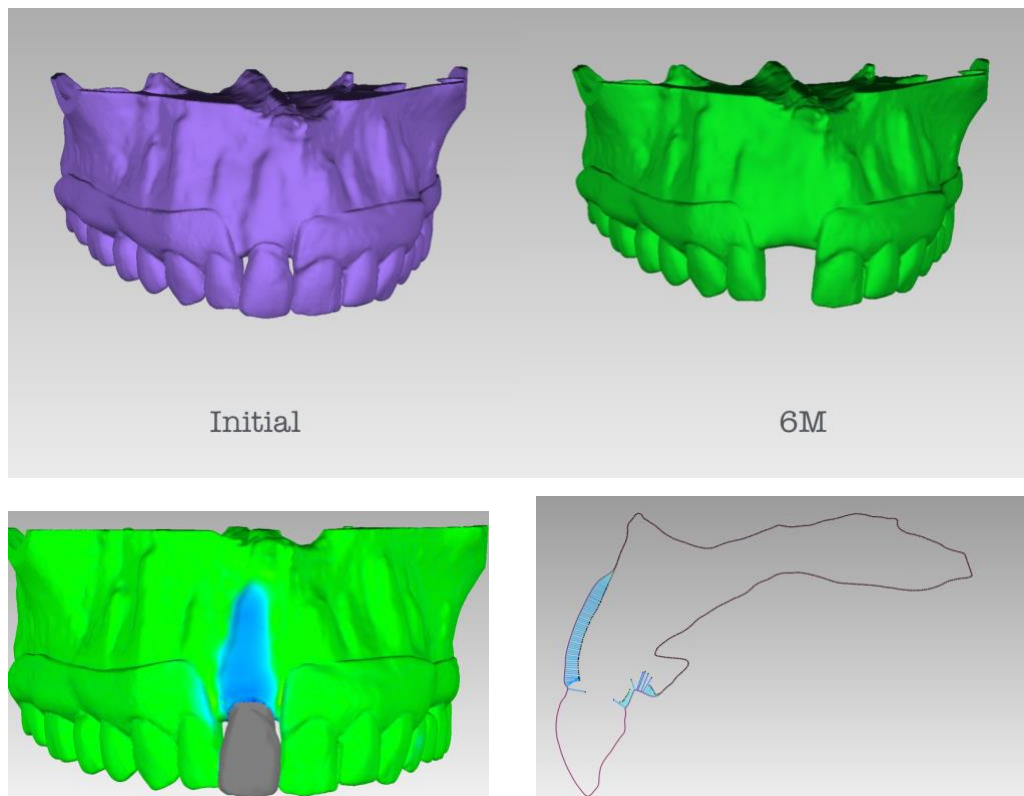
This study will be a randomized clinical trial involving a total of 24 subjects. We propose to recruit subjects into 2 groups: 1) Extraction treated with xenograft bone substitute (BioOss Collagen®) + collagen dressing (HeliPlug®), 2) Extraction treated with xenograft bone substitute (BioOss Collagen®) + 3D-collagen matrix (Mucograft Seal®). All subjects recruited will have already been approved and treatment planned for extraction + implant placement by non-study personnel to avoid any potential conflict of interest. All subjects will have radiographs that show the tooth planned for extraction. Each subject will be eligible for only 1 tooth extraction + dental implant rehabilitation. After tooth extraction, subjects will receive a standard site preservation therapy consisted with xenograft bone substitute + collagen dressing or the alternative site preservation therapy consisted with xenograft bone substitute + 3D-collagen matrix. After the conventional 6-month healing period, subjects will receive a dental implant in the previous extracted site. During the dental implant procedure, a 2x5mm bone core biopsy + a 2mm gingival biopsy will be obtained from the implant site.

Biopsy samples will be stored for future histological and histochemical analysis. After dental implant placement, all subjects will receive a healing abutment for soft tissue healing prior to implant restoration.

During the 6-month healing time after tooth extraction and site preservation therapy, subjects will return at week-1, week-2, week-4, month-3, and month-6 for intra-oral scanning for soft tissue volumetric acquirement. Subjects will receive a Cone beam computed tomography (CBCT) prior to extraction for the baseline hard-tissue volume measurement and appropriate extraction planning and at 6-month post-extraction for volumetric measurement and appropriate implant treatment planning.

Hard tissue analysis will be performed to compare linear ridge remodeling (baseline vs. 6-month healing). CBCT images will be analyzed by non-contact reverse engineering system (Geomagic software). Soft tissue volumetric analysis will be performed to compare the soft tissue healing between BioOss Collagen + Mucograft Seal and BioOss Collagen + Collagen Dressing. Images captured with an intra-oral scanner (Trios, 3Shape) collected at baseline, week-1, -2, -4, month-3, and month-6.

Figure 2. Surface analysis representation from baseline and month-6 post-extraction with blue surface representing the loss of hard-tissue after tooth extraction.



3.1 MASKING

This study will be conducted in a single masked manner such that all volumetric assessments will be performed without knowledge of the subjects' type of treatment.

3.2 RANDOMIZATION

Qualified subjects will be assigned randomly into one of two groups: 12 subjects into the xenograft + 3D-collagen group (Test) and 12 subjects into the xenograft + collagen dressing group (Control).

The study coordinator will place 24 identically sized slips of paper, 12 reading "Test" and 12 reading "Control", into a sealed envelope. The study coordinator will select one sealed envelope for each qualified subject, and record the randomization results and staple the slip of paper into the subject study folder.

4.0 HUMAN PARTICIPANTS

The subject population will be 24 adult patients recruited from the general population by means of advertisements and flyers in local media, and from the research patient database. These 24 subjects will be categorized into 2 groups: 1) Extraction treated with xenograft bone substitute (BioOss Collagen®) + collagen dressing (HeliPlug®), 2) Extraction treated with xenograft bone substitute (BioOss Collagen®) + 3D-collagen matrix (Mucograft Seal®). Subjects who require antibiotic prophylaxis prior to dental treatment or those with medical contraindication to dental treatment will be excluded. All study participants will read, have explained by study personnel, and sign a consent form that details the risks, benefits, and requirements for participation in the proposed study.

4.1 INCLUSION CRITERIA

- † Subjects must be adult males or females age 18 to 80 years (inclusive).
- † Subjects must be able and willing to follow study procedures and instructions in English.
- † Subjects must have read, understood and signed an informed consent form in English.
- † Subjects must have a maxillary premolar, canine, lateral incisor, or central incisor with a restorative or periodontal hopeless prognosis (Kwok and Caton 2007), in which an implant is indicated without any sinus lift required.
- † Subjects undergoing implant placement should be in adequate periodontal health prior to implant placement. This includes having probing depth ≤ 4 mm for all remaining teeth at the same quadrant of the proposed implant placement. Patients with periodontal probing sites with probing depths of up to 5 mm may also be included if bleeding on probing in these sites is absent. Each subject should be considered to be periodontally stable prior to the implant surgery.

4.2 EXCLUSION CRITERIA

- † Individuals who have a chronic disease with oral manifestations.
- † Individuals who exhibit gross oral pathology.
- † The use of either antibiotics or chronic use (more than 7 days) of NSAIDs within 1 month prior to screening examination.
- † Individuals that require antibiotic prophylaxis prior to dental treatment.
- † Chronic treatment (i.e. two weeks or more) with any medication known to affect periodontal status (e.g. phenytoin, calcium antagonists, cyclosporine, Coumadin) within 1 month prior to screening examination.
- † Uncontrolled diabetes mellitus (HbA1c >7) within 3 months prior to screening examination.
- † Individual with uncontrolled parafunctional habits, such as clenching and bruxing on objects, that could adversely impact implant survival.
- † Individuals with a history of intravenous bisphosphonates.
- † Individuals with active infectious diseases such as hepatitis, HIV or tuberculosis.
- † Current cigarette smokers.
- † Individuals who are known to be pregnant, breastfeeding or planning to become pregnant within 6 months.
- † Individuals with blood disorders (hemophilia) and /or currently taking anticoagulant medications, such as heparin, warfarin, or clopidrogel.
- † Individuals receiving any therapy known to affect healing, such as high dose corticosteroids, radiation therapy or chemotherapy.
- † Individuals allergic to topical or local anesthesia.
- † Individuals who require maxillary sinus augmentation prior to dental implant therapy.
- † Individuals with dehiscenced, fenestrated, or fractured labial/buccal alveolar bone plate determined after baseline CBCT or after tooth extraction where more than 50% of the buccal bone height is not present. In this case, if the surgeon determines that guided bone regeneration (bone graft and membrane) is needed to repair the defect, it will be done at no cost to the subject, but the subject will be excluded from the study protocol.

4.3 CONTINUANCE CRITERION

There should be no major changes in subjects' medical status during the entire study period for continuation of the protocol. Subjects not meeting this criterion may be withdrawn. Any observed infection around the implant will be reported as an adverse event and subject will be treated and followed until resolved. Clinical judgment of the dental provider will be used to determine presence and severity of undesired healing response. Clinical judgment will also be used when determining whether the dental implant should be removed upon poor healing response and/or infection.

4.4 SUBJECT IDENTIFICATION

At screening, participants will be assigned a 3-digit counter/screening number by the study center (001, 002, etc.). At treatment baseline/series, each subject will receive a unique 4-digit study number (1001, 1002, etc.) that will identify their group status in the study. Participants who do not complete the study will be replaced until 24 participants have completed the study.

4.5 RECRUITMENT

Participants will be recruited by advertisement from the patient, student, and staff population at the University of North Carolina at Chapel Hill. In accordance to UNC HIPPA Research Policy, a request to release PHI (both physical records and electronic records) for the purpose of research may be made to aid in potential participant recruitment. If additional participants are needed, they may be recruited from the general population. We will not recruit participants employed by any of the following UNC School of Dentistry departments: Prosthodontic, Periodontology or GO Health Center.

5.0 SCHEDULE OF PROCEDURES

Periodontally healthy subjects who are eligible and treatment planned for tooth extraction and implant placement will be recruited and examined for this study. Screening and examination procedures may encompass up to 9 outpatient visits over an approximate 8-month period.

5.1 PRE-SCREENING EXAMINATION

Subjects will contact the study coordinator by telephone for information regarding participation in the study. Study coordinator/assistant will perform a brief telephone interview to determine whether or not the patient will qualify based on age and basic inclusion and exclusion criteria. Study coordinator/assistant will read a list of basic inclusion and exclusion criteria to potential subjects and ask potential subjects if they believe they would qualify. Subjects indicating they may qualify would be scheduled for a screening examination appointment.

5.2 VISIT 1: SCREENING EXAMINATION

Study personnel will provide each study candidate with a written informed consent form at the initial visit prior to administration of any research related treatment. Prior to enrolling a subject, study personnel will explain to each subject the protocol, procedures and objectives of the study, and the patient's role in the study, before obtaining consent. Subjects will be given the opportunity to read the informed consent document. Study personnel will answer all questions that the subject may have and ensure that the subject understood all aspects of the study. When the subject understands and is willing to participate in the clinical trial, he/she must sign and date the Institutional Review Board (IRB) approved Informed Consent Form.

This screening visit will consist of the following procedures:

- All subjects will complete a medical health history questionnaire.
- The reason for extraction of the hopeless tooth will be documented (caries, periodontal disease, infection, fracture, resorption).
- Full mouth clinical measurements including probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP) and gingival index (GI) will be performed on all teeth.
- Standardized cone beam computed tomography (CBCT) will be taken.
- 3Shape Trios scanner will be used to make a digital impression of the maxillary arch. This will be used for surgical planning, volumetric measurements, and to fabricate surgical guides for implant placement.

5.3 INTERVENTIONS

All surgeries will be performed under local anesthesia using lidocaine with epinephrine, (Xylocaine 2%®- Epinephrine 1:100,000 and 1:50,000, Dentsply Pharmaceutical, York, PA, USA).

5.3 VISIT 2 (DAY 0): BASELINE

The baseline visit should be completed within 2 weeks after visit 1 (Screening). The surgeon will extract the hopeless tooth in the following fashion. He/she will make facial and lingual intrasulcular incisions with a 15-C scalpel only at the tooth requiring extraction. A periosteal elevator will then be used at the mesial and distal aspects of the tooth to sever subcrestal periodontal attachment fibers and expand the periodontal ligament space. If needed to allow periosteal elevator insertion or facilitate removal of a root tip, a fine long diamond bur (e.g. 859-010;

Brasseler, Savannah, Ga, USA) may be used to remove bone along the side of the tooth. An elevator will be used to mobilize the tooth and then forceps will be used to deliver the tooth. Finally, the socket will be curetted to remove all granulosomatous tissue and irrigated with sterile isotonic saline solution.

1. Extraction treated with xenograft bone substitute + collagen dressing:

The debrided socket from the control group will receive Geistlich Bio-Oss® Collagen (250mg) or the necessary amount to successfully fill the extraction socket. The bone substitute material will be rehydrated with subject's blood or sterile saline solution. A collagen dressing (HeliPlug®) will be used to cover the grafted extraction socket and sutured with resorbable suturing material (5-0 Vicryl – Ethicon, Inc., Somerville, NJ) to stabilize the wound.

2. Extraction treated with xenograft bone substitute + 3D-collagen matrix:

The debrided socket from the test group will receive Geistlich Bio-Oss® Collagen (250mg) or the necessary amount to successfully fill the extraction socket. The bone substitute material will be rehydrated with subject's blood or sterile saline solution. A 3D-collagen matrix (Mucograft Seal®) will be used to cover the grafted extraction socket and sutured with non-resorbable (6-0 Prolene – Ethicon, Inc., Somerville, NJ) and resorbable (5-0 Vicryl – Ethicon, Inc., Somerville, NJ) suturing material to stabilize the collagen matrix over the extraction socket.

Subjects in both groups will be instructed to rinse twice daily with 0.12% chlorhexidine gluconate for 30 seconds and avoid brushing or touching the area of extraction for 2 weeks. After 2 weeks, subjects may resume gentle brushing of the surgical site with a soft toothbrush. Sutures will be removed 2 weeks following the surgical appointment. Subjects will return at 1 week and 4 weeks to assess plaque control and wound healing.

Subjects will be given prescriptions for postoperative medications as stated in Table 1. Patient will assume all costs for prescription medications. Temporary appliance to replace the missing tooth will not be delivered as part of the study. However, subjects can have their referring dentists fabricating and delivering a temporary appliance to replace the missing tooth during the first 6 months of the study. The temporary appliance will not be covered by the study.

5.4 VISIT 3 (DAY 7 +/- 2 DAYS)

Visit 3 may occur within 7 days of visit 2 (+/-2 days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.
- Two (2) gingival crevicular fluid (GCF) samples will be collected from the surgical site for archiving and later regenerative and inflammatory biomarker analysis. The GCF will be collected from the interproximal site of the surgical site without disturbing the healing.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- The participant will be re-instructed to defer oral hygiene measures in the surgical site.
- Adverse events will be monitored and recorded as necessary

5.5 VISIT 4 (DAY 14 +/- 2 DAYS)

Visit 4 may occur within 7 days of visit 3 (+/-2 days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.
- Two (2) GCF samples will be collected from the surgical site for archiving and later regenerative and inflammatory biomarker analysis. The GCF will be collected from the interproximal site of the surgical site without disturbing the healing.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- Sutures will be removed if still present.
- The participant will be instructed to resume oral hygiene measures in the surgical site.
- Adverse events will be monitored and recorded as necessary

5.6 VISIT 5 (DAY 28 +/- 2 DAYS)

Visit 5 may occur within 14 days of visit 4 (+/-2 days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.

- Two (2) GCF samples will be collected from the surgical site for archiving and later regenerative and inflammatory biomarker analysis. The GCF will be collected from the interproximal site of the surgical site without disturbing the healing.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- The participant will be instructed to continue oral hygiene measures in the surgical site.
- Adverse events will be monitored and recorded as necessary

5.7 VISIT 6 (MONTH 3 +/- 7 DAYS)

Visit 6 may occur within 3 months of visit 2 (+/-7days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- Adverse events will be monitored and recorded as necessary

5.8 VISIT 7 (MONTH 6 +/- 7 DAYS)

Visit 7 may occur within 6 months of visit 2 (+/-7days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.
- Standardized cone beam computed tomography (CBCT) will be taken for implant surgical planning.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- Adverse events will be monitored and recorded as necessary

5.9 VISIT 8 (IMPLANT PLACEMENT +/- 7 DAYS)

Visit 8 may occur within 2 weeks of visit 7 (+/-7days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.

- The surgeon will prepare the osteotomy sequential drills as dictated by the Straumann surgical kit and place a bone level, threaded titanium alloy implant with an internal connection using a surgical guide. Implants will be placed approximately 3-4mm below the free gingival margin or 2-3mm below the cemento-enamel junction of adjacent teeth. The implant insertion torque will be recorded at implant placement. A healing abutment will be placed for proper soft tissue healing.
- Biopsy collection of gingival and bone tissues. Biopsy collection will be done during the dental implant surgery when the surgeon removes discarded tissues over the implant site using a punch or a blade. Bone biopsy will be collected with a 2x5mm trephine bur at the site planned for implant placement.
- As part of standard operating procedure, intra-operative periapical radiographs (PA) will be taken after implant placement to verify implant placement.
- 3Shape Trios scanning will be completed for later volumetric analysis.
- Patients will be given prescriptions for postoperative medications as stated in Table 1. Patient will assume all costs for prescription medications.
- Adverse events will be monitored and recorded as necessary

5.10 VISIT 9 (POST-OP)

Visit 9 may occur 2 weeks after visit 9 (+/-2days). The following procedures will be performed:

- Study personnel will record changes in medical history and concomitant medications since the previous visit and ask continuance criteria questions.
- Participant vital signs (blood pressure and pulse) will be recorded.
- 3Shape Trios scanning will be completed for volumetric analysis.
- The participant will be instructed to resume oral hygiene measures in the surgical site.
- Adverse events will be monitored and recorded as necessary.

6.0 STUDY PROCEDURES AND EVALUATIONS

6.0 STUDY OUTCOMES

The primary outcome examined in this study will be the radiographic and soft tissue volume results following socket graft + use of collagen dressing or 3D-collagen matrix.

6.1 MODIFIED GINGIVAL INDEX, LOBENE ET AL (1986)

Full mouth gingival scores shall be visually assessed by segmenting marginal and papillary units, 6 sites per tooth: distobuccal, buccal, mesiobuccal and distolingual, lingual, mesiolingual surfaces. The last tooth in each quadrant will not have a distal site. Gingival inflammation shall be recorded at each site on a scale of 0 to 4.

0 = absence of inflammation;

1 = mild inflammation or with slight changes in color and texture but not in all portions of gingival marginal or papillary;

2 = mild inflammation, such as the preceding criteria, in all portions of gingival marginal on papillary;

3 = moderate, bright surface inflammation, erythema, edema and/or hypertrophy of gingival marginal or papillary;

4 = severe inflammation: erythema, edema and/or marginal gingival hypertrophy of the unit or spontaneous bleeding, papillary, congestion or ulceration.

6.2 PROBING DEPTH (PD)

Linear distance from the gingival margin (GM) to base of the pocket. If a PD reading falls between two millimeter readings, the rule shall be to round down and the lower of the two readings will be recorded.

6.3 BLEEDING ON PROBING (BOP)

Presence or absence of bleeding to manual probing recorded as a dichotomous variable.

0- No bleeding within 10 seconds after probing.

1- Bleeding within 10 seconds after probing.

6.4 CLINICAL ATTCHMENT LEVEL (CAL)

Linear distance from the cemento-enamel junction (CEJ) to base of the pocket. If a CAL reading falls between two millimeter readings, the rule shall be to round down and the lower of the two readings will be recorded.

6.5 RADIOGRAPHIC ANALYSIS

Cone Beam Computed Tomography (CBCT) will be performed following screening and at 6 months post-extraction prior to implant placement. CBCT will be used for pre-surgical planning for both the tooth extraction and implant placement. Hard tissue linear measurement analysis will be performed to compare ridge remodeling (baseline vs. 6-month healing). CBCT images will be analyzed by non-contact reverse

engineering system (Geomagic software). Fickl and collaborators demonstrated in an animal study the reliability of using this software to measure the tissue alterations after tooth extraction (Fickl, Zuhr et al. 2008).

For superimposition of the original DICOM data (Digital Imaging and Communications in Medicine) of the two CBCT scans, a computer-assisted superimposition will be done in selected areas of the data set, where no changes had taken place during the 6 months (e.g. the cranial base in the maxilla or the lower border and angle in the mandible respectively). By this step, the two data sets will be aligned and manually checked for perfect match. Subsequently, the measurements will be made at baseline and at 6 months using the same reference points and lines. To set a reference, the most apical point of the extraction socket will be defined in the baseline image and two reference lines will be subsequently drawn. The vertical reference line will be drawn in the center of the extraction socket crossing the apical reference point. The horizontal reference line will be drawn perpendicular to the vertical line crossing the apical reference point. The following measurements with respect to these reference points and lines will be performed in the center of the extraction socket:

- Thickness of the buccal bone plate at three levels (1mm, 3mm, and 5mm below the lingual bone crest).
- Height of the alveoli at the mid-buccal and mid-lingual aspect.
- The horizontal ridge width measured at three levels (at -1mm, -3mm, -5mm) below the most coronal aspect of the crest.
- Linear changes overtime will be assessed based on the measurements performed at baseline and at 6 months.

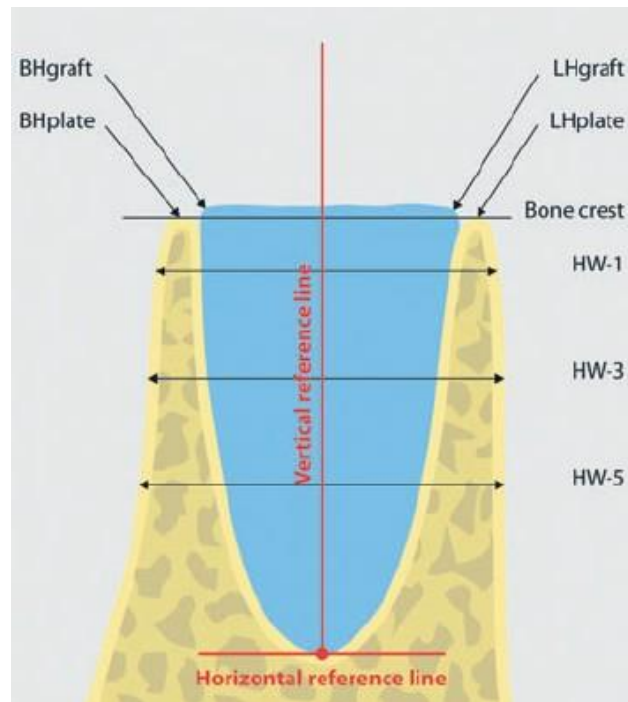


Figure 3. CBCT slice section. HW-1 (at -1mm), HW-3 (at -3mm), and HW-5 (at -5mm) represent measurements performed at 3 levels below the bone crest.

6.6 SOFT TISSUE ANALYSIS

Soft tissue volumetric analysis will be performed to compare the soft tissue healing between the test and control groups. Images captured with an intra-oral scanner (Trios, 3Shape) collected at baseline, week-1, week-2, week-4, month-3, and month-6. Soft tissue volumetric analysis will be performed to compare soft tissue ridge remodeling. STL files originated from intra-oral scanning images will be analyzed by non-contact reverse engineering system (Geomagic Qualify, Raindrop Geomagic, Research Triangle Park, NC, USA). A precision analysis study determined that surface reconstruction on Geomagic Qualify software provides a reliable analysis with a maximum deviation of 0.06mm, standard deviation of 0.003mm, and an average error of 0.002mm (Wang 2014). For superimposition of the original STL data (Stereolithography) of the intra-oral scans, a computer-assisted superimposition will be done in selected areas of the data set, where no changes had taken place during the 6 months (e.g. incisal edges or occlusal surfaces of teeth not included in the treated area). By this step, the data sets will be aligned and manually checked for perfect match. Volumetric changes overtime will be assessed based on the measurements performed baseline, week-1, week-2, week-4, month-3, and month-6 by subtraction analysis and expressed in percentage values.

7.0 STATISTICAL ANALYSIS

Descriptive statistics (means and standard deviations for continuous variables and frequencies for categorical variables) will be produced for vital signs, demographic characteristics, medical history and clinical variables, both overall, and for each of the two groups of study participants. Summaries of clinical variables will be presented at baseline and at study exit. Adverse events (including onset, duration, treatment, outcome and suspected causality) and reasons for withdrawals will be listed and summarized.

A power analysis was performed using a statistical power calculator (SAS Power Procedure, Cary, NC). This study will have a sample size of 24 subjects, 12 in each of the two groups. We will have at least 90% power (with a Type I error rate of 5%) to detect a difference of 2.5mm in the horizontal ridge width measured at 3mm below the most coronal aspect of the crest, assuming a standard deviation of 1.6mm, as determined by a previous study (Jung, Philipp et al. 2013). This power calculation takes into account the estimated 10% of subjects drop out. A “p” value of less than 0.05 will be considered statistically significant.

For soft tissue analysis, the primary outcome was the within-participant difference between the linear and volume changes at the test and control groups. These differences were measured in each participant prior to surgery, as well as 3 and 6 months after surgery, leading to a series of three longitudinal differences for each participant. For each group, the differences at all three time points were analyzed simultaneously using a linear mixed model (LMM), in which the actual linear and volume measures were modeled as a function of time (categorical), treatment group, and the interaction of time and treatment, while accounting for the repeated measures on each participant with a random participant effect. Given that both time and treatment are categorical, our approach was a generalized version of repeated measures ANOVA, as our LMM allowed for differing variability in linear and volume measures at each time point. Within each LMM, we also tested for a difference between the two treatment groups with respect to the overall time pattern in linear and volume measures. Due to the exploratory nature of the analysis, no Bonferroni correction for multiple testing was applied. Statistical significance was defined as a p -value < 0.05 .

For hard tissue analysis, to test the working hypothesis of systematic differences between the treatment groups, a two-sample equal variance student t-test with a two-tailed distribution was performed comparing the two groups for each of the linear measurements as well as for the volumetric analysis. Statistical significance was defined as a p -value < 0.05 .

8.0 SAFETY EVALUATIONS

8.1 DATA COLLECTION AND ANALYSIS

Data collection will be conducted on desktop and laptop computers located chairside in the GO Health Center,

UNC-School of Dentistry. These computers are stored in a locked area, and are password protected. Daily data backup is performed on a password protected network which moves the data to a secure server. This prevents any inadvertent breach in confidentiality of the data collected. Personal identifying information is stored in a separate secure database from the research data. Hard copies of the data sheets are kept in a locked office. Research samples will be identified only by unique numbers assigned to the participants. The specimens will

be coded. Linkage to the code will be retained by the study coordinator in a combination-locked workspace accessible only by study personnel.

8.2 VITAL SIGNS MEASUREMENTS

Vital signs (pulse, respiration, blood pressure) will be measured at each visit. At baseline height and weight will be determined. During test cylinder placement and removal standard clinical vital monitoring will be performed.

8.3 EXAMINATION OF THE ORAL CAVITY

At each study visit, an evaluation of patients' extra- and intraoral structures will be conducted. Each examination will include a survey of the face, lymph nodes, lips, buccal mucosa, floor of the mouth, tongue, hard and soft palates, gingiva, edentulous ridges and teeth. Findings will be recorded as normal or abnormal. Abnormal findings will be described with respect to onset, location, size (severity) and diagnosis. Standardized dental exam will be conducted by a calibrated dentist or hygienist with experience in conducting periodontal exams. Even though discomfort is minimal, each person's tolerance level can be different. The consent form explains to the subject they can stop the dental exam at any time. The instruments and materials used for the screening exam are a periodontal probe, an examination mouth mirror, a dental explorer and 2"x2" gauze. These four items are sterilized in an autoclave for 30 minutes in 275 degrees Fahrenheit (as recommended per OSHA standards in sterilization of dental instruments). The examination package with these three items is opened immediately before the exam so that it remains sterile. The examiner wears a gown uses gloves and wears a mask. For radiographs, standard precautions including using the lowest dose possible and using a lead apron during the x-rays to minimize exposure.

8.4 PATIENT DEMOGRAPHICS AND MEDICAL HISTORY

At screening, the patient's age, sex, racial, and ethnic group, and smoking status will be recorded. In addition, the subject's medical history will be reviewed; concurrent medications will be recorded and height and weight will be measured. At every study visit medical history will be updated, weight will be measured; concurrent medications and infections will be reviewed.

9.0 CONDITION FOR DISCONTINUING PARTICIPANTS

Participants in this clinical study may be discontinued for any of the following reasons: 1) concurrent illness that would compromise immune response or healing; 2) protocol violations; 3) administrative reasons; 4) withdrawal of consent; or 5) poor healing response.

Subjects with dehiscence, fenestrated, or fractured labial/buccal with dehiscence, fenestrated, or fractured labial/buccal alveolar bone plate determined after baseline CBCT or after tooth extraction where more than 50% of the buccal bone height is not present. In this case, if the surgeon determines that guided bone regeneration (bone graft and membrane) is needed to repair the defect, it will be done at no cost to the subject, but the subject will be excluded from the study protocol. If after tooth extraction more than 50% of the buccal bone height is not present, the surgeon will perform guided bone regeneration (bone graft and collagen membrane) to repair the defect, it will be done at no cost to the subject, but the subject will be excluded from the study protocol.

Any subject presenting with healing response that in the judgment of the clinical provider may result in either infection, loss of osseous structure or soft tissue healing abnormalities to any of the surgical procedures, will have the graft material or dental implant removed immediately. If any healing problems arise, a second therapist not associated with the investigation will evaluate the patient to decide whether the subject should be exited or can continue. Moreover, each subject with poor tissue response or exited for any reason will be monitored until healing has resolved and appropriate care is provided to restore existing structures.

8.1 HANDLING OF WITHDRAWALS

All participants prematurely discontinued from the study, regardless of cause will be encouraged and given the opportunity to be seen for a final evaluation. The reason(s) for withdrawal will be recorded in the CRF by the study coordinator and/or investigator.

10.0 PROTOCOL DEVIATIONS

Protocol Deviations will be recorded by the study coordinator.

11.0 ADVERSE EVENTS

An adverse experience (AE) is any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse experience includes any untoward event that is fatal or life-threatening, is permanently disabling, requires or prolongs hospitalization, is a congenital anomaly, cancer, result of an overdose, or requires intervention to prevent permanent damage. In

the event of a serious adverse experience, the principal investigator or study coordinator must be contacted immediately by telephone. In the event that the principal investigator or study coordinator cannot be directly reached, a message must be left by voice mail within 24 hours of the incident.

All adverse events will be recorded although a distinction will be drawn between reactions normally experienced in conjunction with conventional periodontal therapy extractions and experiences not usually encountered. Unanticipated or possible related adverse events will be evaluated by open questioning throughout the trial. Examples of adverse events that may warrant subject removal from study participation include: infection, loss of primary stabilization, excessive inflammation, swelling, bleeding or pain. The onset, duration, treatment, and outcome of all such unanticipated adverse experiences must be recorded on the appropriate case report forms and reported within 7 business days to the Biomedical IRB. All anticipated and unrelated adverse experiences will be recorded on the appropriate case report forms.

The following definitions of severity should be used in the evaluation of AEs:

- Mild*: an AE that is easily tolerated and does not interfere with daily activities.
- Moderate*: an AE that is sufficiently discomforting so as to interfere with daily activities or receive interventional treatment.
- Severe*: an AE that prevents normal everyday activity.

The following definitions of relationship to implant surgery should be used in assessing the suspected causality of an AE:

- Probably Related*: there is a direct cause and effect relationship between the AE and the surgical procedure
- Possibly Related*: a direct cause and effect relationship between the surgical procedure and the AE has not been demonstrated, but is likely, possible, or cannot be ruled out, even if improbable
- Unlikely Related*: a direct cause and effect relationship between the surgical procedure and the AE has not been demonstrated, and, from the available data, indicate that a relationship probably does not exist, but cannot be definitely ruled out
- Remote*: a direct cause and effect relationship between the surgical procedure and the AE has not been demonstrated, and, the event appears to have been caused by something other than the study device
- Not related*: a direct cause and effect relationship between the AE and a source other than the surgical procedure has been demonstrated and documented

12. APENDIXES

Table 1. Prescription Drugs

| Following Implant Surgery |
|---------------------------|
| Rx Amoxicillin 500mg |
| Disp 30 tabs |

| |
|--|
| Sig Take 1 tab three times daily |
| If Penicillin Allergy: Rx Azithromycin 250mg Disp 6 tabs Sig Take 2 tabs 1 st day then 1 tab qd for 4 days |
| Rx Ibuprofen 600mg Disp 20 tabs Sig Take 1 tab every 6h for two days then prn pain |
| Rx Hydrocodone/APAP 5/325mg Disp 20 tabs Sig Take 1 tab every 4-6h prn pain |
| Rx 0.12% Chlorhexidine Rinse Disp 1 X 1.8 oz bottle Sig Rinse with ½ oz for 30 seconds twice daily |

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