INFLUENCE OF ENAMEL MATRIX DERIVATIVES FOR THE TREATMENT OF PERI-IMPLANT-RELATED OSSEOUS DEFECTS WITH MINIMAL FLAP APPROACH. Randomized clinical trial.

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Key words:

Reconstructive surgical therapy, peri-implantitis, peri-implant bone defects, bone graft

Title:

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Background:

Periimplantitis is a pathological condition that occurs in the tissues surrounding dental implants. It is characterized by inflammation of the peri-implant connective tissue and loss of progressive support bone (1). In a recent systematic review, a 22% prevalence of peri-implantitis has been described (2). If the literature is analyzed, it can be verified how different percentages of prevalence are reported due to the different definition of this pathological condition depending on the study analyzed, being from 1% to 47% (3). In addition, it has been suggested that this bone loss is time-dependent and that the follow-up time of the different studies can also affect the percentage of prevalence described (4, 5)

The objective of the treatment of peri-implantitis is to resolve the inflammation of the soft tissues and stop the additional loss of the peri-implant support bone. Recent systematic reviews report that regardless of the non-surgical treatment modality used, it is insufficient to stop the disease (6), while surgical treatment has shown greater efficacy and in the longer term (7) (8). Furthermore, it is demonstrated that factors such as the surface of the implant have a significant influence on the results of surgical treatment (8) (9). The anatomical configuration of the peri-implant bone defect has been shown to be another relevant factor, especially when selecting the type of surgical approach to be performed (10). The

goal of reconstructive procedures for peri-implant bone defects is to restore the implant support tissues (11) (12) and thus improve aesthetics and achieve a hypothetical re-osseointegration (13)

The potential benefit of using bone substitutes / biological agents in reconstructive procedures for the treatment of periimplantitis remains undefined for the time being due to the existence of few clinical studies with very heterogeneous designs and different follow-up times.

Concerning to the material that should be used during the reconstructive procedure, the existing literature is heterogeneous. Several studies evaluate the effectiveness of a material without comparing with any control group, while others either compare the use of a material with the performance of only mechanical debridement or with the use of a different material (14) (15) (16) . For this reason it is difficult to draw solid conclusions about the ideal material.

The use of proteins derived from the enamel matrix that have shown such good results in the regeneration of the attachment of teeth with bone defects have also been investigated when reconstructing the support bone lost around the implants. A recent randomized clinical trial (17) reports contradictory results regarding the use of proteins derived from the enamel matrix in the surgical treatment of peri-implantitis. In addition, another cohort study describes the need for better designed clinical trials to be able to analyze correctly the adjunctive use of amelogenins with xenografts and even in combination with antibiotics (18).

There is literature that has evaluated the effectiveness of the use of autologous bone (19), reporting satisfactory results in the reconstruction of peri-implant bone lost and stable at 3 years of follow-up. On the other hand, satisfactory results have also been reported, leading to a reduction in probing depth of 4.23 ± 1.47 mm on average with the use of allograft impregnated in an antibiotic solution (20).

Other material that has been proposed are titanium granules. In a multicenter randomized clinical trial in which its use is compared with performing surgical debridement of the peri-implant lesion (21). In this study, the primary outcome was the radiographic bone filling and although it is true that statistically significant differences were found in favor of the test group, it is necessary to admit the difficulty of distinguishing the biomaterial at the radiographic level. However, other studies describe contradictory results regarding the use of this biomaterial (22, 23).

One of the most investigated biomaterials in the reconstruction of peri-implant bone defects that are the xenografts. A recent clinical trial that compares its use with that of autologous bone, the only outcome in which they described statistically significant differences in favor of the xenograft was the radiographic bone filling (14). A case series in which the use of xenograft is proposed for the reconstruction of peri-implant bone defects obtains predictable results in PPD and radiographic bone filling (24). In addition, they reported that there was no change in the level of the peri-implant mucosa during the entire follow-up. The use of membranes has shown superior results to using bone grafts alone in terms go bone gain around implants prior to or simultaneous to their placement. Nonetheless, around implant with infectious disease the use of membrane has been associated to higher risk of membrane and bone graft particles exposure after wound dehiscence during healing period (25). Two recent randomized

clinical trials reported no clinical benefit of using membrane, both around a xenograft and an allograft (25,26).

Regarding allografts, it must be highlighted that there is not enough evidence, but the studies analyzing the use of allografts to reconstruct the osseous defects around implants have reported favorable outcomes (26,27). This could be due to their biological properties. Furthermore, the use of enamel matrix derivate improves the osteoconductivity of bone grafts (28). Moreover, EMD has antimicrobial effect and a positive effect on wound healing and tissue regeneration. Nevertheless, there is a lack of enough scientific evidence to support the use of enamel matrix derivate in the treatment of peri-implant related intrabony defects (29).

Objective:

The overall objective of the present project is to evaluate the clinical efficacy of the application of enamel matrix derivate with a bovine bone graft and a resorbable membrane in the treatment of peri-implant bone defects and arrest the progression of the peri-implant pathology. Primary outcome is treatment success (absence of BoP/Pus, PPD ≤ 5mm and ≤ 1mm recession of mucosal margin). Secondary outcomes include, volumetric changes, radiographic defect fill, treatment complications appearance and patient-centered outcomes (PROM).

Rationale for the study:

There is little evidence to evaluate the clinical efficacy of adjunctive enamel matrix derivative (Emdogain®) over an allograft in the treatment of peri-implant related intrabony defects with minimally invasive surgical approaches.

Hypothesis:

The enamel matrix derivate simultaneous to intra-bony peri-implant related defect reconstruction with allogeneic bone graft has a better outcome in terms of radiographic defect fill and re-establishing peri-implant health when comparing with using only an allogeneic bone graft with minimally invasive surgical approaches.

Relevance for clinical practice:

The results of this project will help to understand the adjunctive use of enamel matrix derivates in conjunction with allogeneic bone grafts in the reconstructive surgical therapy of peri-implantitis-related bone defects.

Materials & Methods:

Study population, design, and treatment procedures:

The project will be conducted as a two-armed randomized controlled clinical trial of 1-year duration in 2 clinical centers. 40 systemically healthy patients with implants ≥ 1 year in function and diagnosed with advanced peri-implantitis at ≥ 1 implants will be enrolled.

Inclusion criteria:

- Age ≥ 18 years
- Peri-implant bone defect ≥ 3mm assessed radiographically.
- PPD ≥ 5mm combined with bleeding on probing or suppuration
- Intra-surgically, bone defect must have at least a intraosseous component of 3mm and a width of no more than 4mm
- implants ≥ 1 year in function

Exclusion criteria:

- Treated for peri-implantitis during previous 6 months.
- Intake of systemic or local antibiotics during previous 6 months
- Pregnant patients
- Systemically unhealthy patients
- Patients allergic to collagen

Surgical procedures:

Surgical procedures will be performed one month after non-surgical periodontal treatment. The same day of surgical therapy an antibiotic will be administered for 7 days (amoxicillin 500mg / 7 days / 8hours). First minimally invasive surgical flap will be prepared over the implant neck. Large flaps will be avoided to minimize surgical post-operative complications as dehiscence and loss of biomaterial. Control group: surgical reconstructive treatment of periimplantitis by means of implant surface decontamination with a mechanical methods (Labrida BioClean Brush®), and osseous defect reconstruction by means of allogeneic bone graft (Straumann Allograft in particles). Test group: surgical reconstructive treatment of periimplantitis by means of implant surface decontamination with a mechanical methods (Labrida BioClean Brush®), and osseous defect reconstruction by means of allogeneic bone graft (Straumann Allograft in particles) and adjunctive enamel matrix proteins (Straumann Emdogain®). Sutures will be removed 2 weeks after surgical therapy. Clinical examinations will be performed at 4,12,24 and 48 weeks after surgical therapy. Maintenance therapy will be realized at 12, 24 and 48 weeks after therapy.

Clinical assessments:

One calibrated examiner will perform the assessments. The following variables will be assessed at four sites around the implant: Plaque, probing pocket depth (PPD), bleeding on probing (BoP), probing attachment level (PAL) recession (REC). Keratinized mucosa (KM) will be measured in the buccal aspect of each included implant.

Surgical assessments:

One calibrated examiner in each clinical center will perform the assessment. Taking into account the Schwarz et al 2010 peri-implant defect classification, the defect configuration will be measured to understand how much impact it has on clinical outcomes.

<u>Osseous defect related measures / Recording of osseous defect characteristics:</u>

- Defect width (measured in mesial, distal, buccal, and palatal/lingual aspects)
- Distance from implant neck to depth of the osseous defect (measured in mesial, distal, buccal, and palatal/lingual aspects)

- Distance from osseous ridge to depth of the osseous defect (measured in mesial, distal, buccal, and palatal/lingual aspects)

Treatment success:

Treatment success will be defined as the absence of BoP/Pus, PPD ≤5 mm and ≤1 mm recession.

Radiographic assessments:

Intra-oral radiographs will be obtained prior to surgery (baseline) and at 6- and 12-months re-examinations. Analysis of radiographs will be performed by a specialist. The examiner will be blinded to treatment procedures. The assessment will include defect fill in both follow up visits.

Volumetric changes:

Intra-oral scanning will be obtained prior to surgery (baseline) at 6 months and at 12-months re-examination. Analysis of STL archives will be performed by a specialist. The examiner will be blinded to treatment procedures. The assessment will include volumetric changes after matching the baseline intra-oral scanning, 6 months intra-oral scanning and 12-months intra-oral scanning.

Power calculation:

According to Roos-Jansaker et al 2007 and Renvert et al 2018, it was identified that a mean filling of the defect of 1.5mm could be detected with a standard deviation of ± 1.2mm after surgical treatment of peri-implantitis with a bone graft. Including 20 patients for each group a statistical power of 93% would be reached.

Data analysis:

The statistical analysis will consider all the data collected before, during and after the surgical intervention. A descriptive statistic of the data obtained in both groups will be carried out during the study. For the analytical statistics a Shapiro-Wilk normality test will be performed for the quantitative variables.

The changes in the means obtained between the initial situation and 12 months of follow-up will be evaluated using a McNemar test. The patient is the unit of analysis. The data obtained will be analyzed through the SPSS SPSS Statistics Desktop program, V21.00 (SPSS Inc., Chicago, IL, USA

Schedule of investigational events:

The flow chart and time schedule presented below illustrate the overall organization of the study including the sequence of examinations:

1. Ethical approval of protocol by local ethics committee

2. Study announcement and patient recruitment

3. Screening and identification of subjects. Start: 01/09/2023. It is estimated that it will take about 8 months to recruit the total number of patients required for the trial.

4. Baseline clinical examination of implants selected for the study. Non-surgical periodontal treatment. Photographs, data collection of clinical parameters and measurements. Patient perception with peri-implantitis diagnosis will be also collected prior to surgery.

5. Radiographic examination, cone beam computed tomography and intraoral volumetric scanning will we recorded prior to surgery (within 2 weeks)

6. Surgical therapy including test or control treatment procedures. Assessment of PROM, photographs, periapical radiography, and surgery time will be recorded.

7. 2 weeks: suture removal. Assessment of PROM and photographs

8. 4 weeks: photographs

9. 12 weeks: photographs, professional supra-mucosal cleaning, and reinforcement of oral hygiene.

10. 24 weeks: photographs, periapical radiography, collection of possible complications and professional supra-mucosal cleaning and reinforcement of oral hygiene.

11. 48 weeks: photographs, periapical radiography, collection of possible complications, cone beam computed tomography, intraoral volumetric scanning and professional supra-mucosal cleaning and reinforcement of oral hygiene.

Ethical considerations and institutional review:

The protocol is being reviewed by the local Ethics Committee of Basque Country and the study will be registered at isrctn.com.
Each patient will receive oral and written information about study purpose and design, and they will have to sign a consent. Patients must understand that their participation in the study is voluntary, and they can leave it when they want. The study will be carried out following the recommendations of Helsinki declaration. All the included patients will receive surgical treatment of peri-implantitis, and any adverse reaction will be recorded during the follow-up visits.

1. Facilities and expertise:

Study team:

Principal investigator:

Alberto Ortiz-Vigón (Department of Periodontology, Periocentrum Bilbao) has extensive experience in the field of periodontology, implant dentistry and peri-implantitis clinical research.

Study monitoring:

Erik Regidor (Department of Periodontology, Periocentrum Bilbao) has experience in monitoring randomized controlled clinical trials. He will attend all the study during the inclusion period as well as the follow-up period.

Clinical / practical work:

All investigators are trained researchers and specialists in periodontics.
All of them have an extended experience in periodontology, implant dentistry and surgical treatment of peri-implantitis.

2. Organization:

The study will be organized and monitored from Periocentrum Bilbao:

Principal Investigator: Dr. Alberto Ortiz-Vigón (Periocentrum Bilbao, Bilbao, Spain)
Clinical Research Coordinator: Dr. Erik Regidor (Periocentrum Bilbao, Bilbao, Spain)

Data managing: Dra. Ángela Redondo (Periocentrum Bilbao, Bilbao, Spain)
Statistics: Idoia Ayllon and Xabier Marichalar Mendia (Periocentrum Bilbao, Bilbao, Spain)

3. Infrastructure

Periocentrum Bilbao has extended experience in periodontology and clinical research.
Periocentrum Bilbao will be responsible of their data collection and when the study is finished, data analysis and interpretation will be made.
After data interpretation, manuscript will be prepared, and it will be submitted to a pre-reviewed journal.

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