

**Cone beam computed tomography and histomorphometric assessments on the influence a collagen membrane placed on the antrostomy after maxillary sinus floor augmentation. A randomized clinical trial.**

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**Title**

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**Conflict of Interest Statement**

The authors declare no conflict of interest regarding this study.

Straumann, Basel, Switzerland will provide all biomaterials used for sinus floor elevation. Sweden & Martina SRL, Due Carrare, Padova, Italy, and ARDEC Academy, Ariminum Odontologica s.r.l., Rimini, Italy will cover the costs of the study.

## **Abstract**

**Aim:** to evaluate the dimensional variation and osseointegration of mini-implants at augmented sinus with the antrostomy left unprotected or protected with a collagen membrane.

**Material and Methods:** The Schneiderian mucosa will be elevated and the created space will be filled with a natural bovine bone grafting material (Cerabone® 1-2 mm, Botiss Biomaterials GmbH). In ten patients randomly selected (control sties), a native collagen membrane made of porcine dermis (Collprotect®, Botiss Biomaterials GmbH) will be placed on the antrostomy. In ten patients of the test group, the antrostomy will be left without the membrane. The flaps will be sutured and anti-inflammatory drugs and antibiotics will be administrated to the patients. The sutures will be removed after 7 days. After 6 months, two mini-implants with different surface will be installed and retrieved after further 3 months for histomorphometric evaluations.

CBCTs will be taken for all patients before surgery (T0), after 1 week from sinus floor augmentation (T1) and after 9 months of healing (T2) and evaluation of dimensional variations over time of soft and hard tissues will be performed.

## **Introduction**

After sinus floor augmentation using a lateral access, it was suggested to protect the antrostomy with a membrane. In a systematic review on success of sinus floor elevation and implant survival with meta-analysis, it was shown that the best results were obtained using implant with a rough surface and placing a membrane to cover the antrostomy (Pjetursson et al. 2008). However, in a randomized clinical trial,

similar results in new bone formation were observed histologically six months after sinus floor augmentation both with and without the use of a collagen membrane on the antrostomy (Barone et al. 2011). It has been further shown in an experiment in rabbits that, despite the use of a collagen membrane, the healing at the antrostomy was incomplete, as shown both at the histological and microtomographic analyses (Masuda et al. 2019). Moreover, in a clinical report, it was concluded that the use of collagen membrane does not protect from the migration of the biomaterial through the antrostomy (Nosaka et al. 2015). Aiming to improve the healing at the antrostomy and guarantee the closure during and after healing, the repositioning of the bone plate removed during the preparation of the osteotomy has been proposed (Lundgren et al. 2004, Cricchio 2011). In a study in rabbits (Moon et al. 2014), maxillary sinus augmentation was performed bilaterally. At the test sites, the bone window was repositioned while, at the control sites, a collagen membrane was used to cover the antrostomy. Higher and faster bone formation were seen at the test compared to the control sites. In another study in rabbits (Omori et al. 2018), a similar experiment was performed. However, at the test sites, a cyanoacrylate glue was applied to fix the bone window at the antrostomy after sinus floor augmentation. While the healing inside the augmented sinuses was similar in both groups, at the antrostomies the repositioned bone window was incorporated to the new bone formed within the elevated spaces while, at the collagen membrane sites, the healing incomplete, and the antrostomies presented residual defects.

The biomaterial used may affect the healing. Autogenous bone has been shown to produce higher amounts of new bone compared to other biomaterials (Corbella et

al. 2016). However, while autogenous bone is highly resorbed during healing, deproteinized bovine bone mineral is slowly resorbed and this allows its osteoconductive properties to be expressed (Caneva et al. 2017; De Santis et al 2017). In a study on sinus floor augmentation in patients (Riachi et al. 2012), the dimensional variations of two biomaterial, a DBBM and a high temperature decalcified freeze-dried xenografts in granules, were evaluated. After 4 years from surgery, at the evaluation on panoramic x-rays, the DBBM presented a higher loss of vertical height (~33%) compared to the decalcified freeze-dried xenograft (~23%). In a systematic review (Shanbhag et al. 2014), the volume changes over time after maxillary sinus augmentations were evaluated on computed tomographies or cone beam computed tomographies (CBCTs). Volumetric changes from <20% to 45% were reported. It seems clinically relevant to study how the covering of the antrostomy with a collagen membrane may affect the dimensional variations within a sinus augmented with decalcified freeze-dried xenografts. Hence, the aim of the present study was to evaluate the dimensional variation and healing of the antrostomy left unprotected or protected with a collagen membrane.

## **Material and methods**

The Declaration of Helsinki on medical protocols and ethics will be followed for the present study. The protocol was approved by the Ethical Committee of the University Corporation Rafael Núñez, Cartagena de Indias, Colombia (protocol #02-2015; 19 May 2015). This study will be submitted for registration to ClinicalTrials.gov PRS (<https://clinicaltrials.gov>) to obtain the NCT. The procedures and all possible complications will be thoroughly elucidated to each patient included in the study and signed informed consents will be collected. The Consort checklist will be followed for this report (<http://www.consort-statement.org/>).

### *Study population*

For the present randomized clinical trial, all recruitments, surgeries and follow-ups will be carried out at the University Corporation Rafael Núñez, in Cartagena de Indias (Colombia). To calculate the sample size, the data from a radiographic evaluation on height variation over time of the augmented sinus were used and an n=10 was considered sufficient to show differences if they exist (Zijdeveld et al. 2009). An author not involved in the surgery performed the randomization (MF). Sealed and opaque envelopes containing the assignments will be opened after the placement of the filler material within the elevated space.

The following inclusion criteria have to be fulfilled:

- (i) presence of an edentulous atrophic zone in the posterior segment of the maxilla;
- (ii) height of the sinus floor  $\leq 4$  mm;

- (iii) desiring a prosthetic restoration of the zone using a fix prosthesis supported by implants;
- (iv)  $\geq 21$  years of age;
- (v) good general health;
- (vi) no contraindication for oral surgical procedures; (vii) not being pregnant.

The patients will be excluded if they:

- (i) present a systemic disorder;
- (ii) had a chemotherapeutic or radiotherapeutic treatment;
- (iii) are smokers >10 cigarettes per day;
- (iv) have an acute or a chronic sinusitis;
- (v) had a previous bone augmentation procedures in the zone of interest.

#### *Biomaterial used*

The filler material will be Cerabone granulate 1.0-2.0 mm (Botiss Biomaterials GmbH, Zossen, Germany) composed of a ceramic consisting of hydroxyapatite (pentacalcium hydroxide trisphosphate) produced from bovine cancellous bone in a high-temperature process ( $>1200$  °C). The xenograft presents a macroporosity of dimension included within a range of 100-1500  $\mu\text{m}$ .

The membrane to be used to cover the antrostomy at the control sites is a Collprotect membrane (Botiss Biomaterials GmbH) made of porcine collagen obtained from the corium. Both biomaterials are distributed by Straumann, Basel, Switzerland.

A machined and turned mini-implant of 2.4 mm of diameter and 8 mm of length (Sweden & Martina, Due Carrare, Padua, Italy), were installed.

### *Clinical procedures*

After having exposed the lateral wall of the maxillary sinus, an antrostomy of about 5 mm in height and 10 mm long will be prepared using a diamond insert (SFS 109 029), Komet-Brasseler-GmbH, Germany) mounted on a sonic-air surgical instrument (Sonosurgery® TKD, Calenzano, Fi - Italy). The Schneiderian membrane will be elevated and clinical measurements will be performed using an UNC 15 probe (Hufriedy, Chicago, IL, USA). The space obtained underneath the sinus mucosa will be filled with the xenograft and a resorbable collagen membrane will be placed to cover the antrostomy only at the randomly selected control sites. Single silk sutures will be used to secure the flaps. Amoxicillin 875 mg with clavulanic acid 125 mg twice a day for 6 days, non-steroidal anti-inflammatory drugs as needed, and mouth rinses with 0.12% chlorhexidine three times a day for 10 days will be recommended. The sutures will be removed after 7 days, and the patients will be included in a maintenance follow-up system for the full extent of the study.

After 6 months, two mini-implants with modified or turned surface were installed and retrieved after 3 months for histomorphometric evaluations.

### *CBCT imaging procedures*

Cone beam computed tomographies (CBCTs) will be taken in a specialist radiological center at three different periods: (T0) before the first surgery, for diagnostic purposes, to identify bone widths, volumes, presence of septa and possible sinus pathologies; (T1) 1 week after the surgery, to evaluate dimensional variations



compared to T0 and T2; (T2) 9 months after the surgery, to evaluated dimensional variations compared to T0 and T1.

#### *CBCT imaging analyses*

All radiographic evaluations will be performed with the software i-Dixel 2.0 (J. Morita Corporation, Kyoto, Japan). A line will be drawn following the floor of the nose, crossing the sinus cavity both in the coronal view (axis X) and in the lateral view (axis Z).

#### *Histomorphometric analyses*

Bone-to-implant contact and bone morphometry were evaluated along the mini-implant surface. For both analyses, new bone formation, old pre-existing bone residuals, graft residuals, interpenetrating bone network (IBN, new bone formed inside the graft), and soft tissues were assessed.

#### *The Results Data Element Definitions*

The following parameters will be reported at the various period of tomographic evaluation: (MT) mucosa thickness, (C-F) bone crest height, (X-F) nasal floor height, (A-C) anastomosis height and (AD) its diameter, (XW) sinus width, (LM-F) balcony height, (LM-UM) window height, (ZW) sinus length, (ZE) the largest length of the xenograft/ hard tissue. The floor augmentation heights at the medial, middle and lateral aspects in the coronal view will be calculated using the axis X as reference at the various periods evaluated. The T0 X-area and T0 Z-area will be delimited by the sinus bone walls and the axis X and Z in the coronal and lateral views, respectively.

In the coronal view, T1 X-area and T2 X-area will be obtained subtracting to T0 X-area the areas below the X-axis not filled with biomaterial/ hard tissues (residual area and adding the area above the axis X filled with biomaterial/ hard tissues (exceeding area). The T1 and T2 Z-areas will be calculated similarly for the lateral view.

#### *Outcomes tomographic measures*

Primary outcome: Changing in height of the elevated zone.

Description: Measurements will be assessed in the medial, middle and lateral regions of the elevated zone using the cone beam computerized tomographies (CBCTs) taken in various periods. Comparisons among the CBCTs of each participant will be performed.

Timeframe: The CBCTs will be taken before surgery (T0) and 1-week (T1) and 9 months (T2) after surgery.

Secondary outcome: Changing in area of the elevated zone.

Description: The area will be delineated by the sinus bone walls and the sinus mucosa. The changes will be evaluated on the cone beam computerized tomographies (CBCTs) taken in various periods. Comparisons among the CBCTs of each participant will be performed.

Timeframe: The CBCTs will be taken before surgery (T0) and 1-week (T1) and 9 months (T2) after surgery.

Other pre-specified outcomes: MT) mucosa thickness, (C-F) bone crest height, (XF) nasal floor height, (A-C) anastomosis height and (AD) its diameter, (XW) sinus width,

(LM-F) balcony height, (LM-UM) window height, (ZW) sinus length, (ZE) the largest length of the xenograft/ hard tissue.

Description: Measurements will be assessed in the medial, middle and lateral regions of the elevated zone using the cone beam computerized tomographies (CBCTs) taken in various periods. Comparisons among the CBCTs of each participants will be performed.

Timeframe: The CBCTs will be taken before surgery (T0) and 1-week (T1) and 9 months (T2) after surgery.

#### *Outcomes histomorphometric measures*

Primary outcome: Bone-to-implant contact between the different surfaces and between membrane / no membrane groups

Description: Measurements of new bone formation will be assessed on the histological images taken from the slides and performed between the most coronal bone contact to the surface and the apex of the mini-implant. Comparisons among test and control (without or with a collagen membrane of the access window) and between the two different surface conformations will be performed.

Timeframe: three months of healing.

Secondary outcome: Bone density

Description: Measurements of new bone formation will be assessed on the histological images taken from the slides and performed between the most coronal bone contact to the surface and the apex of the mini-implant. Comparisons among

test and control (without or with a collagen membrane of the access window) and between the two different surface conformations will be performed.

Timeframe: three months of healing.

### *Data analysis*

The histomorphometric and radiographic measurements will be performed twice by a well-trained researcher (KAAA) that will be blinded about the differences in the protocols. Mean values will be obtained between the two measurements and used for analyses.

Mean values and standard deviations (SD) will be calculated for each outcome variable. Differences between the test and control groups will be analyzed with the IBM SPSS Statistics software (IBM Inc., Chicago, IL, USA) using the Mann-Whitney test. The level of significance will be set at  $\alpha=0.05$ .

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