TITLE: Bone healing at non-submerged implants installed with different insertion torques. A split mouth histomorphometric randomized controlled trial.

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ABSTRACT

Objectives: to evaluate histomorphometrically the healing at implants installed with standard or very low insertion torque values.

Material and methods: Twelve volunteer patients will be recruited, and two screw-shaped titanium devices will be installed in the distal segments of the mandible using insertion torque values of either <10 Ncm or ~30 Ncm. The implants will be left to heal in a non-submerged fashion. After 8 weeks, biopsies will be retrieved and ground sections will be prepared for histological evaluation.

INTRODUCTION

Very high insertion torque values have been recommended when immediate loading is applied to implants.[1] However, it has been shown that similar clinical outcomes may be achieved even with insertion torque values ≤15 Ncm when implants are splinted together.[2] Nevertheless, in a consensus conference, insertion torque values comprised between 20 and 45 Ncm were recommended for implants immediately loaded with single crowns.[3] Moreover, in animal experiments, the highest rate of osseointegration was observed when insertion torque of 30-35 Ncm were applied.[4-6]

Different insertion torque values have been tested both in human [7-9] and in animals studies.[1,4-6,10-12] A systematic review with meta-analyses summarized data from both animal and human studies and two groups were identified based on the insertion toque values: >25 Ncm or <30 Ncm. [13] No differences were found between the two groups in terms of implant survival rate or marginal bone loss. Nevertheless, in a randomized clinical study,[7] after 12 months of healing, implants installed with torque ≥50 Ncm presented higher marginal bone loss compared to implants with torque included between 20-50 Ncm. Very low insertion torques have been also tested both in animals and humans. After 4 months of healing, in an experimental study in dogs,[5] an osseointegration >55% was

obtained at implant installed with torque close to 0 Ncm. In a clinical study,[8] eleven implants were installed with a torque <10 Ncm. After 4 to 6 months, a reversal torque of 35 Ncm was applied and all implants showed a good stability.

However, it has to be considered that implants presenting a rotational instability during implant installation resulted in a lower survival rate compared to implants installed with higher insertion torque.[14,15]

Due to the contradictory outcomes on the influence of the torque on osseointegration and a lack of histological data in humans, there is a need of more evidences that may support the clinicians in the decision making when an unintentional low insertion torque occur at implants during the daily practice.

Hence, the aim of the present study was to evaluate histomorphometrically the healing at implants installed with standard or very low insertion torque values.

MATERIALS & METHODS

Patient selection

The Declaration of Helsinki on medical protocols and ethics will be followed. The protocol has the approval of the Ethical Committee of the Corporación Universitaria Rafael Núñez, Cartagena de Indias, Colombia with protocol #04-2014 on October 8, 2014. All treatments will be performed in that institution starting from November 2016. All surgical procedures and possible complication will be clearly explained to each participant and a written informed consent was signed by all patients. The study will be reported according to the CONSORT guidelines.

For sample calculation, data from a dog experiment were used [5] and a sample of 12 subjects was calculated for matched pairs considering a difference in bone-to-implant contact of 10% being clinically relevant. A power of 0.8 and α=0.05 were used.

The following inclusion criteria will be required:

(i) presence of at least two edentulous zone in the posterior segment of the mandible

(ii) ≥ 25 years of age

(iii) smoking ≤ 10 cigarettes per day

(iv) Good general health

(v) No contraindication for oral surgical procedures.

(vi) Not being pregnant.

The following exclusion criteria will be adopted:

(i) Presence of systemic disorders

(ii) Chemotherapy or radiotherapy;

(iii) Smokers >10 cigarettes per day

(iv) Previous bone augmentation procedures in the region.

Device

Customized solid titanium screw-shaped devices will be used (Sweden & Martina, Due Carrare, Padua, Italy). The devices have an intraosseous portion with a moderately rough surface[16] (ZirTi® surface, Sweden & Martina, Due Carrare, Padua, Italy). The intraosseous portions will be 4 mm long, with a diameter of 2.65 mm at the apical aspect and 3 mm at the coronal margin. A polished neck 2.4 mm long junction represents the transmucosal portion of the implant.

Randomization

Each patient will receive two mini-implants, installed in recipient sites prepared either to reach torque of <10 Ncm or ~30 Ncm. The two recipient sites will be selected prior the surgery, while the type of site preparation will be randomly decided. The randomization will

be performed electronically (randomization.com) by a researcher neither involved in the selection of the patients nor in installation of the devices (DB). Sealed opaque envelopes will be prepared and opened at the time of surgery by an author not involved in the surgery (DB). Surgeon and patients will be blinded.

The histological slides will be coded so that the assessor will be blinded about the type of site preparation when the histological slides will be evaluated.

Clinical procedures

The surgical procedures will be performed by an expert surgeon. After the injection of local anesthesia, small crestal and releasing incisions will be performed in the distal segments of the mandible, and small full-thickness muco-periosteal flaps will be elevated. The test sites (<10 Ncm) will be over-prepared with drills of larger diameter compared to those used at the standard sites (~30 Ncm). All site preparations will be performed deeper compared to the length of the implant so that the implant apex cannot reach the bottom of the osteotomy. This, in turn, means that the final torque will be produced by the lateral pressure against the bone walls, as described in a previous animal experiment.[4] The mini-implants will be subsequently installed and the final insertion torque will be measured with wrench calibrated on a newton-meter (Newton; Leader Italia, Cinisello Balsamo, MI, Italy). A cover screw will be placed on the top of the mini-implants, and the flaps will be sutured allowing a non-submerged healing.

Maintenance

Antibiotics (amoxicillin 875 mg/clavulanic acid 125 mg twice a day for 6 days) and non-steroidal anti-inflammatory drugs as needed (Ibuprofen 400 mg) will be prescribed. Mouth rinses with 0.12% chlorhexidine three times a day for 10 days will be also recommended.

After 7 days, the sutures will be removed, and the patients will be recalled every 2 weeks after surgery.

Biopsies

After 8 weeks of healing the patients will be recalled to the clinic for biopsies retrieval. Full-thickness flaps will be elevated and biopsies including the mini-implants will be retrieved using the trephine in an eccentric position to reduce the size of the donor site and obtain sufficient hard tissue at least at one side of the biopsies. [17]

Histological preparation of the biopsies

The biopsies will be washed in saline solution and immediately stored in 10% buffered formalin. The histological process will be performed in the Histology Laboratory for Hard Tissues at the University of Chieti-Pescara, Italy. All biopsies will be first dehydrated in an ascending series of alcohol and subsequently embedded in resin (Technovit® 7200 VLC; Kulzer, Wehrheim, Germany). After polymerization, the biopsies will be sectioned following the longitudinal axis using a precision diamond disk. Specimens of ~150 microns of width will be obtained that will be afterwards ground to ~30 μm of width. A staining with acid fuchsine and toluidine blue will be applied.

Histomorphometric evaluation

The histomorphometric evaluations will be performed twice by an expert examiner, and mean values will be used. The examiner will be blinded, and no indications will be reported on the histological slides that may allow the identification of groups. All histological analyses will be performed in ARDEC facilities (Ariminum Odontologica, Rimini, Italy) using an Eclipse Ci microscope (Nikon Corporation, Tokyo, Japan) that will be coupled with a digital video camera (Digital Sight DS-2Mv, Nikon Corporation, Tokyo, Japan). The

measurements will be taken using the software NIS-Elements D 4.10 (Laboratory Imaging, Nikon Corporation, Tokyo, Japan). The percentages of new bone, pre-existing (old) bone, soft tissue (marrow spaces, Haversian canals, BMUs canals), bone debris/ clot remnants, and marrow spaces (soft tissue) will be evaluated both in contact with the implant surface and surrounding the implant to a distance of 0.4 mm from the surface. All measurements will be performed at x200 magnification from the most coronal contact of bone to the implant surface (B) to the apical extension of the tissues (A). The total mineralized bone will be assessed as sum of new and old bone. For the morphometrical measurements of the tissues surrounding the implant surface (tissue density), a point counting procedure will be adopted, using a lattice with squares of 50 microns superimposed over the histological image, at a magnification of x200.

Outcomes measures

Primary outcome: New bone in contact with the implant surface

Description: The percentages of new bone will be evaluated both in contact with the implant surface

Timeframe: After 8 weeks of healing

Secondary outcome: Bone density around the implant surface

Description: The total mineralized bone will be assessed as sum of new and old bone

Timeframe: After 8 weeks of healing

Other pre-specified outcomes: pre-existing (old) bone, soft tissue (marrow spaces, Haversian canals, BMUs canals), bone debris/ clot remnants, and marrow spaces (soft tissue)

Description: The percentages of pre-existing (old) bone, soft tissue (marrow spaces, Haversian canals, BMUs canals), bone debris/ clot remnants, and marrow spaces (soft tissue) will be evaluated all in contact with the implant surface

Timeframe: After 8 weeks of healing.

Data analysis

The primary variable will be new bone in contact with the implant surface. New bone (bone density) around the implant surface will be the secondary variable.

Mean values and standard deviations as well as 25th, 50th (median), and 75th percentiles will be calculated for each outcome variable. Means, standard deviations and 95% confidence intervals of the differences between test and control sites will be calculated for each variable analyzed.

A Wilcoxon test will be used to analyze differences between sonic and drill groups. The level of significance will be set at α 0.05.

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