IMPACT OF ORAL HYGIENE INSTRUCTIONS IN THE RESOLUTION OF PERI-IMPLANT MUCOSITIS. A RANDOMIZED CLINICAL TRIAL

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1. Introduction

Peri-implant mucositis (PM) is a highly prevalent disease characterized by inflammation of the peri-implant mucosa without loss of the supporting bone (Berglundh, Armitage, et al., 2018; Ferreira et al., 2006; Koldsland et al., 2010; Romandini et al., 2019; Romandini, Lima, et al., 2021; Wada et al., 2019). Its main clinical sign is the presence of bleeding on (gentle) probing (BoP) (Berglundh, Armitage, et al., 2018). If untreated, PM may progress into peri-implantitis, which is further characterized by the loss of supporting bone and may ultimately lead to implant loss (Costa et al., 2012; Derks et al., 2016).

Similarly to the etiology of periodontal diseases, multiple clinical studies have described a cause-effect relationship between the accumulation of experimental plaque and the development of PM (Pontoriero et al., 1994, Zitzmann et al., 2001). However, soft tissues around implants develop a stronger inflammatory response to experimental plaque buildup when compared to inflammation developed around teeth (gingivitis) (Salvi et al., 2012).

The treatment of PM is focused on the disruption of the dental implant biofilm and aimed at achieving treatment success/disease resolution (i.e., absence of BoP), or at least a reduction in the number of bleeding sites (i.e., BoP extent) or of its severity (e.g., modified bleeding index or mBI; Mombelli et al., 1987; Renvert et al., 2018). Therefore, after a patient's behavioural phase including oral hygiene instructions (OHI), the affected implants usually undergo non-surgical instrumentation, which may be realized through mechanical (e.g., curettes, ultrasonics, air-polishing) and/or physical (e.g., laser) approaches (Baima et al., 2022; Renvert et al., 2019). Adjunctive measures (e.g., antiseptics) may also be used (Jepsen et al., 2015). Many studies have shown that non-surgical mechanical treatment can successfully control PM, reducing plaque and bleeding scores (Renvert et al., 2008).

As mentioned before, the occurrence of PM is mainly influenced by plaque accumulation and therefore effective oral hygiene practices are fundamental in their prevention and management. In fact, there is evidence from experimental human studies that PM resolution may occur with adequate biofilm control (Meyer et al., 2017; Salvi et al., 2012; Schincaglia et al., 2017). The reversibility of experimental PM after the re-institution of plaque control has been confirmed by the decrease to baseline values of crevicular fluid levels of host-derived biomarkers (Salvi et al., 2012). And as it was stated in the latest expert consensus on the prevention and treatment of peri-implant diseases (Herrera et al., 2023), even though, the traditional treatment of PM includes mechanical professional cleaning, up to date the added benefit of professional mechanical/physical instrumentation as compared to OHI alone is not known.

It is therefore the aim of this randomized clinical trial to identify if there is any superiority of mechanical/physical instrumentation over OHI alone.

2. Objectives

-Primary objective:

Evaluate the resolution of the disease, by means of reduction of modified bleeding index (mBI), by individualized OHI and proper oral hygiene measures conducted by the patient after 1 and 3 months of protocol instauration in comparison to the combination of indivifdualized OHI and professional mechanical debridement.

-Secondary objectives:

- Evaluate microbiological changes by individualized OHI and proper oral hygiene measures conducted by the patient after 1 and 3 months of protocol instauration in comparison to the combination of individualized OHI and professional mechanical debridement.
- Determine if the extent of inflammation measured as the initial mBI could have any impact in the PM resolution after treatment.

3. Hypothesis

- The proper oral hygiene measures conducted by the patient after individualized OHI will achieve resolution of PM in a clinically relevant proportion of patients.
- The proper oral hygiene measures conducted by the patient after individualized OHI will reduce the expression of peri-implant pathogens as much as the combination of individualized OHI and professional mechanical debridement in a clinically relevant proportion of patients.
- The proper oral hygiene measures conducted by the patient after individualized OHI will reduce mBI as much as the combination of individualized OHI and professional mechanical debridement in a clinically relevant proportion of patients.
- The extent of inflammation measured as the mBI could be related with the degree of resolution of the disease according to the treatment.

4. Material and methods

ETHICAL ISSUES

This study will be performed according to the principles outlined in the Declaration of Helsinki and Ethical Conduct for Research with Human Beings and after the approval of the Ethics Committee of the Universitat Internacional de Catalunya (UIC).

STUDY DESIGN

The present study will be a prospective randomized controlled intervention trial with a 3-month follow-up.

Randomization of patients will be performed using a computer-generated list with permuted blocks of four. Allocation concealment will be assured by using sealed opaque envelopes that assigned patients to their respective treatment groups. These envelopes will be labelled with the patient study number and only open once after patient has received OH

STUDY POPULATION

Patients attending to the Department of Periodontology at UIC and diagnosed with PM will be recruited consecutively. One calibrated investigator (B.dT) will evaluate patients for screening and will be responsible of enrolling them in the study if they fulfilled the following inclusion and exclusion criteria.

Inclusion criteria:

(1) Presence of, at least, one titanium implant that have been more than one year in function and exhibits PM, defined as bleeding on gentle probing (0.20 N) in at least one peri-implant site.
(2) No signs of loss of supporting bone after initial bone remodelling. In cases where baseline radiograph is available, it will be used for comparison, otherwise a maximum of 2 mm of crestal bone loss will be accepted (Sanz et al. 2012).
(3) Presence of >1 mm of keratinized peri-implant mucosa.
(4) Absence of systemic diseases that could influence the outcome of the therapy (i.e. controlled diabetes, with HbA1c<7, patients will be included).
(5) Non-smoker or light smoking status in smokers (<10 cigarettes/day).

Patients will be excluded if:

(1) Untreated periodontal conditions.

(2) Pregnant or lactating women.

(3) Patients who received systemic antibiotics in the last 3 months.

(4) Patients who received treatment of PM in the past 3 months.

(5) Patients receiving corticoids or medications known to have effect on gingival growth (i.e., calcium channel antagonists, immunosuppressants or antiepileptic drugs).

In those cases diagnosed with peri-implantitis, individualized treatment will be provided, apart from the present study.

TREATMENT

All patients (test and control) will be instructed to brush the implants twice daily to remove supragingival biofilms with a low-abrasive dentifrice and to use specific cylindrical or conical brushes (Interprox®, Dentaid, Barcelona, Spain) in the interproximal area. Patients will be indicated to brush under, around, and in the peri-implant crevice circumferentially. In those cases with no access for proper OHI, prosthesis will be modified according to the protocol described by de Tapia et al. 2019. The interproximal brush device used will be chosen for the patient individually, according to the interproximal space available, the thicker brush that can be used comfortably will be the selected one. It will be previously tested on the patient and its use will be taught, patients should demonstrate proficiency.

- Control group: On the affected implants, supra- and sub-gingival debridement of the implant surface, the implant neck, and the abutment will be carried out by means of a combination of ultrasonics (DTE-D5, Woodpecker®, Guilin, China) with a plastic tip (Hu-Friedy®, Rockwell St, Chicago, IL, USA) and plastic curettes (Hu-Friedy®). Finally, the prosthetic components will be polished with a rubber cup.
- Test group: No further treatment will be provided.

EXAMINATIONS:

A guidebook will be prepared to standardize procedures throughout the protocol, step by step, for all questionnaires and evidence collection. The data will be transferred to a computerized database.
The study variables will be recorded in a case report form (CRF) specially designed for the study. Each study patient will be assigned a numerical code comprising a 3 digit patient code (assigned correlatively as they are included in the study). Only the study investigator will be able to identify the patient by their code.

Anthropometric and socio-demographic data

An initial questionnaire will be conducted to obtain information regarding age, race, gender,

medical history, medication, and health behaviors (smoking habits). Smoking behavior will be specified as 3 categories: never smoker, former smoker, or current smoker (light smokers: < 10 cigarettes/day). Patients will be asked about their tobacco smoke exposure in terms of consumption (i.e. the number of cigarettes consumed per day); duration (i.e. the number of years of smoking); and life-time exposure (i.e. the accumulated exposure as formed by the product of consumption and duration: cigarette-years). In case of former smokers, patients will be asked about the smoke-free time following cessation.

Clinical, radiographic and microbiological examination

At baseline, 1 (1m) and 3 months (3m) after treatment, two calibrated examiners (A.B and L.M) will record the following clinical variables using an electronic, pressure-calibrated probe (PA_ON Probe, Orange Dental®**,** Aspachstr, Biberach, Germany), with a standardized probing force of 0.20 N.

At the full-mouth level, the following parameters will be evaluated:

(1) Full mouth plaque Index (FMPI), assessed dichotomously at four sites per tooth (mesial, buccal, distal, and lingual).
(2) Full mouth bleeding index (FMBI), assessed dichotomously as presence or absence of bleeding after 30 seconds of gently probing (Ainamo and Bay, 1975).
(3) Full mouth probing pocket depth (FMPPD), measured at six sites around each tooth, except third molars.

At local level, in six sites around each implant, the following clinical variables will be recorded:

(1) Modified plaque index (mPI) (Mombelli et al., 1987)
(2) Modified bleeding index (mBI) (Mombelli et al., 1987), dichotomized in presence/absence of bleeding and selected as the primary outcome (BOP).
(3) Suppuration on probing (SOP), assessed dichotomously as presence or absence of suppuration within 30 seconds after probing.
(4) Implant probing pocket depth (PPDi), measured from the mucosal margin to the bottom of the probable pocket.
(5) Implant mucosal recession (MRi), measured from the implant neck to the mucosal margin.

Disease resolution will be considered when a mBI <0.16 is achieved, as it was stablished in the last consensus performed to develop the clinical practice guidelines on the treatment of peri-implant diseases (Herrera et al. 2023).

Individual acrylic resin occlusal stents, exhibiting six vertical grooves per implant (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual and distolingual), will be built in order to allow a reproducible direction and angulation during probing.

A periapical radiograph of all implants involved in the study will be taken using a paralleling cone technique and a film-holder (7mA- 60kV/20ms) at baseline and at 3 months after treatment, in order to detect any loss of supporting bone.
Furthermore, sampling for microbiological test will be conducted at baseline, 1m and 3months after treatment.

SAMPLE SIZE CALCULATION

The unit of analysis will be set at the patient. In those patients with more than one implant fulfilling the inclusion criteria, a mean of the implants included will be taken into consideration for the analysis. Sample size was calculated according to the main outcome "complete disease resolution". Taking into account that previous studies showed a disease resolution around 66.6% (de Tapia et al. 2019) after treatment by means OHI and mechanical debridement, we estimate that at least 50% of patients receiving OHI as a single therapy could present a complete resolution. Accepting an alpha risk of 5% and a beta risk of 10% in a two-sided test, 28 subjects are necessary. It has been anticipated a drop-out rate of 15%. In order to include a second group of patients receiving an usual management as control group, we will include a total of 56 patients (28 in each group).

CALIBRATION

The examiners (A.B and L.M) will follow a calibration exercise by evaluating peri-implant soft tissue parameters (PPDi and mBI) in 5 patients with PM, in two subsequent visits, 48 hours apart. The intra-examiner reproducibility will be accepted when a minimum intra-class correlation coefficients of 0.80 is achieved.

5. Results analysis

The data contained in the CRFs will be entered into a database for data analysis and preparation of the final report.
The socio-demographic and clinical characteristics and other variables of interest of the patients included in the study will be described. Data will be presented as mean ± SD; categorical data will be shown as percentage of positive patients.
The relationship between two qualitative variables will be calculated using the chi-squared test or Fisher's exact test (frequency < 5)
For ordinal variables, linear regression will be calculated using Kendall's tau coefficient.

Quantitative variables will be compared using the Student's t-test (< 2 categories), analysis of variance [ANOVA] (> 2 categories), linear regression test and Scheffé's multiple comparisons test or U Mann Whitney.

The linear relationship between the quantitative variables will be calculated using Pearson's correlation coefficient or Spearman's rank correlation test (when variable not normally distributed).

Changes *versus* baseline will be analyzed by Wilcoxon non-parametric test or Mc Nemar test.

A logistic regression model will be set in order to determine whether the initial extent of the inflammation, mBI, is related to disease resolution

Level of significance will be set at 0.05. The SPSS version 19.00 software (SPSS Inc., Chicago, IL, USA) will be used for all analyses.

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ANNEX 1. Diagram

Visit Number	Day	Procedure
V-1	Screening and treatment	Informed consent Measurements of clinical variables (FMP,FMBI,FMPPD,mPI,mBI,PPDi,MRi) Microbiological test Periapical x-ray
V-2	1-Month	Measurements of clinical variables (FMP,FMBI,FMPPD,mPI,mBI,PPDi,MRi) Microbiological test
V-3	3-Month	Measurements of clinical variables(FMP,FMBI,FMPPD,mPI,mBI,PPDi,MRi) Microbiological test Periapical x-ray