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EFFECT OF TERIPARATIDE ON MAXILLARY SINUS AUGMENTATION AND OSSEOINTEGRATION

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SUMMARY

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Objectives: The aim of this study is to analyze the effect of a dose of teriparatide combined with a xenograft on maxillary sinus augmentation, to observe the microarchitecture of the neoformed bone and the primary and late stability of implants installed in these grafts. Material and Method: The sample, is composed of 42 participants who have clinical and radiological indication of subantral grafting for presenting residual bone height ≤ 5 mm in the posterior maxillary region for the installation of dental implants. The sinus augmentation will be grafted with Bio-Oss® or Bio-Oss® combined with 1 dose (20 µg) of teriparatide (Forteo®). Three months after grafting, at the time of installation of the dental implants, bone biopsies will be obtained using a short 2mm trephine drill. These bone nucleous will be fixed in 4% paraformaldehyde and will be submitted to histological and histomorphometric analysis. The stability of the implants will be measured, at the time of their installation, through the insertion torque, and through the use of resonance frequency equipment (Ostell®) in three moments: immediately and at 3 and 6 months after the installation of the dental implants. The bone level will be evaluated by cone beam tomography at four times: T0 (baseline), T1 (1 week after maxillary sinus enlargement), T2 (3 months after maxillary sinus enlargement and before implant insertion) and T3 (6 months after prosthetic connection). The parametric data obtained will be submitted to the normality test (Shapiro-Wilk test). Once the normality of the data found is confirmed, the effect of the treatment will be determined by the paired t-test at 95%. Otherwise, the Mann-Whitney test should be used, considering alpha=5%. The effect of time on the bone level in relation to baseline and the resonance frequency will be evaluated by ANOVA or Kruskal-Walis test, depending on the normality of the data, also considering alpha=5%. The data will be expressed in terms of mean or median and 95% confidence interval. The calculations will be performed in Prism (Graphpad Software).

Keywords: Teriparatide, Bio-Oss®, bone regeneration, bone substitutes, maxillary sinus floor enlargement, dental implants .

INTRODUCTION

Severe tooth loss is related to the absence of fewer than nine teeth in the oral cavity and includes the total absence of teeth or edentulism. The main cause of this is advanced tooth loss, periodontal disease, trauma, congenital deformities and pathological lesions. Losing teeth and living with reduced or absent teething can be psychologically traumatic, socially harmful, and functionally limiting for the affected individual. [38.41]

According to the National Health Survey 2016-2017 (ENS 2016-2017) 32.3% of the Chilean population has non-functional dentition (presence of less than 20 teeth in the oral cavity). Regarding the use of removable prostheses, 22.4% of the population makes use of it, and 36.8% belong to the range between 45 and 64 years and 65.8% to the group over 65 years. Of the dental prosthesis users, 85.4% use bimaxillary prosthesis, 13.4% maxillary prosthesis and 1.2% mandibular prosthesis[38]. In Brazil, the prevalence of dental use and the need for dental prosthesis is 78% and 68.7%, respectively.

Several studies have described common biological complications associated with the use of removable dentures and fixed dentures on dental parts, as well as a greater deterioration of patients health when compared to the use of prostheses on implants. High rates of pillar tooth loss, high rates of caries, increased biofilm and gingival indices, increased loss of supporting tissue, presence of stomatitis, and exacerbation of temporomandibular disorder symptoms have been reported[39].

The increased use of implants for rehabilitation of edentulous jaws, through implant-supported prostheses, has led several specialists to face challenging cases, with little bone remaining, especially in the posterior area of the maxilla. In these cases, bone repair may be insufficient, especially in large defects, classified as critical defects[5]. Faced with this challenge, bone augmentation procedures become essential for extreme anatomical situations of decreased bone quantity and quality.

There are several techniques and materials that can solve this challenge. All of them have as the main objective to increase the volume and quality of the alveolar bone. One of the most predictable techniques is the technique of lifting the maxillary sinus by opening a window on

the lateral wall of the sinus, which allows to increase the critical edges with a height of 3 to 5 mm. Several authors advocate the use of bone grafts in residual maxillary processes, critical, less than 4 mm high[62]. However, recent studies advocate the use of the combination of other bone substitutes in alveolar processes smaller than 3mm, also verifying that the failure rates of implants installed in non-grafted edges smaller than or equal to 5mm are higher when compared to edges equal to or greater than 10mm[27,62].

To date, the survival rate of implants installed in grafted maxillary sinuses varies between 61.7% and 100% in 3 to 5 years[20]. Currently, we understand that the survival success of implants installed in enlarged maxillary sinuses is directly related to the materials used in the grafts, in the design of the implants and in the improvement of surgical techniques. Another important factor that should be considered is the repair period before the implants are installed. Traditionally, longer periods of bone repair can improve graft maturation and bone quality, leading to better implant survival rates[42.] Some studies report that a period of 9 months, in a maxillary sinus grafted with demineralized bovine bone, increases the success rate of the implant to 98.9%[15]. Other investigations have demonstrated in vivo models that bone/early implantation contact in grafted maxillary sinuses is more favorable with autogenous bone than in those installed where a mixture of 50% autogenous bone and 50% lyophilized demineralized bovine bone (Bio-Oss®) was made after the 12-week period[28].

Within the materials that can be used in bone regeneration techniques we can include autogenous, allogeneic, xenogeneic and synthetic grafts[9,14,17,36,55]. Autogenous grafts are considered the "gold standard" due to their osteogenic, osteoinductive and osteoconductive characteristics, respectively. However, they have several disadvantages, such as the need for a second surgical bed, complications related to surgery of the donor area and, in addition, are subject to a decrease of up to 60% of their volume in 10 months after the installation of the bone graft[35].

Inorganic bovine bone (demineralized xenogeneic graft) has been widely used as a filling material both in increasing the alveolar process and in increasing the floor of the maxillary sinus[34]. Can be found in the literature several studies regarding its use in conjunction with various materials[61]. It is a graft that has been described as nonabsorbable, but it has been observed to

have a resorption rate when compared to synthetic grafts such as hydroxyapatite[40,44]. In cases of increased alveolar process, the inorganic bovine bone graft with 10% collagen (Bio-Oss®) presents better results in the rates of resorption and maintenance of bone microarchitecture when compared to hydroxyapatite[7].

A variety of materials, such as growth factors, morphogenic proteins, leukocyte- and platelet-rich fibrin, interferon-gamma, and synthetic parathyroid hormone, have been used in conjunction with bone substitutes to increase both bone quantity and quality in areas of bone defects[2,7,11,31,32,35,37]. In recent years, teriparatide, a homologue of parathyroid hormone, has become the object of study in the process of repairing bone defects. Teriparatide (rhPTH(1-34)) is a molecule identical to the 34-amino acid N-terminal sequence of endogenous human parathyroid hormone, which is manufactured using recombinant DNA technology[12,18]. It is associated with the stimulation of osteoblasts in bone formation and subsequently osteoclasts for resorption, thus regulating bone remodeling.

Teriparatide is the only anabolic approved by the *Food and Drug Administration* (FDA) for the treatment of osteoporosis, thus making it the first- and second-line drug for the treatment of this disease in several countries. It has also been shown to significantly reduce the time of union of bone fractures by increasing the formation of bone callus[10,21,49]. In dentistry it has been used in the treatment of medicament related osteonecrosis of the jaw (MRONJ)[6,56,58,59].

Because of these effects, teriparatide is being widely explored in alveolar bone regeneration, in the treatment of chronic periodontitis, osseointegration of implants, maxillofacial trauma, in orthodontics and dentofacial deformities treatment respectively[2,8,26,33,60]. Most publications in the dental field are related to animal models and indicate traditional subcutaneous administration. Only one study evaluated its use in a single dose, demonstrating a positive effect on the integration of an allogeneic graft and suggests, together with other studies, that clinical trials are needed to investigate the efficacy of teriparatide in bone regeneration[26].

In this context, it is believed that teriparatide may be an important ally when used in conjunction with a bone substitute in the increase of the maxillary sinus floor in patients with atrophic jaws, candidates for rehabilitation with implants. Based on this analysis, the following question is asked: does the local use of a single dose of teriparatide associated with lyophilized

demineralized bovine bone graft in the maxillary sinus floor augmentation accelerate and improve the bone repair process of patients with atrophic edges that are candidates for rehabilitation with implants? The hypothesis of this study is that the combination of a local dose of teriparatide with lyophilized demineralized bovine bone, used to increase the sinus floor, stimulates, and improves the bone morphology of patients with atrophic jaws who are candidates for rehabilitation with implants.

AIMS

General aim

The aim of this study is to evaluate the effect of a single and local dose of teriparatide (20 µg, Forteo®, Technopharma, Chile) combined with demineralized lyophilized bovine bone graft (Bio-Oss®) on the maxillary sinus floor enlargement of patients with residual bone height ≤ 5 mm (Misch SA-4 classification) candidates for implants in the posterior maxillary region.

Specific aims

- To describe histologically the effect of a single dose of teriparatide, associated with a mineralized lyophilized bovine bone graft, on bone repair of sinus floor augmentation.
- To analyze through histomorphometry the effect of a single dose of teriparatide, associated with a mineralized lyophilized bovine bone graft, on bone repair of sinus floor augmentation.
- To evaluate through cone beam tomography the maintenance of bone volume of mineralized lyophilized bovine bone graft combined with a local dose of teriparatide in sinus floor augmentation.
- To evaluate the stability of implants installed in grafted maxillary edges with the association of a single dose of teriparatide, associated with a mineralized lyophilized bovine bone graft.

JUSTIFICATIONS

Maxillary sinus augmentation is considered one of the most predictable and conventional procedures for the treatment of alveolar borders with insufficient bone volume and density. It is a procedure that aims to increase bone height through the placement of bone grafts/substitutes and consequently allows the installation of dental implants. It is also a procedure that should be performed in two stages (grafting and subsequent implant installation) in cases of severe atrophy (<5 mm residual height) with the aim of increasing the bone volume of the region to achieve primary stability at the time of installation of dental implants.

Along with this, several researchers have focused on studying the effectiveness of different bone substitutes to ensure optimal results both in the bone repair process and in the proper bone integration around dental implants, vital for the rehabilitation of edentulous patients. Teriparatide (PTH1-34) has been shown through several studies to have positive effects on bone regeneration through cellular mechanisms of proliferation and differentiation and thus improving trabecular bone formation.

In addition, it has been described that xenografts treated locally with teriparatide show clear evidence of increased cortical bone thickness, increased mineral apposition, and decreased amount of bone graft particles due to an increase in bone regeneration through the process of bone remodeling and replacement, in which bone graft particles are replaced by new bone[19]. We believe that the local mixture of teriparatide with xenograft accelerates bone mineralization in addition to increasing the hardness of regenerated bone, factors that directly influence the osseointegration of implants installed in these sectors.

Finally, sinus floor augmentation represents an excellent model to study the behavior of bone repair based on bone substitutes, since a sample of the repaired bone can be taken at the time of implant installation, precisely in the same place where it will be placed. The relevance of this study is to show the importance of developing protocols that favor the prompt installation of dental implants after repair of the maxillary sinus floor augmentation with the objective that patients can be rehabilitated in a shorter time. Being the use of teriparatide, in local dose, mixed with a xenograft, an excellent possibility to improve both the quality of the repaired bone, as well

as to reduce the waiting time between the surgical steps and the prosthetic steps. Thus, a prompt oral rehabilitation can be guaranteed, improving the quality of stomatognathic health, and consequently improving the quality of life of patients.

EXPECTED RESULTS

The results of this study, once proven, may present the use of teriparatide as a protocol for the regeneration of critical bone defects not only in implantology, also be used in the reconstruction of defects associated with dentofacial anomalies, in the treatment of complications and bone sequelae related to trauma and oral and maxillofacial pathologies.

MATERIAL AND METHODS

This project corresponds to a randomized, triple-blind controlled clinical study that is part of the Doctoral Program in Dentistry, Concentration Area of Oral and Maxillofacial Surgery and Traumatology of the Fluminense Federal University - UFF (Niterói, Rio de Janeiro, Brazil) that will be carried out at the Department of Oral and Maxillofacial Surgery and Traumatology of the School of Dentistry of the University of Valparaíso in conjunction with the Biomedical Research Center of the School of Medicine of the Valparaiso University between the years 2022 and 2025.

The universe of study are patients treated at the Dental Clinic of the Faculty of Dentistry of the University of Valparaíso, Chile, for rehabilitation with dental implants. Patients should be evaluated for rehabilitation by the Postgraduate Course in Oral and Maxillofacial Implantology in conjunction with surgical planning by the Postgraduate Course in Oral and Maxillofacial Surgery and Traumatology of the School of Dentistry of the University of Valparaíso. Within the inclusion criteria, participants must be between 25 and 70 years of age, requiring the installation of implants in the upper jaw and presents pneumatization of maxillary sinus of ≤ 5 mm in height (according to conebeam tomography baseline) and must sign the free and informed consent for participation in this study. Exclusion criteria are: residual edges smaller than 4 mm in height, uncontrolled systemic disease (ASA 3, 4, 5 and 6), presenting with osteoporosis or any disease of bone metabolism, having undergone radiotherapy, patients with cancer, any systemic condition that affects calcium absorption, kidney disease, having coagulation disorders, history of sinusitis, maxillary sinus pathology, heavy smoking (> 1 pack per day), drug or alcohol users, pregnancy, treatment with drugs that affect bone metabolism , treatment with immunosuppressants, allergies, uncontrolled periodontal pathology and tooth extractions in the last three months.

The sample was calculated using https://www.sealedenvelope.com/power/continuous-superiority/. The calculation was performed based on the results of previous studies, with a standard deviation of 5.62% for the first variable (amount of bone formed) and a difference of 6.5% between the test and control groups, obtaining an effect size of 0.98.[61] Occupying this effect size with a margin of error of 0.05 and a confidence level of 90%, a sample size of 38 participants was obtained, 19 for the control group (CG) and 19 for the study group (GTP), respectively.

Projecting the withdrawal of participants add up to 2 more participants in each group, so each group will have 21 participants counting with 42 participants as a total sample.

This study was approved by the Scientific Ethical Committee of the University of Valparaíso (CEC 256-22) following Law No. 20,120 (Law of Scientific Research on Human Beings) and Law No. 20,584 (Law of Rights and Duties of the Patient) issued by the Ministry of Health of the Government of Chile. And following the normative for controlled clinical trials, the protocol is being submitted to the registration of protocols in *Clinical Trials.* All participants must sign the free and informed consent where the essential aspects of this investigation, its purpose, benefits, risks and alternative procedures and treatments are made known. This consent will provide adequate, sufficient, and understandable information in relation to the investigation. The participant shall have the right not to authorize the investigation or to revoke his/her consent at any time if he/she so wishes.

All selected participants should be evaluated imaging through a conebeam tomography of the maxillary region at the following moments: preoperative (T0 or baseline; inclusion criteria), one week after maxillary sinus enlargement (T1), at 3 months after maxillary sinus enlargement and before implant insertion (T2), and finally 6 months after prosthetic connection (T3). All images should be used for linear measurement of the floor of the maxillary sinus and should include from the lowest point of the alveolar process to the most superior radiopaque point of the floor of the maxillary sinus exactly in the region where the grafts will be performed and later the installation of the implants.

To standardize the imaging evaluation, all participants should take the images in the same radiological center, under the attention of the same radiologist, performed in the same conebeam taking equipment (Instrumentarium OP300 Maxio, Instrumentarium®, Finland), with FOV 6x8 with corresponding voxel, participants patterned with octagonal lights, using a radiographic guide, made by the researcher. All images will be digitized and analyzed by the same radiologist through the Cliniview™ software (Instrumentarium®, Finland).

For randomization, the system provided in https:// www.sealedenvelope.com. In order to reduce the risk of bias on the part of the surgeon (principal investigator) once the patient enters the center surgical, a member of the staff of this, will be responsible for to perform the

randomization and upload this information (participant identification and graft used) to a spreadsheet shared with one of the alternative researchers. For the TPG (study group) will be made the mixture of 20µg of teriparatide (Forteo®, Ely Lilly, France, Technofarma- Chile), 0.64ml of saline solution (Sodium chloride 0.9%, Baxter, Chile) with 1g of Bio-Oss® (Geistlich, Dentalmax, Santiago, Chile). In the CG (control group) will be made the mixture of 1gr of Bio-Oss® (Geistlich, Dentalmax, Santiago, Chile) with 0.72ml of saline solution (sodium chloride 0.9%, Baxter, Chile).

The volumes of saline needed to hydrate 1gr of Bio-Oss® of the study (TPG) and control (CG) groups, respectively, were calibrated in the laboratory of the Biomedical Research Center of the Faculty of Medicine of the University of Valparaíso by the principal investigator. In TPG a dose of Forteo ® is applied (20µg of teriparatide per dose of 80µl) to 1gr of Bio-Oss®. In order to obtain complete hydration of the graft, through a BioPette ™ (Plus Single-channel 20 – 200µl pipette (Labnet, Edison, NJ- USA) 80µl of saline solution (0.9% sodium chloride, Baxter, Chile) were applied until hydration of the graft was achieved, calculating a total of 640 µl. For CG, which does not present teriparatida, occupying the same pipette, 720 µl of saline solution (0.9% sodium chloride, Baxter, Chile) were used. It should be noted that the employee responsible for the randomization will be the same to perform the preparation of the grafts. For this procedure this employee will be calibrated by the principal investigator in the use of pipette and mixture of grafts.

The surgical procedures will be performed in the Surgical Center of the School of Dentistry of the University of Valparaíso by the principal investigator (maxillofacial surgeon) belonging to the Service of Oral and Maxillofacial Surgery and Traumatology of this School. All maxillary sinus augmentations should be performed by the same surgeon and assistant. Participants should be premedicated with antibiotic therapy, nasal decongestant, and anti-inflammatory drugs 24 hours prior to surgery. Fisiolimp (sodium chloride 0.9%, Pasteur Laboratory, Chile) will be indicated as a decongestant, administering a puff in each nostril every 6 hours from three days before the procedure; amoxicillin 1g (Ambiotic 1 g, Laboratorio Chile, Teva) and naproxen sodium 550 mg (Laboratorio Chile, Teva), both 1 hour before surgery. For the procedure, local anesthesia will be used with Articaine 4% 1:100,000 (Septanest 4% 1:100,000, Septodont, France). A mucoperiosteal flap will be raised to access the anterior wall of

the maxillary sinus. Access to the maxillary sinus will be done through osteotomy, using a piezosurgery (VarioSurg, NSK, Nakanishi Inc, Japan) under saline irrigation. Subsequently, the Schneider membrane will be raised carefully and, according to the randomization process, the graft material (Bio-Oss® mixed with saline solution or Bio-Oss® mixed with Forteo®) will be delivered for placement on the floor of the maxillary sinus below the Schneider membrane.

Next, the access window to the maxillary sinus and the Schneider membrane will be protected with resorbable membrane of bovine collagen type I (Bio-Gide® Membrane 25x25mm, Geistlich, Dentalmax, Santiago, Chile). The mucoperiosteal flap will be repositioned and closed with Vycril 4.0 (Ethicon, J&J Surgical Technologies, USA). All patients will be indicated for postoperative Amoxicillin 1gr (Ambiotic 1gr, Laboratorio Chile, Teva) 1 tablet every 12 hours for 7 days, Naproxen Sodium 550mg 1 tablet every 12 hours for 5 days (Laboratorio Chile, Teva), Paracetamol 500 mg 1 tablet every 8 hours for 3 days. All participants should be monitored 7 days after surgery for post-surgical control and radiographic control (T1).

The installation of the implants (Mis SEVEN, Mis Implants, Mis® Implants Technologies, Israel, MBM Business Group SpA, Chile) will be planned once the images (T2) are evaluated 3 months after the graft placement. The Mis Seven implants feature a conical design, internal connection type *platform switch* and surface treated through blasting and acid attack. At this stage, the implant placement surgery should be performed by the same team of surgeons as in the first stage of the surgery. On this occasion, local anesthesia will be performed with 4% articaine 1:100,000 (Septanest 4% 1:100,000, Septodont, France). A mucoperiosteal flap will be raised in the area for implant installation and a bone core 10 mm high and 2 mm in diameter will be removed with a 2 mm trephine drill (DSP Medical, Dental Tech, Santiago, Chile). The bone biopsied through this nucleus is part of the region where the implant will be installed, and the height of the sample depends on the surgical planning previously performed (radiographic control 3 months). The sequence of drills will continue for implant placement, installation of the implant itself and finally the verification of the insertion torque and measurement of the resonance frequency with the Osstell ® (W&H; Göteborg, Sweden) in the implant already installed. The mucoperiosteal flap should be repositioned and sutured with Vycril 4.0 (Ethicon, J&J Surgical Technologies, USA). For the postoperative period naproxen sodium 550 mg 1 tablet every 12

hours for 5 days (Laboratory Chile, Teva) and Paracetamol 550 mg 1 tablet every 8 hours for 3 days. All participants should be controlled 7 days after surgery. Three months after the installation of the implants, a radiographic and clinical control (T3) will be performed to evaluate the osseointegration, graft and measurement of the resonance frequency with the Osstell®, for subsequent referral to functional and aesthetic procedures in the Post-Graduation in Oral and Maxillofacial Implantology of the School of Dentistry of the University of Valparaíso, Chile.

For the beginning of the histological and histomorphometric analysis, the bone nuclei removed in the implant placement surgery should be fixed with 4% paraformaldehyde (PFA 4%) and stored at 4°C for 24 hours before the beginning of the laboratory procedures. These samples will be worked together with the collaborators of the Center for Biomedical Research, of the Laboratory of Morphological Analyses of the Faculty of Medicine of the University of Valparaíso.

All bone samples should be decalcified in 10% EDTA solution for 2 weeks at room temperature. Subsequently, these samples must be subjected to an ascending series of alcohol, starting 50, 70, 80, 95, 100, then Xylol. Then they should be soaked in paraffin blocks and these should be cut into serial sections 5 µm thick along the central axis of the biopsies, deparaffinized, rehydrated and stained with hematoxicillin and eosin.[23,24] Three sections of each sample should be randomly and blindly analyzed by an experienced pathologist who should perform descriptive histological analysis using a millimeter scale fitted to the 40x magnification eyepiece of a BH2 microscope (Olympus Optical Company, Ltd., Tokyo, Japan) for counting blood vessels, mesenchymal stromal cells, osteoblasts, osteoclasts, and osteocytes per mm2. In addition, a histomorphometric analysis of separately quantified areas will be performed by means of a point system that should be stored in the ImageJ® SOFTWARE (NIH, USA, http://rsb.info.nih.gov/ij) in 10 random images captured at 10x magnification under a microscope with DP70 digital camera (Olympus) to study the following parameters: necrosis, inflammation, vascularization and angiogenesis, fibrosis, presence of medullary adipose tissue, bone neoformation and foreign body reaction. It is noteworthy that the collaborators who will work in the histological evaluation of the samples will be blind as to the attribution of the graft, because the samples donated by the participants will have a registration number that replaces the name of the participant (e.g. PARTICIPANT 1) in order to reduce the risk of bias, in addition to maintaining the anonymity

during the study. However, these antecedents are recorded in the database of the principal investigator, so it will be known to which sample each participant corresponds.

The implant stability coefficient (ISQ) will be evaluated by measuring the resonance frequency (Osstell ®, Göteborg, Sweden) and the insertion torque at the time of implant installation. The value of the implanted stability coefficient will be measured in two mutually perpendicular directions (distal/medial and palatine/bucal).

Statistical calculations will be performed in Prism (GraphPad Software). The parametric data obtained should be submitted to the normality test (Shapiro-Wilk test). Once the normality of the data is confirmed, the effect of the treatment will be determined by the paired t-test at 95%; Otherwise, the Mann-Whitney test should be used, considering alpha= 5%. The effect of time on the bone level in relation to baseline and the frequency of resonance will be evaluated by ANOVA or Kruskal-Walis test, depending on the normality of the data, also considering alpha= 5%. Data are expressed in terms of mean or median and 95% confidence interval.

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