Title

A histomorphometric analysis of bone formation following sinus augmentation with two different bone graft materials.

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Research Project

A histomorphometric analysis of bone formation following sinus augmentation with two different bone graft materials.

A Pilot study in humans

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Title:

A Histomorphometric Analysis of Bone Formation following sinus augmentation with Two Different Bone Graft Materials. A pilot study in humans.

Introduction:

Sinus augmentation procedure is a well-accepted and predictable surgical procedure that is used to increase the bone volume to facilitate implant placement for individuals who otherwise present with inadequate bone quantity in the posterior maxilla.[1-4] In 1980, Boyne and James published a technique for maxillary sinus augmentation using autogenous bone.[5] Since then, several different techniques have been developed and are currently being utilized for sinus augmentation.[6-9] The original sinus augmentation protocol utilized autogenous bone from either intraoral or extra oral sources.[5,10] The disadvantages of utilizing autogenous bone are requirement of an additional surgical procedure, increase in surgical time and post-surgical morbidity. Moreover, autogenous bone has reported high and unpredictable resorption rate.[11,12] Therefore, various grafting materials such as allografts, xenografts, alloplastic materials, and mixtures of various materials have been utilized in sinus floor elevation.[1,13-18] Del Fabbro et al. concluded in their systematic review that bone-substitute materials are as effective as autogenous bone when used alone or in combination with autogenous bone.[2]

Anorganic bovine bone mineral (Bio-Oss, Geistlich, Princeton, NJ) (ABBM) is a bone substitute that is manufactured from bovine bone mineral having a microscopic structure similar to human cancellous bone. In humans, ABBM alone or mixed with other materials was found to be highly osteoconductive and provided a scaffold for new

bone formation in extraction sockets or sinus augmentations. The results of sinus augmentations with xenografts are complete and well documented.[14-24] Jensen T et al.[24] reported that there is no statistical difference between the use of ABBM alone and a mixture with autogenous bone as graft material for maxillary sinus augmentation.

Inteross (Sigma Graft) is another anorganic bovine bone mineral bone substitute that is manufactured from bovine bone and is supposed to have a similar microscopic structure to Bio-oss but with more surface area. This will be an attempt to compare the clinical performance with histomorphometric analysis of the bone that is formed using the two different graft materials.

Objective:

The purpose of this investigation is to compare new bone formation by means of histomorphometric analysis following maxillary sinus augmentation using two different bone graft materials.

Null Hypothesis:

There is no histomorphometric difference in new bone formation in maxillary sinuses augmented using two different materials, ABBM (Bio-oss) and ABBM (InterOss).

Material & Methods:

Patient selection:

20 patients who require sinus augmentation prior to implant placement in the posterior maxilla at Loma Linda University School of Dentistry (LLUSD), Advanced Education Program in Implant Dentistry will be selected to participate in this study. Patient will complete a medical history form and be selected using the following inclusion and exclusion criteria.

Inclusion Criteria:

1. Over 18 years old who are able to read and sign an informed consent form.
2. Patient who has good oral hygiene (Full-mouth plaque score <25%).
3. Subject would be available for study monitoring and follow-up visits.
4. Patients with missing teeth in the maxillary posterior region who will require sinus augmentation for implant placement. The patients may be partially or completely edentulous.
5. Patient is a candidate for delayed implant placement approximately 8 months following sinus grafting.
6. Patient will be evaluated for the dimensions of the maxillary sinus after initial CBCT evaluation and patient with the following minimum dimensions will be included. Length (anterior-posteriorly) – 25mm

   Width (medial-laterally) – 18mm

   Height (coronally-apically) – 25mm

Exclusion Criteria:

A medical history that will complicate the outcome of the study such as

1. Alcohol, drug dependency.
2. Signs or symptoms of chronic maxillary sinus disease.
3. Current smoker.
4. History of head and neck radiation treatment.
5. Poor health, conditions like uncontrolled diabetes, uncontrolled hypertension or other uncontrolled systemic disease.
6. Physical or psychological reason that might affect the surgical procedure or the subsequent prosthodontic treatment and/or required follow-up examinations.
7. Also, subjects who are nursing or pregnant will be excluded from the study.

A guideline and treatment protocol for patient care will be submitted to the Institutional Review Board (IRB) of Loma Linda University (LLU) and the research review committee for approval. All clinical procedures will be performed at the Center for Implant Dentistry, Loma Linda University School of Dentistry.

Informed Consent:

In accordance with the standards of conduct established by the Institutional Review Board of Loma Linda University, participants will be required to sign an informed consent. The purpose and the nature of the study will be explained to the subjects by one investigator (SU) and patient who will meet our inclusion criteria will then be invited to participate. Subjects will be required to read, understand, and sign the consent form before being enrolled in the study. Hard copy will be retained following the standard protocol set by the Institutional Review Board of Loma Linda University.

Randomization – Quickcalcs software from Graphpad (Graphpad software Inc, La Jolla, CA USA) will be used to randomly assign patients. All patients will undergo sinus augmentation and will be randomly placed into two groups according to the graft material to be used in the surgical procedure. If a patient requires bilateral sinus augmentation, (two sinus on either side in the same patient) each sinus will be considered as one unit for the randomization procedure.

Group A: 10 Maxillary sinus augmentation using ABBM (InterOss).

Group B: 10 Maxillary sinus augmentation using ABBM (Bio-Oss).

Clinical Procedure:

Diagnosis and Treatment Plan

1. Subjects will be informed in detail about the sequencing of the events that would take place during the study. This will include risks, benefits and alternatives for treatment.
2. Preliminary impressions will be made with polyvinyl siloxane impression material (Exafast, GC America Inc., Alsip, IL). Diagnostic casts will be fabricated in type III dental stone (Microstone, Whip Mix, Louisville, KY).
3. The diagnostic casts will be articulated with the use of a face-bow on a Panadent semi-adjustable articulator (Panadent Corporation, Colton, CA) using interocclusal record made with polyvinyl siloxane (Exabite, GC America Inc., Alsip, IL) and wax record bases.
4. The diagnostic waxing of the missing teeth will be fabricated with tooth-colored wax (Pro-Art, Ivoclar Vivadent, Inc., Williams, Amherst, NY), and then will be duplicated in type III dental stone for partially edentulous patients. In case of completely edentulous patients, denture teeth will be set up in an optimal position on a base plate based

on the conventional complete denture fabrication. A silicone lab putty (Polysiloxane Coltene Lab-Putty, Coltene Whaledent Inc. Cuyahoga Falls, OH) impression will be taken of this denture setup.

5. A vacuum-formed radiographic template (Polypropylene Coping Sheet, Ultradent Products, South Jordan, UT) with auto-polymerizing acrylic resin (Jet, radiopaque teeth color, Lang Dental, Wheeling, IL) will be fabricated from the duplicated cast for partially edentulous patients. For completely edentulous patients, a radiographic template will be fabricated from the silicone putty impression with radiopaque color auto-polymerizing acrylic resin for teeth and clear color for the base (Jet, radiopaque teeth color, Lang Dental, Wheeling, IL). These templates will be used in conjunction with the cast for identifying the desired locations of the dental implants.

6. All patients will undergo radiographic evaluations before sinus augmentation. A cone-beam computed tomography (CBCT) scan (NEWTOM full volume scan of the maxilla) would be taken with the radiographic template. (The radiographic evaluation prior to sinus augmentation is standard protocol)

Pre-operative procedure

1. At a pre-surgical appointment, the patient's vital signs (blood pressure, pulse rate) will be recorded and the patient's medical history will be updated. At this point, patients will be randomly assigned to Group A or B.

2. Patients will be given the following three choices of anesthesia for the sinus surgery:

    a) Local anesthesia (LA) only.

    b) LA in conjunction with oral sedation (Halcion 0.25mg, Roxane Laboratories Inc., Columbus, OH). Administered 30 minutes before the appointment.

c) LA in conjunction with intravenous (IV) sedation.

A patient who chooses IV sedation will have a pre-surgical interview with the anesthesiologist (Surgery Center for Dentistry, Loma Linda University School of Dentistry) who will conduct sedation at the time of the surgery.

3. All patients will be questioned regarding drug allergy and prescribed with appropriate antibiotics (Amoxicillin 500 mg or Clindamycin 300mg, TID for 10 days, to start day 1 before the day of surgery) analgesic (Ibuprofen 800 mg) to take 1 tab 1 hour before the surgery and for post-operative usage as needed for pain. The patient will also be instructed to rinse with 0.12% chlorhexidine gluconate solution (Peridex, Zila Pharmaceuticals Inc., Phoenix, AZ) twice a day starting 1 week before the surgery to continue for 2 weeks after the surgery.

4. The radiographic template will be converted into a surgical template. The proposed implant locations in the radiographic template will be finalized and modified if necessary after reviewing the CBCT scan with the template in place. The location of the anterior wall of the sinus cavity will be marked on the surgical template.

5. All pre-operative and postoperative instructions will be given to the patient in an oral and written format. All of the patient's questions about the instructions will be answered.

Surgical procedures

1. On the day of surgery, the patient will be asked to rinse their mouth with 0.12% chlorhexidine gluconate solution (Peridex) for 3 minutes prior to the surgery. After being seated, the patient will be monitored for blood pressure, pulse rate, and oxygen level and circumoral area will be scrubbed with a Povidone-Iodine swab stick (Aplicare,

Aplicare Inc., Branford, CT) and the patient will be draped. Oxygen will be provided to the patient through the nasal cannula at a minimum rate of 3 liters/minute, if the patient chooses to be sedated.

2. All the patients will be treated with the same surgical technique consisting of sinus floor augmentation via a lateral approach. All surgeries will be performed by one surgeon (SU). After appropriate local anesthetic administration (2% Xylocaine with epinephrine 1:100,000, Dentsply International Inc., York, PA) administration, a mid-crestal incision will be made and a vertical releasing incision will be made anteriorly at the appropriate location. A full-thickness flap will be reflected to expose the lateral wall of the sinus.

3. Each antrostomy will be outlined with a round carbide bur (KOMET USA, Rock Hill, SC) ensuring that the inferior border will be at least 2 mm superior to the sinus floor. If the lateral bone window is not completely separated from the surrounding bone, a mallet and chisel (H & H Company, Ontario, CA) will be used to facilitate complete separation.

4. Sinus membrane will be carefully elevated to create space for the bone graft. The bony remnant from the window will be elevated with the sinus membrane to form the roof of the future space for the bone graft material. The membrane's integrity will be checked visually and with the Valsalva test. If a perforation to the sinus membrane occurs, the surgeon will evaluate the site prior to proceeding. If the perforation is < 5 mm in diameter and is able to be repaired, the perforation will be isolated and a resorbable collagen membrane (Bio-Gide, Geistlich, Wolhusen, Switzerland) will be placed over the area, in such a position so as to overlay unaffected membrane by at least 3 mm in all directions. Then, the surgeon will continue with the procedure as

planned. Any perforation > 5 mm will be excluded from this study. Prior to the placement of the graft, the mesial and distal margins of the lateral window will be marked on the surgical template. A line connecting these two marks will be made following the outline of the inferior margin. The inferior and superior margins will be measured from this line and these measurements will be recorded.

5. ABBM (InterOss large particle 1-2mm) or ABBM (Bio-Oss® large particle 1-2mm) will be placed into the each sinus compartment for the two groups. Approximately 2-3 grams of graft material will be placed in each sinus compartment as per the individual case requirements.

6. Primary closure of the flap will be performed using a 5-O expanded poly tetrafluoroethylene (Gore-Tex, W.L. Gore and Associates, Inc. Newark, DE) suture material for the crestal incision and polyglactin 910 suture material (Vicryl 6-0, Ethicon, Somerville, NJ) for the vertical incision.

Post-operative instructions

All patients will be instructed to maintain a liquid diet for 2 weeks after the sinus surgery, continue on a soft diet for one month and general diet for the remaining duration of the healing phase. If a patient presents with a removable prosthesis, the prosthesis will be evaluated for proper tissue adaptation. If the tissue adaptation is poor, the prosthesis will be relined using a soft reline material (GC Reline Soft, GC, Alsip, IL) following the surgery. The patient will be advised to avoid nose blowing and placing any undue pressure on the surgical site. The patient will be instructed to rinse gently with 0.12% chlorhexidine gluconate solution (Peridex) for the first two weeks following the surgery. Recall examinations will be scheduled two weeks following the surgery for suture removal and at 1, 3, and 6 months after sinus augmentation and 2 weeks before

biopsy and implant placement. The biopsy and implant placement procedure will be performed 8 months after the grafting procedure. A CBCT scan will be taken 2 weeks before implant placement to determine the final implant position and size. (The post operative CBCT scan after sinus augmentation and prior to implant placement is standard protocol)

Surgical and post-operative complications

Surgical and post-operative complications such as perforation of the sinus membrane, acute or chronic sinus infection (pain, suppuration, swelling, nasal fluid leakage), bleeding, wound dehiscence, and exposure of the graft will be recorded.

Biopsy Procedure:

1. After 8 months of healing, a full-thickness flap will be reflected and previous antrostomy site will be located using the same surgical template. Two trephines (2.75mm internal diameter and 3.5mm external diameter, ACE Surgical Supply Company, Inc., Brockton, MA) will be used to collect at least 8mm length biopsy specimen. Two cores will be taken from each patient site; one core from the previous lateral window of each sinus augmentation site without interfering with implant placement and one core from the implant osteotomy site. When obtaining the core from the implant osteotomy site, at least 8mm in length of the grafted bone will be included in the core. The trephines are marked at 8mm,10mm,13mm,15mm.The core samples will be kept in the trephine in 10% buffered formalin, coded and mailed to the laboratory for the histomorphometric analysis.

2. The alveolar ridge will be prepared for implant placement, in accordance with the conventional surgical protocol, and implants of appropriate dimensions will be placed.

Immediately after insertion the stability of the implants will be recorded by measuring the ISQ values.

3. Post-operative care instructions will be provided as described previously.

4. Appropriate healing time for the implants will be allowed for osseointegration, and definitive restorative prostheses will be constructed accordingly.

Confidentiality:

All patient's data will be collected as part of standard care, stored dental record. Bone samples sent to the outside laboratory will be coded. The list will be stored in a locked cabinet or locked office. All information provided to the Principal Investigator by SigmaGraft, Inc, or their designates including non-clinical data, protocols, clinical research findings, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the Ethics Committee. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to SigmaGraft, Inc. or their designates.

Histology / MicroCT assessment

The trephine with the retrieved specimens will be placed in 10% neutral buffered formalin. Each specimen will be labeled and packaged in an individual container, which will then be numerically coded to keep the patient's information confidential and exam-

iners will be blinded. Specimens (40) will be sent to the Hard Tissue Research Laboratory, University of Minnesota School of Dentistry for histomorphometric analysis. Or the specimens will be analysed by using a MicroCT at the university of Loma Linda, center for radiation research. The microCT will give us digital reconstruction of the 3D structure of the core material. This will be analysed for new bone formation, amount of graft material remaining, interaction between the graft and the patient's native bone.

Non-decalcified histologic processing and histomorphometric analysis include the followings:

-Dehydration and infiltration with resin.

-Retrieval of the core specimen from the trephine with as much care as possible at a specific point during infiltration with resin.

-Embedding in specialized Kulzer 7200 light polymerizing resin.

-Preparation of slides to 45-50 μm.

-2 slides will be made from each of the core specimens unless there are extenuating circumstances for a specific specimen making it possible to only produce one good slide.

-Slides will be cut in a longitudinal section unless cross sections are requested.

-Staining of the slides.

-The specimen slides will be stained with Stevenel's blue and Van Gieson's picro-fuchsin. This stain differentially stains material within the specimens. Precise determinations of the percentage of vital, non-vital bone and non-bone components will be conducted using computerized image analysis.

-Vital bone stains bright red with variations in intensity depending on the maturity of the bone.

-Non-vital bone and osteoid stain bright green.

-Nuclei of cells, including osteoblasts, osteoclasts and osteocytes, stain blue.

-Connective tissue stains various shades of green.

-Non-biologic materials such as ceramic material, hydroxyapatite, membranes, etc., are not affected by the stain and are easily visualized and analyzed.

Two slides will be prepared from each core. Specimens will be cut vertically through the center of the core.

Histomorphometric analysis:

All the specimens will be digitized at the same magnification using a NIKON ECLIPSE 50i microscope (Nikon corporation, JAPAN) and a SPOT INSIGHT 2 mega sample digital camera (Diagnostic instruments Inc, USA). Histomorphometric measurements will be completed using a combination of SPOT 5.1 Advanced Software (Diagnostic instruments Inc, USA) and Adobe Photoshop (Adobe Systems, Inc.).

The measurements to be obtained and presented in tabular form are:

1. Percentage of the area of the core, which is bone. Of the bone, the percentage of vital and non-vital bone will be determined.
2. Percentage of non-bone material. (ABBM)
3. Percentage of connective tissue.

The histomorphometric data for each specimen will be recorded as the average of the 2 slides from the specimen.

Statistical analysis:

Statistical package for the social science (SPSS) version 21(SPSS®, IL) computer software will be used for descriptive and inferential statistics in all parameters. Descriptive statistics will be presented for each clinical parameter. Primary hypothesis will be analyzed if it is normally distributed. ANCOVA procedure will be used to test the relation between the primary variables and control the influences of the covariates. Statistical significance is denoted when $P < .05$.

Adherence to Protocol:

Departure from the protocol will not be permitted except for medical conditions that require management not specified in the protocol. Changes in the protocol may be made only by written amendment agreed upon by the sponsor and subsequently approved by the Institutional Review Board.

Patient Withdrawal and/or Replacement:

If a subject decides to withdraw from the study prior to sinus augmentation, this individual will be replaced with another subject. If a perforation of the sinus membrane (> 5 mm) occurs during the surgical procedure, the site will be closed and the augmentation procedure will be aborted. This individual will be replaced with another subject.

If a subject is withdrawn from the study following sinus augmentation, all data associated with this individual will be reported but not included in the final results and analysis. If the subject is unable to attend the required post-operative sessions or is uncooperative, this individual may be dismissed from the study.

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