RESEARCH PROPOSAL

Treatment of peri-implant mucositis using an Er: YAG laser or an ultrasonic device. A randomized clinical trial.

Background and Significance

Peri-implantitis is an inflammatory process resulting in loss of supporting bone whereas peri-implant mucositis has been defined as a reversible inflammatory change of the peri-implant soft tissues without bone loss (Renvert et al 2018, Berglund et al. 2018). The prevalence of peri-implant mucositis and peri-implantitis ranged from 19 to 65% and from 1 to 47%, respectively. Meta-analyses estimated weighted mean prevalence's of peri-implant mucositis and peri-implantitis of 43% (CI: 32–54%) and 22% (CI: 14–30%), respectively (Derks et al. 2015). With an increasing population with dental implants the prevalence of implant related infections will increase and cause major challenges to the profession and society.

Approximately 65% of all infectious diseases are associated with biofilms including periodontal and peri-implant infections (Costerton et al. 1999, Lamont and Jenkinson 2000, Socransky & Haffajee 2005, Lee et al. 1999, Leonhardt et al. 2003, Roos-Jansåker et al. 2003). Bacterial colonization on oral implant surfaces occurs rapidly (Quirynen et al. 2006, Fürst et al. 2007, Salvi et al. 2007). The development of a tightly fixed layer of plaque, the so-called bio-film is critical and would in principle cause an irreversible binding to the implant surface (Lamont and Jenkinson 2000). The goal with non-surgical therapy of peri-implantit mucositis is to eliminate or significantly reduce the levels of pathogens to a level allowing healing and a clinically healthy situation.

Eradication of pathogens by mechanical means on the implant surface with threads and often a rough surface structure may be difficult using conventional means of therapy. Dental implants have generally a screw shaped design and in order to facilitate healing and osseo integration the surface structure is often rough. In case of infection and microbial colonization of the implant surface these features, positive for the initial stabilization and healing of the implant, becomes treatment complicating factors. Treatment models effectively used to treat the root surfaces of the tooth with periodontal disease like scaling and root-planning are difficult to use on the rough threaded implant surface. This surface gives the micro organisms "protected areas" with the roughness of the surface. In a consensus paper on the treatment of peri-implant mucositis it was concluded that" It has not been documented that mechanical

therapy alone is effective in reducing bleeding o probing" (Lindhe & Meyle 2008). Accordingly, methods have been aiming at eradication of the micro-organisms from a distance. In this aspect, the adjunct of local antibiotics has been attempted. (i.e. Flemmig 1994, Kao et al. 1997, Lang et al. 1997, Porras et al. 2002, Renvert et al. 2004,2006, Persson et al. 2006, Jorgensen et al. 2004, Bonito et al. 2005, McColl et al. 2006). The adjunct effects using local antibiotics are, however, not conclusive.

Another new treatment model, the use of lasers has been proposed for the treatment of peri-implant mucositis and peri-implantitis. The use of a laser can be considered a minimally invasive technique, that may result in less discomfort than traditional mechanical treatment approaches. Furthermore, lasers may have bio stimulatory effects that are reported to result in better wound healing compared to traditional approaches and in periodontal tissue regeneration (Aoki et al. 2004). In an experimental peri-implantitis model in dogs, it was demonstrated that favorable formation of new bone was observed on the laser-treated implant surface, and the laser group showed a tendency to produce greater bone-to-implant contact than the curette group (Takasaki et al. 2007). In a randomized clinical trial comparing the use of an Er:YAG laser and an air abrasive device in the treatment of peri-implantitis it was found that bleeding on probing (BOP) and suppuration (SUP) decreased in both the groups ($p<0.001$). The mean probing depth (PPD) reductions in the air abrasive and laser treated groups were 0.9mm (SD $\pm$ 0.8) and 0.8mm (SD $\pm$ 0.5) (Renvert et al. 2011).
In a recent review of the evidence using lasers in the treatment of peri-implant diseases it was concluded that the current evidence shows laser therapy in combination with surgical/nonsurgical therapy provided minimal benefit in Pocket depth (PD) reduction and clinical attachment (CAL) but when adjunct to non-surgical therapy might result in more BOP reduction in the short term (Lin et al. 2018). It was also concluded that data on adjunctive laser treatment for peri-implant mucositis are
scarce. Therefore, future clinical trials are needed to evaluate the potential benefit of this approach.

In summary, peri-implant mucositis is a very common clinical entity in patients with dental implants. This inflammation in the peri-implant mucosa may develop into peri-implantitis and result in implant loss. Early and effective treatment of peri-implant

mucositis is therefore an important continuous task for the dental professions. It is imperative to perform randomized trials comparing treatment alternatives to control implant infections. The present research project is designed to compare a conventional non-surgical approach using an ultrasonic device with an Er: YAG laser device (Morita Corporation, Japan). Clinical outcome measures of therapy will be used under observer masked conditions.

Specific aims

To assess the clinical outcome over 6 months following treatment with non-surgical debridement using a Er: YAG laser device (AdvErL EVO, Morita corporation, Japan) or with the use mechanical therapy using ultrasonic device with a specially designed tip (EMS, Switzerland)

Materials and methods

Outcome variables

- The extent of gingival inflammation (bleeding on probing - BOP)
- Clinical probing pocket depth values
- Clinical registration of suppuration
- Recession of the peri-implant mucosal margin at test and control sites between baseline and at study endpoint (6 months)
- The treatment times
- Changes in “bone levels” (measured from periapical radiographs (see below)
- The prevalence of implant loss

Subject screening

Exclusion criteria

- Subjects with uncontrolled diabetes mellitus (HbA1c > 6.5)
- Subjects requiring prophylactic antibiotics
- Subjects taking prednisolone
- Subjects taking medications known to have effects on gingival growth

- Subjects with a history of taking systemic antibiotics in the preceding 1 month

Inclusion criteria - Presence of peri-implant mucositis

Following a review of the medical history (see exclusion criteria) a full mouth routine periodontal examination, including analysis of available radiographs, will be performed. Subjects who consent and:

1. Have a minimum of one or more peri-implant sites with probing depth ≥ 4 mm combined with bleeding and/or pus on probing using 0.2 N probing force.
2. No peri-implant marginal bone loss (as determined from a comparison of the bone level one year following implant reconstruction with the bone level at screening (screening radiograph)
3. A limited allowed bone loss ≤ 2mm measured from the implant shoulder (as a consequence of remodeling during the healing process)

Intraoral radiographs

Intraoral standardized radiographs of the site of interest will be taken at baseline and at 6 months. Radiographs will be analysed by an independent and blinded examiner.

Treatment procedure

Baseline measurements will be performed, and the patients are randomized into treatment groups A or B. The treatment will be performed by a dentist not involved in the registrations in order to avoid bias. Following treatment, the patients will be instructed in proper homecare using a toothbrush and interproximal aids as needed.

Group A will be treated using the ER: YAG laser device (AdvErL EVO, Morita Corporation, Japan). The tip is placed in the pocket mesially, lingually, distally and buccally. Careful attempts are to cover the full circumference of the implant. Moving motion would be from bottom to coronal, sweeping motion also covering the soft tissue surface.

Group B will be treated using an ultrasonic device with PEEK coated tips (EMS, Switzerland). The tip is placed in the pocket mesially, lingually, distally and buccally. Careful attempts are to cover the full circumference of the implant.

Material and settings

The device used for the clinical study for Group A will be an Er:YAG laser device (AdvErL EVO, J. MORITA MFG. CORP., Japan) using a below prameter. Group B will receive standard of care using an ultrasonic device with plastic coated tips.

Parameter of Er:YAG laser AdvErL EVO (on the display)

Tip:PS400T

Power:30-50mJ

Frequency:10PPS

Air/Water:7/7

Patient entry

The study will be submitted to the Ethics committee in Uppsala and written consent will be obtained from all subjects to be entered in the study. Once the entry criteria have been confirmed the subject will be entered to the study and assigned a patient number.

After having been entered into the study, subjects will be randomly assigned to one of the two treatment regimens. Random assignment will be performed according to pre-defined randomisation.

Subject protection – monitoring of adverse events

At each visit the clinician will evaluate patients for any adverse events. Should a patient require any treatment during the course of the study, the necessary treatment will be provided at the discretion of the clinician and according to the current standard of care. All adverse events related to the treatment provided will be recorded. The investigation will be performed according to the principles of the Declaration of Helsinki on experimentation involving human subjects.

Measurements

One and the same examiner, unaware of treatment group for the patient, will perform all the measurements. Before treatment the following baseline measurements will be recorded:

1. Intraoral photographs of the implant site
2. Presence/absence of hyperplasia
3. Full mouth plaque score (FMPS). Presence of dental plaque along the gingival/mucosal margin recorded after use of disclosing dye and expressed as a percentage of examined sites within each patient (4 sites per tooth and implant).
4. Local Plaque Score. Presence of dental plaque along the mucosal margin at 6 sites of each treated implant recorded after use of disclosing dye and expressed as a percentage of implant sites within each patient.
5. Probing pocket depths (PPD) at the implant (6 sites/implant). Recorded at 6 sites of each treated implant to the nearest mm using a plastic probe.
6. Recession of the mucosal margin relative to the restoration margin (REC) at the implant buccally. Position of the mucosal margin apical to the restoration margin is positive recession (+), position of the mucosal margin coronal to the restoration margin is negative recession (-).
7. Bleeding on probing (BOP) graded 0-3 at the implant (6 sites/implant). Bleeding appearing after measurement of probing depth and expressed as: 0=no bleeding, 1=a dot of bleeding, 2=a line of bleeding, 3=a drop of bleeding
8. Presence /absence suppuration (SUP) at the implant (6 sites/implant).
9. Presence/absence of bleeding on probing (BOP) at all teeth/implants (4 sites)
10. Treatment times
11. Patient evaluation of the treatment: Visual analog scale for pain during treatment, the same day after treatment, one day after treatment and three days after treatment. Visual analog scale for aesthetic/satisfaction before the baseline examination and before the examination at 6 months. Postoperativ complications

is asked for in the examination protocol as an open question. Oral health impact profile is measured with the OHIP-14 version.

- All probing measurements will be made using a manual plastic probe.
- Clinical indices concerning probing pocket depths (PPD), bleeding on probing (BOP), plaque and suppuration will be recorded as 6 sites per implant: mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual, mesio-lingual.
- Full mouth plaque scores (FMPS) will be recorded as the percentage of total surfaces (4 aspects per tooth/implant) that revealed the presence of plaque (O'Leary et al. 1972). Full mouth bleeding scores (FMBS) will be recorded as the percentage of total surfaces (4 aspects per tooth/implant) that revealed the presence of bleeding.

Statistical power analysis

If BOP is reduced to 30 % ± 10 in Group A and with 30 % decrease in group B is to be detected at α = 0.05 and a power of β = 0.2, the appropriate number of subjects would be around n = 38. Hence, it is foreseen to incorporate 45 subjects in the study if some of the individuals will not fulfil the study.

Allocation concealment

Assignment to test and control group will be made using pre-prepared randomization in groups A or B. Cards with group identification will be prepared and placed in numbered envelopes after randomization. This will be done by a person not involved in the treatment or diagnosis of patients. As a new patient is admitted to the study the treating clinician takes the next numbered envelope then assigning the patient to either group A or B. The code for treatment A and B will be broken once the study is completed and the data set is locked.

Clinical registrations and treatment at baseline

- Clinical photo
- Presence/absence of plaque (6 sites/implant)
- PPD (6 sites/implant)

- Recession of the buccal mucosal margin
- BOP (6 sites/implant) graded
- Presence/absence of suppuration (6 sites/implant)
- FMPS (4 sites per tooth/implant)
- FMBS (4 sites per tooth/implant)
- Prescence/absence of hyperplasia
- Radiograph of the treated site
- Oral hygiene instruction + subgingival treatment in accordance to randomization
- Patient evaluation of the treatment including a VAS scale for pain. And another for aesthetic/satisfaction. OHIP-14 for quality of life assessment in relation to oral health.

Clinical registrations - 1 month

- Clinical photo
- Presence/absence of plaque (6 sites/implant)
- PPD (6 sites/implant)
- BOP (6 sites/implant) graded
- Presence/absence of suppuration (6 sites/implant
- FMPS (4 sites per tooth/implant)
- Re-instructions in oral hygiene procedures

Clinical registrations and supportive treatment at 3 months

- Clinical photo
- Presence/absence of plaque (6 sites/implant)
- PPD (6 sites/implant)
- Recession of the buccal mucosal margin
- BOP (6 sites/implant) graded
- Presence/absence of suppuration (6 sites/implant)

- Presence/absence of hyperplasia
- FMPS (4 sites per tooth/implant)
- FMBS (4 sites per tooth/implant)
- Oral hygiene instruction + subgingival treatment in accordance to randomization
- Patient evaluation of the treatment including a VAS scale for pain.

Clinical registrations and therapy at 6 months

- Clinical photo
- Presence/absence of plaque (6 sites/implant)
- PPD (6 sites/implant)
- Recession of the buccal mucosal margin
- BOP (6 sites/implant) graded
- Presence/absence of suppuration (6 sites/implant)
- Presence/absence of hyperplasia
- FMPS (4 sites per tooth/implant)
- FMBS (4 sites per tooth/implant)
- Radiograph of the treated site.

- Oral hygiene instruction + Subgingival treatment in accordance to randomization
- Patient evaluation of the treatment including a VAS scale for pain and another for aesthetic/satisfaction. OHIP-14 for quality of life assessment in relation to oral health.

Table1. Summary of study design.

Group	**Baseline**	**1 month**	**3 months**	**6 months**
A	Clinical data Radiographs **Treatment 1**	Clinical data Oral hygiene instructions	Clinical data Oral hygiene instructions	Clinical data Radiographs

			Treatment 1	Oral hygiene instructions **Treatment 1**
2	Clinical data Radiographs **Treatment 2**	Clinical data Oral hygiene instructions	Clinical data Oral hygiene instructions **Treatment 2**	Clinical data Radiographs Oral hygiene instructions **Treatment 2**

Timetable: This project will be initiated during 2021 and completed during 2023.

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