Ridge Preservation with Hardening Calcium Phosphate Bone Substitutes and Resorbable Membrane for Implant Site Development on Non-containable Extraction Sites: A Clinical and Histological Prospective Case Series in Humans.

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Tooth extraction is one of the most widely performed procedures in dentistry today and it has been well documented that this affect dimensional changes of the alveolar ridges. Oral rehabilitation with dental implant prostheses can provide more variety of treatment options to patients since high survival rate of implant therapy is well documented. The obstacles that all clinicians have dealt with is how to manage extraction sites to prepare better site for the future dental implant placement or to minimize ridge shrinkage for a fixed or removable prosthesis delivery. Excellent functional and esthetic restoration of an implant largely depends on its placement in an ideal location that will achieve the restorative goals. If management of the extraction site was performed inadequately, the resulting shrinkage of the ridge dimension can require additional ridge augmentation prior to implant placement. That results in prolonged treatment time, multiple additional invasive surgery, and increasing cost for patients. The key processes of tissue modeling and remodeling following extraction have been well documented in both animal [1, 2] and human models. [3, 4] In a dog model, Araujo showed that the buccal bone plate was considerably thinner than the lingual plate, and that horizontal resorption may also cause vertical reduction of the buccal wall. Also sequenced histology suggested that the resorption on the buccal and lingual bone of the extraction site occurred in two types of phases. The bundle bone resorption initiated and the resorbed area was replaced with newly formed woven bone in the first phase. This is because that the bundle bone lost blood supply from periodontal ligament and the lack of blood supply causes vertical bone loss too. In following the first phase, bone remodeling and resorption initiated from the outer surfaces of both bone walls.[1] A human study by Schropp reported that, with regard to the width of the ridge, a reduction of up to 50% was found in 12 months after extraction, of which two thirds occurred during the first 3months of healing period. [5] A systematic review written by Tan assessed the magnitude of dimensional changes for the hard and soft tissues of the alveolar ridge dimensions up to 12 months after the extraction site in humans. Twenty studies were included in the review, and the authors concluded that human reentry studies showed loss of horizontal dimension of 29% to 63% and vertical loss was 11% to 22% following 6 months tooth extraction. These studies demonstrated rapid resorptions in the first 3 to 6 months, and followed by slow rate of reductions for longer time period.[6] Alveolar ridge preservation is a simple procedure aimed at preventing or minimizing dimensional changes following tooth extraction to provide an adequate volume and quality of bone for dental implant placement. Extraction sites treated with ridge preservation have been documented well to have less horizontal and vertical dimensional change as well as increased vital bone formation compared to controls not treated with ridge preservation procedures. [7-12] Ten Heggeler [13] performed a systematic review on the effectiveness of socket grafting procedures at the time of extraction in non-molar teeth in human. The results of this review showed that for ridge preservation procedure, the outcome with the freeze-dried bone allograft group revealed the best in terms of height gain, however, a loss in width of 1.2mm was inevitable. Socket/ridge preservation may contribute to reducing of the ridge dimensional changes after a tooth is extracted. However, they cannot fully prevent the bone resorption because, depending on the technique, on the basis of the included papers one may still expect some loss in three dimensionally. Systematic reviews by Horvath [14], Morjaria [15] concluded

similar results from previous systematic reviews that post-extraction three dimensional changes with ridge preservation therapy might be limited, but cannot be completely eliminated by grafting procedures. Horowitz [12] concluded in his review that the scientific evidence from all of these systematic reviews suggested that socket/ridge preservation techniques contributes to significant benefit with reducing horizontal bone loss of the alveolar ridge. Nonetheless, ridge dimension is important for future implant placement, grafting procedure on the socket at the time of extraction may be very important.

Alveolar ridge preservation adjunct with extraction of teeth can be achieved successfully using a many types of materials such as autografts, allografts, xenografts, and alloplasts. In the past several decades, along with the increasing popularity of implant therapy, the use of graft materials and techniques for alveolar ridge preservation has been studied well. Vignoletti [16] conducted a systematic review regarding surgical protocols for ridge preservation after extractions. This review article revealed that the potential benefit of socket preservation therapies was demonstrated. These grafted procedures resulted in significantly less both vertical and horizontal shrinkage of the alveolar ridge dimensions compare to without grafting procedures. However, the scientific evidence did not determine the guidelines in which type of biomaterial or surgical procedure shows the best outcome for ridge preservation. Hammerle [17] summarized the biology and treatment of extraction and ridge preservation procedures based on the reviews. The variety of materials used in the extraction socket was evaluated in the clinical studies, this review paper did not show any significant differences between materials except collagen plug alone, which caused negative outcomes.

Autogenous (as block or particulate form) bone grafts has been considered as a gold standard for ridge augmentation procedures, however, donor site morbidity associated with block harvest has taken more attentions to concern the second surgical area, and the amount of autogenous graft is limited.[18] For those reasons above, the use of autogenous graft from second surgical site for alveolar ridge preservation procedures remain questionable.

Allografts have been widely used for various regenerative treatment including ridge augmentation and grafting around the periodontal involved teeth. Allografts, especially Freeze-Dried Bone Allograft (FDBA) are generally considered to possess primarily osteoconductive properties. On the contrary, Demineralized freeze-dried bone may also exhibit osteoinductive properties, but this varies with each donor and each tissue bank, and it may even vary between batches within the same bank. [19, 20] However, some patients do not want to have allograft material implanted into their body because of some cultural, religious, and/or psychological reasons due to the nature of the process and source of allografts. As matter of fact, still now, in many countries and regions, allografts have not been official approved by their own FDA (Food and Drug Administrations).

Xenografts have been used with good outcomes in oral regenerative procedures, such as ridge augmentation and sinus graft procedures. The use of deproteinized bovine bone mineral (DBBM) has been well documented. This material has been shown to maintain their natural microporous structure following process in the factory, so that it conducts cell proliferation, migration and new blood vessel formation. The characteristic of the large internal surface enables more contact surface with new bone area and a crystalline structure. This advantage allows the graft material to integrate into the natural bone remodeling process.[21, 22] However, due to the slow resorption rate, many histologic studies

have shown the presence of graft remnants from implanted site even following months after the grafting.

Alloplastic bone substitutes have been used extensively for regeneration and preservation of alveolar ridge in extraction socket. Ideally, these materials are biocompatible; otherwise, the implant will be encapsulated by a fibrous tissue, and lead to a device failure and requirement of a second operation. The variety types of bioactive ceramics have been developed and are clinically used in the daily practice, such as hydroxyapatite (HA), tricalcium phosphate (TCP), HA/TCP biphasic ceramic, and bioactive glass. Calcium phosphates possess osteoconductive ability, and excellent biocompatibility, presumably due to their similar chemical and crystal structure to natural bone minerals.[21, 23-25] The use of β-TCP as a graft material following tooth extraction to preserve the socket dimensions has been reported in few clinical studies. [21, 26, 27] Araujo demonstrated the early healing process of an extraction socket with β-TCP in canine model. The healing site involved the formation of a coagulum, granulation tissue and a provisional matrix, and woven bone formation in those area.[26] From a clinical stand point, bone graft substitutes should be moldable during application, display a self-stabilizing and hardening potential, and form a stable, but still porous scaffold in the defect. This approach would ease the clinical application and, would greatly reduce the need for membranes to retain loose graft materials in the defect, resulting in shortened and simplified surgical procedures. Schmidlin [23] evaluated regenerate potential of hardening polylactide coated ß-tricalcium phosphate (TCP) (easy-graft®) in the calvarial bone in rabbits compared to hardening polylactide-coated biphasic calcium phosphate (BCP), and deproteinized bovine bone matrix (DBBM). The authors found that all tested materials showed good biocompatibility. Semi-quantitative analysis and pairwise comparison suggested that BCP showed better efficiency to form centripetal bone compared to β-TCP. After 4 weeks, significantly bone formation in the β-TCP or BCP sites was found compared with the non-grated sites. There was no sign of biodegradation in the BCP and DBBM sites, on the other hands, the β-TCP showed partial resorption after 16 weeks. Leventis [28] showed a case report with an alloplastic in-situ hardening bone substitutes (GUIDOR® easy-graft® CLASSIC, Sunstar). Following extraction and thorough debridement and rinsing with sterile saline, easy-graft® was utilized in the socket. It consists of β-TCP granules, which are coated with polylactic-co-glycolic acid (PLGA). The granules are mixed in a syringe with the provided BioLinker® (N-methyl-2-pyrrolidone solution, Sunstar). Upon contact with blood or saliva the graft granules adhere to each other forming a sticky, easy-to-handle, moldable mass that begins to harden. The grafted socket was left uncovered in order to heal secondary intention. At re-entry 4 months, the post extraction site was filled with newly formed bone. Residual graft material was slightly visible and embedded in the newly formed tissue. An implant was placed with satisfactory insertion torque, and restored after 3months implant placement. The author concluded that the in-situ hardening property of this material may enable clinicians to utilize a flapless procedure without primary wound closure the reduced patient morbidity, preserving the attached keratinized tissue and allowing for further production of keratinized tissue. However, the average of buccal bone thickness on the anterior esthetic area on both maxillary and mandibular arches is very thin. The mean of buccal bone thickness on the anterior area was 0.3m to 2.09mm. [29, 30] Spray et al reported that a minimal width of 2mm of the buccal bony wall is a prerequisite to maintain the vertical dimension of the alveolar crest following implant placement. Additional surgical procedures such as soft and hard tissue augmentation will be needed to obtain optimal esthetical and functional outcomes. [31] At the time of extraction, even minimal traumatic extraction was utilized, buccal bone fracture could happen. Also those thin buccal bone might be resorbed due to chronic or acute inflammation such as periodontitis, or trauma, tooth fracture, endo-

related lesions. Once buccal bone is missing due to any reasons at the time of extraction, simultaneous ridge preservation and augmentation with bone substitutes and guided barrier membranes. [8, 9]

In previous studies, the change of ridge dimensions were measured with probe by using reference points during procedures. UNC probe only has 1mm measurements, and literature suggested the inaccuracy of evaluation of ridge dimension change. Shneider evaluated that the accuracy of the digital determination of gingival recession and papilla height on virtual jaw models, given the hypothesis that they show lower interrater variability than conventional linear measurements taken clinically or on cast models. They found that the use of digital technologies by intraoral scanning or scanning of cast models improved the reproducibility and lowered the variance of measurements within one individual and between different investigators.[32]

To our best knowledge, there is no study was performed to investigate the combination of GUIDOR® bioresorbable matrix barrier and GUIDOR® easy-graft® for extraction ridge preservation procedures for non-containable sockets in non-molar sites. Thus, the purpose of the current study is to clinically (primary outcome) and histologically (secondary outcome) evaluate alloplastic in-situ hardening bone substitutes (GUIDOR® easy-graft® CLASSIC, Sunstar) and resorbable membrane (GUIDOR® bioresorbable matrix barrier) in alveolar ridge preservation following extraction of non-molar teeth with non-containable extraction sockets. In addition, those dimension change will be measured digitally scanned cast to evaluate the accuracy of the measurements, and cone beam computed tomography.

Material and Methods

The Institutional Review Board of the Indiana University School of Dentistry, Indianapolis, Indiana will review and approve the protocol prior to this study. All participants will provide written informed consent before treatment and will be given a copy of the signed informed consent documents. Up to twenty subjects who have been diagnosed with a need of extraction of single tooth followed by ridge preservation will be recruited to the study.

The procedures listed below including the combination use of the two alloplasts are all within standard care for a tooth extraction with regenerative therapy to preserve the ridge dimensions following extractions with the exceptions of:

- The CBCT (one or more) taken immediate following extraction to evaluate the dimensions of extracted ridge.
- The second CBCT if the subject is not receiving implant therapy.
- The core biopsy (only conducted on those receiving implant therapy)

No data collected for this study will be taken from sources outside of those mentioned above and that are already recorded for standard of care procedures.

Inclusion/Exclusion Criteria,

The following site inclusion criteria will be used: 1) adequate restorative space for a dental implant restoration, if the subject decides previous to study participation that they would like an implant. Note,

agreement to implant placement is not a requirement of the study; 2) minimum of 10-mm vertical bone without impinging on adjacent vital structures (Maxillary sinus, neurovascular bundles); 3) single-rooted tooth to be extracted; 4) ASA class I or II; 5) age >18 years old: 6) subjects who had >50% of height on any portion on the buccal wall of dehiscence and/or fenestration of the extraction socket following extraction will be included from this study: 7) adjacent teeth to extraction site will be present during healing period 8) willingly sign informed consent and authorization. The following exclusion criteria will be used: 1) did not meet any inclusion criteria; 2) pregnancy or nursing woman; 3) subjects with active systemic or localized infection (exclude chronic periodontitis); 4) subjects with a history of any medical conditions that contraindicated or weighed against dental implant placement such as history of bisphosphonate drug use, chemotherapeutic or immunosuppressive agents, autoimmune disease, or poorly controlled diabetes (HBA1c>7%), and 5) subjects with smoking habit (more than 10 cigarettes per day). [33, 34]

Continuance Criteria

Continuance criteria will be updated at each visit to determine subject's eligibility to continue in the study. Continuance criteria questions will encompass the exclusion criteria with the exception of Exclusion Criteria # 1, 3, 4 and 7 are not being captured. Adverse events resulting from responses to the continuance criteria questions will be addressed and documented accordingly. Issues with subjects who do not meet the continuance criteria will be addressed and the PI will determine the subject's ability to continue in the study.

Removal of Subjects from the Study

Subjects may withdraw from the study at any time for any reason. The Investigator may also remove subjects from the study at any time. The Investigator will document the reason for withdrawal for any discontinued subjects. Subjects withdrawn for medical reasons will be referred to a physician/dentist by the study personnel and will have their condition monitored to resolution or until deemed clinically non-significant.

Surgical Protocol

Silicone impressions will be taken for all participants prior to extractions and study models will be made for the purpose of obtaining clinical measurements. Intravenous conscious sedation will be administered at the discretion of the surgeon and the patient request. No pre-surgical antibiotics will be provided and all subjects will receive a single dose of 600 mg ibuprofen before extraction unless patients have some restrictions.

After local anesthesia, the tooth will be extracted in a minimally traumatic manner with periotomes and the socket will be thoroughly debrided. Envelop design (No vertical incision) minimal flap was reflected more than 3mm beyond the alveolar crest. Following extraction, the socket will be examined for defects. If the site meets the inclusion criteria, GUIDOR® bioresorbable matrix barrier will be trimmed and utilized over the socket to cover the defect edge at least 2 mm of edge. Alveolar ridge preservation using the material (GUIDOR *easy-graft* ® CLASSIC, β-TCP granules, which are coated with PLGA) will be mixed in a syringe with the provided BioLinker® (N-methyl-2-pyrrolidone solution, Sunstar) following by instructions by the manufacturer. Graft material will be placed only to coronal to the existing alveolar crest in the sites. After the membrane is tucked on the lingual side with minimal reflection of flap (at

least 3mm over the alveolar crest), the socket orifice with resorbable sutures (5-0 Vycryl). Postoperative instructions will be given, and all patients will be prescribed 500 mg amoxicillin, three times daily for 1 week unless an allergy to penicillin was present, in which case 100 mg doxycycline, once daily for 10 days will be given. All patients will be instructed to rinse for 30 seconds twice daily with alcohol free 0.12% chlorhexidine gluconate (Perodex® Sunstar) for 2 weeks.

Cone beam computed tomography (CBCT) will be obtained from all participants immediate after extraction with ridge preservation procedure as a baseline (T0). CBCT will be obtained with Kodak-9000 (85kV, 1mA, 10.8S) for patient needing one extraction site. If patients need multiple extractions, CBCT will be obtained with i-CAT science international (120kV, 18.54mA, 8.9S). Occlusal and buccal photographs of the surgical site before and after the surgery will be obtained.

Patients will be seen at approximately 1, 2, 4, 12 weeks for follow up visits. Sutures will be removed 2 weeks after the ridge preservation is rendered. Occlusal and buccal photographs of the surgical site will be obtained at every follow up visit. Wound dehiscence and/or membrane exposure will be reported. Adverse events will be recorded. Patients will return approximately 3 months after the extraction for a cone-beam computerized tomographic scan with radiographic stent if patient is receiving implant therapy. Based on the number of CBCT scans taken at baseline, the same number will be taken at this visit. (T1) For those subjects not receiving an implant a follow up CBCT scan will be taken but will not be considered standard of care. New silicone impressions will be taken to evaluate the dimensions of the alveolous before implant placement.

For patients receiving implant therapy, the ridge width and buccal and lingual height will be measured during the implant procedure as described previously. Also during the procedure, a trephine drill with a 2.0mm internal diameter will be used to take a core biopsy up to 8mm in length in the central portion of the alveolar ridge which will be placed in 10% neutral buffered formalin (this procedure is not considered standard of care).

Digital Measurements

Pre- and post-treatment casts will be made from silicon impressions that will be scanned with a digital scanner or determining changes in ridge dimensions. Software Netfabb® software (Autodesk Netfabb®, Parsberg, Germany) will be used to measure the difference of the thickness. The pre- and post-treatment images will be superimposed with adjacent teeth and the change in ridge dimensions will be measured at 1mm, 3mm, 5mm from the most coronal portion of buccal gingiva from post-op data.

Histologic Processing

Core biopsies will be decalcified, embedded in paraffin and sliced to a 4-µm thickness. A single section per individual will be selected for histological evaluation in its entirely from its most apical end to its most coronal end. If the multiple sections are available for analysis, preference will be given to the innermost aspect of the original core biopsy. If the innermost section is not available for analysis due to artifact, the section nearest is examined. Hematoxylin and eosin counterstain will be used in preparation for light microscopy. Histomorphometric analysis will be completed by one examiner who is masked to the treatment group during examination of all cores. Each section is subsequently traced into three component layers (vital bone, residual graft, and non-mineralized connective tissue) and measured the ratio with software.

CBCT analysis:

This protocol will be submitted to Indiana University Radiation Safety for review and approval previous to the study start. To perform radiographic measurements, CBCT scans at baseline and at 3 months will be processed using an CBCT viewing software (Invivo6; Anatomage, San Jose, USA). 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 will have taken place during the 3 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 are aligned and are, thereafter, manually checked for perfect match. Subsequently, the measurements will be made at baseline and at 3 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. Three horizontal references line (1, 3, 5 mm from the crestal of T0) will be drawn perpendicular to the vertical line crossing the apical reference point (HW1, HW3, HW5). [35, 36]

Statistical Analyses

For all treatment group comparisons of bone core percentages and ridge dimensional data, due to the nature of this pitot study, no sample size justification estimated were performed. Means and standard deviations for all parameters will be calculated. The paired-sample t test will be used to assess the statistical significance of the difference between the initial and the 3-month visit within group. Difference will be considered statistically significant at the $P < .05$. All data analysis will be performed using statistical software. (Microsoft Excel.)

Adverse Events

Subjects will be questioned regarding any general health or oral complaints and symptoms they have experienced during their visit. Any findings will be documented on the AE CRF. In the event of subjects reporting AEs outside the scheduled clinical visit, the Investigator will assess them at the earliest opportunity.

All AEs, regardless of severity or relationship to the device or study procedures, will be recorded. Serious AEs include any events resulting in death, decreased life expectancy, life-threatening situations, persistent or permanent disability/incapacity, hospitalization, or congenital anomaly/birth defect or other important medical event.

Any medical condition that is present at the time the subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

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