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Anti-infective surgical therapy of peri-implantitis. A 12-month prospective clinical study

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Key words: anti-infective treatment, chlorhexidine, implant surface, peri-implantitis, surgical debridement, systemic antimicrobials

Abstract
Aim: The aim of this prospective cohort study was to evaluate an anti-infective surgical protocol for the treatment of peri-implantitis.

Materials and methods: Thirty-six implants in 24 partially dentate patients with moderate to advanced peri-implantitis were treated using an anti-infective surgical protocol incorporating open flap debridement and implant surface decontamination, with adjunctive systemic amoxicillin and metronidazole. Treatment outcomes were assessed at 3, 6 and 12 months. Patient-based statistical analyses using multiple regression analyses were performed.

Results: There was 100% survival of treated implants at 12 months. At 3 months, there were statistically significant ($P < 0.01$) reductions in mean probing depths (PD), Bleeding on Probing (BoP) and suppuration. The greater the mean PD at baseline, the greater the PD reduction at 3 months. At 3 months, there was also a significant mean facial mucosal recession of 1 mm ($P < 0.001$). All these changes were maintained at 6 and 12 months. At 12 months, all treated implants had a mean PD $< 5$ mm, while 47% of the implants had complete resolution of inflammation (BoP negative). At 12 months, 92% of implants had stable crestal bone levels or bone gain. There were no significant effects of smoking on any of the treatment outcomes.

Conclusions: For the treatment of peri-implantitis, an anti-infective protocol incorporating surgical access, implant surface decontamination and systemic antimicrobials followed by a strict postoperative protocol was effective at 3 months with the results maintained for up to 12 months after treatment.

Peri-implantitis is defined as an inflammatory lesion in the surrounding peri-implant tissues with loss of supporting bone [Zitzmann & Berglundh 2008]. Peri-implantitis is diagnosed when there is Bleeding on Probing (BoP) in addition to radiographic evidence of loss of supporting bone (i.e. crestal bone loss exceeding that which is expected following crestal remodelling after implant placement and insertion of the reconstruction). Additional clinical findings, including suppuration, deep probing depths (PD) $>$5 mm) or mucosal recession are frequently observed [Heitz-Mayfield 2008; Lang & Berglundh 2011].

The prevalence of peri-implant disease has been documented in three cross-sectional studies from Scandinavia, reporting that peri-implantitis is a common complication in implant therapy with 28% of subjects affected in one Swedish study [Fransson et al. 2008], 47% in another study in Norway [Koldsland et al. 2010] and $\geq 56\%$ of patients affected in another study in Sweden [Roos-Jansaker et al. 2006; Zitzmann & Berglundh 2008].

The primary goals of peri-implantitis therapy are to resolve inflammation and to arrest the progression of disease. As the aetiology of peri-implantitis is similar to that of periodontitis, anti-infective protocols comparable to those used to treat periodontitis have been adopted to treat peri-implantitis [Lang et al. 2000; Heitz-Mayfield & Lang 2010]. However, few clinical studies are available evaluating...
the effectiveness of these protocols to achieve the mentioned primary goals (Claffey et al. 2008; Lindhe & Meyle 2008; Sahrmann et al. 2009). Thus, the aim of this study was to assess an anti-infective surgical protocol aimed at decontamination of the implant surface and resolution of inflammation for the treatment of peri-implantitis.

Material and methods

Patient selection
Patients with one or more implants diagnosed as being affected by peri-implantitis [i.e. bone loss ≥ 2 mm, compared to crestal bone levels at the time of placement of the reconstruction, with BoP] and with at least one site with PD ≥ 5 mm were included. Patients were recruited from specialist periodontal practice, one private clinic (West Perth Periodontics, Western Australia) and two university clinics (The University of Bern, Switzerland, The University of Geneva, Switzerland). A total of 24 patients were included, so that using statistical significance α = 0.05, there would be 80% power of detecting a mean PD reduction of 1 mm and a reduction in mean number of sites with BoP of 0.9.

Exclusion criteria
Patients with uncontrolled diabetes, pregnant or lactating women, patients who had received systemic antimicrobials in the past 3 months, or patients with a known allergy to either amoxicillin or metronidazole were excluded.

An investigator meeting was held prior to commencement of the study to standardize the examination and treatment protocols.

Ethics approval
All participating centres obtained ethics approval from the appropriate ethics committee in their region prior to the commencement of the study. Patients were provided with written information regarding the aims of the study and provided informed consent.

Pre-surgical treatment
Patients received conventional periodontal treatment if required prior to entry to the study. All patients had a full mouth plaque score (FMPS) < 25%, a full mouth bleeding score (FMBS) < 25% and < 25% of sites with PD > 5 mm prior to entry to the study. Oral hygiene instruction and non-surgical debridement at implants were provided approximately 4 weeks prior to baseline measurements and the surgical phase of treatment.

Baseline measurements
Baseline clinical measurements, including PD, level of the peri-implant mucosal margin in relation to the restorative margin, presence or absence of plaque, BoP and/or suppuration, were obtained at four sites (mesial, distal, facial and oral) per implant. Probing measurements were made using a graduated probe with a light probing force (approximately 0.2–0.3 N). Periapical radiographs, using a long-cone paralleling technique, were taken to evaluate the extent of bone loss. Restorative margins were classified as supramucosal or submucosal.

Treatment protocol
At the implants diagnosed with peri-implantitis, full thickness mucoperiosteal flaps were raised to gain access to the implant surface. Where required, vertical releasing incisions were made. Inflammatory tissue was removed using hand instruments. The implant surface was cleaned using titanium coated Gracey curettes (HuFriedy®, Chicago, IL, USA) or carbon fibre curettes (KerrHawe®, SA, Bioggio, TI, Switzerland) to remove any calculus, excess cement or plaque deposits, followed by copious irrigation with sterile saline and rubbing of the implant surface with surgical gauze soaked in sterile saline. No resective therapy or implantoplasty was done.

The bone loss was evaluated intrasurgically and the depth and width of the bone defect surrounding the implant was measured at four aspects (mesial, distal, facial, oral). The flaps were replaced, sutured and postoperative instructions were provided.

Postoperative protocol
Systemic antimicrobials and antiseptic mouthrinses were prescribed starting immediately after surgery. A combination of amoxicillin (500 mg) and metronidazole (400 mg) three times a day, for 7 days, was prescribed. Patients were instructed to rinse for 1 min with 0.2% chlorhexidine twice daily for 4 weeks following the surgery. Sutures were removed 7–10 days following the surgery. Patients were seen at weekly intervals for the first 4 weeks to monitor healing and then at three monthly intervals, or as required, for maintenance care.

Re-evaluation at 3, 6 and 12 months following treatment
At 3, 6 and 12 months, re-evaluation was carried out, recording the clinical parameters: PD, level of the peri-implant mucosal margin and presence or absence of plaque, bleeding and/or suppuration on probing at four sites per implant. The periodontist providing the treatment also evaluated the treatment outcomes. At 12 months, radiographs were taken using a long-cone paralleling technique. Radiographs at baseline and 12 months were compared using reproducible landmarks, such as the threads on the implants, as a reference for determining bone loss, bone gain or no change. Any adverse events throughout the study period were also recorded.

Statistical analysis
The outcome variables of interest following the treatment were [i] mean PD at the treated implants [four sites measured], [ii] number of sites with BoP positive at the treated implants, [iii] presence or absence of suppuration at the treated implants, and [iv] mucosal recession at the facial aspect of each implant. These variables were assessed at baseline and at 3, 6 and 12 months after treatment.

The following possible confounding covariates were also recorded.

1. Smoking history (non-smoker, former smoker, current smoker).
2. History of treated periodontitis (yes or no).
3. FMPS.
4. FMBS at baseline and 12 months.
5. Submucosal restoration margin at baseline (yes or no).
6. Intrabony defect depth [mm].
7. Intrabony defect width [mm].
8. Number of implants present.
9. Number of implants treated for peri-implant disease.
10. Number of sites with plaque at the treated implant at baseline [for 3 months treatment outcome], at 3 months [for 6 months treatment outcome] and at 6 months [for 12 months treatment outcome].
11. Treatment centre.

For the purposes of statistical analyses, when a patient had more than one implant treated and the implants were adjacent, the parameters recorded at each implant were averaged. When a patient had more than one implant treated and the implants were not adjacent, the implants were included in the statistical analysis as independent values.

Multiple regression analysis was used to quantify the outcomes with their means expressed as functions of the above covariates and the outcome at the previous examination. Only statistically significant covariates were retained, using a backward elimination process; this enabled contributions from all of these covariates to the outcomes to be assessed. As three responses (difference
between baseline and 3 months, difference between 3 and 6 months and difference between 6 and 12 months) were considered for each outcome, a Bonferroni correction of tripling all P-values was made, so that a significance level of 0.017 was the requirement for individual covariate retention.

Results

Patient characteristics
A total of 36 implants in 24 partially dentate patients (mean age 56 ± 8.5 years) were treated and re-examined at 3, 6 and 12 months. Fifteen patients had one implant treated, whereas nine patients had more than one implant treated (seven with two, one with three and one with four).

The majority of patients were non-smokers [12] or former smokers [6] whereas six patients were smokers (all smoked <20 cigarettes per day). Eight patients had a history of treated periodontitis. Patients had low FMPS throughout the study period and low FMBS at baseline and at 12 months (Table 1) indicating good compliance.

Description of implant characteristics (N = 36)
At baseline, 27 implants had moderate bone loss (2–4 mm) and nine implants had more advanced bone loss (>4 mm). Treated implants were located in anterior and posterior positions in both the maxilla and the mandible. Treated implants had a range of surfaces including: a turned surface (Nobel Biocare AB, Göteborg, Sweden) (five implants); a titanium plasma-sprayed surface, TPS (Straumann, AG Basel, Switzerland) (three implants); a grit-blasted surface, TiOblast (Astra Tech AB, Mölndal, Sweden) (two implants); a porous anodized surface, TiUnite (Nobel Biocare AB, Göteborg, Sweden) (nine implants); a Sandblasted Large grit Acid-etched surface, SLA (Straumann) (11 implants); an acid-etched surface (Entegra, Sybron Implant Solutions, Anaheim, CA, USA) (one implant); a titanium plasma-sprayed surface (Frialit-2, Dentsply, Friadent, Mannheim, Germany) (two implants) and a hydroxyapatite coating (CalciTek, SULZERmedica, Carlsbad, CA, USA) (three implants).

Of the 36 implants treated, 21 had submucosal restoration margins. Cemented or screw-retained restorations supported by the treated implants, included single crowns, splinted single crowns, implant-retained fixed partial dentures and combined implant and tooth-supported restorations. All restorations were accessible for oral hygiene and none required modification.

Table 1. Patient full mouth plaque (FMPS) and full mouth bleeding scores (FMBS)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMPS %</td>
<td>16.8 (12.7)</td>
<td>11.3 (9.9)</td>
<td>13.3 (12)</td>
<td>11.1 (9.2)</td>
</tr>
<tr>
<td>FMBS %</td>
<td>13.9 (11.6)</td>
<td>Not evaluated</td>
<td>Not evaluated</td>
<td>6.9 (5.4)</td>
</tr>
</tbody>
</table>

Patient-based statistical analyses
Mean PD changes
There was a highly significant [P < 0.001] reduction in the mean PD with greater reductions for higher baseline values, 3 months following the surgical treatment of peri-implantitis. Estimated expected changes are shown in Table 5. None of the other covariates had significant effects [P > 0.10], although there was an (non-significant) tendency for smaller PD reductions, when there were greater numbers of implants treated in one patient.

The PD reductions achieved at 3 months following the treatment were maintained at 6 and 12 months, with no statistically significant overall changes [P > 0.10]. Although there was a significant effect of 6-month PD [P < 0.05], with slightly greater reductions at 12 months associated with higher values, the differences were not considered clinically relevant. Of the non-significant covariates, higher numbers of treated implants and greater deepest defect depth were associated with smaller reductions in mean PD from 6 to 12 months.

Bleeding on Probing
Changes in BoP from baseline to 3 months
At 3 months, significantly more patients experienced a reduction in the number of sites with BoP than those experienced an increase [P < 0.01]. Of the covariates, a history of treated periodontitis had a significant effect [P < 0.05], with a greater expected reduction in BoP for patients with a history of treated periodontitis (2.2 sites) compared with patients without a history of periodontitis (1 site).
Changes in BoP from 3 to 6 months
Although there were more patients experiencing a reduction in the number of sites with BoP than those experiencing an increase, the difference was not statistically significant ($P > 0.10$). Of the covariates, only the number of sites with BoP at 3 months had any significant effect ($P < 0.001$) on the number of sites with BoP at 6 months with expected changes shown in Table 6.

Changes in BoP from 6 to 12 months
There were no significant changes in the number of sites with BoP between 6 and 12 months ($P > 0.10$) and none of the covariates had any significant effects ($P > 0.10$).

Facial mucosal recession
Recession from baseline to 3 months
There was a highly significant ($P < 0.001$) recession of the facial mucosal margin from baseline to 3 months, with an estimated mean of 1 mm. None of the covariates had any significant effects on recession ($P > 0.10$); however, presence of a submucosal restoration margin and current smoking tended to increase the recession.

Recession from 3 to 6 months
There was no significant overall change in recession ($P > 0.10$) from 3 to 6 months. Regression analysis showed that a history of treated periodontitis and defect width had statistically significant effects ($P < 0.05$). These are shown in Table 7, where patients with a history of treated periodontitis and/or lower defect width experienced less mucosal recession on average. Of the non-significant covariates, higher numbers of treated implants were associated with more recession.

Recession from 6 to 12 months
No statistically significant change in recession was noted from 6 to 12 months ($P > 0.10$) and none of the covariates had any significant effects ($P > 0.05$).

Suppuration
There was a highly significant reduction in suppuration ($P < 0.001$) at 3 months with this improvement maintained over the next 3 months and for a further 6 months.

Adverse effects
Six patients reported adverse effects following the treatment. All side effects related were related to mild gastro-intestinal complaints (five patients) or vaginal thrush (one patient) and resolved without intervention. All patients reported completion of the course of antimicrobials.

Discussion
The results of this study demonstrate that moderate to advanced peri-implantitis can be treated successfully, in the majority of patients, when a strict anti-infective protocol is followed. Significant clinical improvements demonstrated by resolution of or reduction in inflammation (BoP and suppuration), and reduction in mean PD were achieved at 3 months. Moreover, the results were maintained up to 12 months. All implants had mean PD <5 mm, 12 months after the treatment. The reduced PD results in an environment less conducive for proliferation of peri-implant pathogens [Shibli et al. 2008] and facilitates access for maintenance care.

Although there were significant clinical improvements, as shown in a substantial reduction in the number of sites with BoP, only 47% of the implants had complete resolution of BoP at 12 months.

At three implants, in three patients, there was continued bone loss detected on the 12-month radiographs. Therefore, 88% of the patients and 92% of implants were treated successfully without disease progression at 12 months. An extended follow-up period would be required to determine the long-term success of treatment.

There are few clinical studies evaluating a non-rective, non-regenerative surgical
protocol for the treatment of peri-implantitis, available for comparison with the present study [Leonhardt et al. 2003; Maximo et al. 2009]. The majority of studies evaluating peri-implantitis therapy have assessed regenerative techniques aimed at filling the osseous defect. Although these studies have reported various degrees of success in terms of defect fill, they have not addressed the primary goal of treatment, that is, disease resolution [Claffey et al. 2008].

Leonhardt et al. (2003) reported 58% success, 5 years following the surgical treatment in conjunction with systemic antimicrobials. In that study, nine patients with 26 turned surface implants were treated. Seven implants in four patients were lost, four implants had ongoing bone loss (≥1 thread), six had bone gain (≥1 thread) and nine had unchanged bone levels [Leonhardt et al. 2003].

Maximo et al. (2009) reported a 3-month study evaluating surgical access without adjunctive systemic antimicrobials for treatment of peri-implantitis. These authors reported a significant reduction in PD and BoP (Maximo et al. 2009). However, similar to the results of the present study, resolution of inflammation was not achieved at all implants, with 45% of implants still displaying BoP at one or more sites following the treatment.

In the present study, patient-based analyses were made to account for the effect of multiple implants in one patient. Favourable outcomes were observed regardless of smoking history, in contrast to the findings by Leonhardt et al. (2003). A history of treated periodontitis did not seem to have a detrimental effect on treatment outcome. This effect, or lack of effect has not previously been reported.

The regression analyses showed that where there were multiple implants treated within the same patient, there was a tendency for smaller improvements. Generally, the less positive the response at one review examination, the greater the absolute improvement at the next review. This, in turn, means that in some patients, it took a little longer to gain the maximum clinical improvements.

Pre-surgical debridement and oral hygiene instruction were carried out prior to baseline evaluation and surgical therapy. Due to the extent of bone loss and the implant topography, surgical intervention was required to obtain access to the implant surface. After flap elevation, the implant surface was decontaminated using sterile saline without implantoplasty. Sterile saline was chosen as the decontamination method because experimental and clinical studies evaluating a range of decontamination protocols, including sterile saline, chlorhexidine, citric acid, hydrogen peroxide and CO2 laser, have not shown any one method as being superior (Claffey et al. 2008).

As there are currently no randomized controlled studies evaluating adjunctive use of systemic antimicrobials for the treatment of peri-implantitis, the rationale for the use of systemic antimicrobials in the tested protocol was the aggressive nature of the peri-implantitis lesion.

Histopathological features of peri-implantitis lesions include the apical extension of an acute inflammatory lesion, and its proximity to the bone marrow spaces observed in experimental [Lindhe et al. 1992; Albouy et al. 2008, 2009] and human [Berglundh et al. 2004] biopsies. These features reinforce the importance of a powerful antimicrobial strategy to stop a destructive pathological process rapidly and efficiently.

Amoxicillin and metronidazole, were prescribed for 7 days starting on the day of surgery. A previous prospective cohort study showed beneficial effects of non-surgical debridement of peri-implant lesions supplemented with metronidazole alone [Mombelli & Lang 1992]. However, the combination of metronidazole and amoxicillin has the potential to suppress a wider range of pathogens frequently associated with peri-implant disease [Mombelli & Decailliet 2011]. This antimicrobial combination seems to be effective in suppressing suppuration from periodontal pockets (Rooney et al. 2002; Cionca et al. 2009). The present study suggests that this is also the case for purulent peri-implantitis.

Twenty-five per cent of patients experienced adverse effects related to the systemic antimicrobials following the treatment. Although the majority reported mild gastrointestinal disturbances, the likelihood of adverse events should be discussed with the patient prior to therapy.

The results of this study have demonstrated that following the access surgery, mucosal recession of 1 mm should be expected. This expected peri-implant mucosal recession may result in a compromised aesthetic outcome, and should be discussed with the patient prior to treatment. Surgical protocols, involving modification of the implant surface using burs [implantoplasty] and resection of the surrounding bone (Romeo et al. 2007), have reported greater recession than those encountered in the present study.

The present study included implants with a range of surface topographies. Of the three implants with continued bone loss, one had a porous anodized surface, one a titanium plasma-sprayed surface and one a machined surface. A recent experimental dog study, evaluating the influence of implant surface characteristics on the outcome of surgical treatment of peri-implantitis showed a poorer outcome, when a porous anodized surface (TiUnite) was used compared to a machined surface, an acid-etched surface and an SLA surface (Albouy et al. 2011). As the majority of the implants in the present study were treated successfully, no conclusions regarding the influence of implant surface on treatment outcome can be made.

In the present study, three specialist periodontal clinics were involved, two University centres and one periodontal private practice. Treatment outcomes were similar between centres, indicating that the protocol described can be successfully applied by clinicians in different settings. For practical reasons, the clinician providing the treatment also evaluated the treatment outcomes, possibly introducing an element of bias.

The importance of a strict postoperative protocol, optimal plaque control and compliance with maintenance protocols should not be underestimated. Patients rinsed with chlorhexidine for 4 weeks following the surgery, and were seen at three monthly intervals for the first 6 months and then as required for the remaining 6 months of the study period.

The FMPS and FMBS were low (≤20%) throughout the 12-month study period, indicating optimal plaque control and compliance with maintenance care.

In conclusion, the results of this prospective cohort study show that in the majority of patients, moderate to advanced peri-implantitis can be successfully treated using a specific anti-infective protocol incorporating: (i) pre-surgical debridement and oral hygiene instruction, (ii) access flap and implant surface decontamination, (iii) systemic antimicrobial therapy with amoxicillin and metronidazole, (iv) a postoperative care protocol, including chlorhexidine mouthrinsing followed by regular maintenance care, and (v) a high standard of self-performed plaque control.

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