Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial


Abstract

To compare the effectiveness of two anti-infective protocols for the treatment of peri-implant mucositis.


DOI: 10.1111/j.1600-0501.2010.02078.x
PMID: 21251076
Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial

Key words: anti-infective treatment, chlorhexidine, non-surgical debridement, oral hygiene, peri-implant mucositis, RCT

Abstract
Aim: To compare the effectiveness of two anti-infective protocols for the treatment of peri-implant mucositis.

Materials and methods: Twenty-nine patients with one implant diagnosed with peri-implant mucositis (bleeding on probing [BOP] with no loss of supporting bone) were randomly assigned to a control or test group. Following an assessment of baseline parameters (probing depth, BOP, suppurative presence of plaque), all patients received non-surgical mechanical debridement at the implant sites and were instructed to brush around the implant twice daily using a gel provided for a period of 4 weeks. The test group (15 patients) received a chlorhexidine gel (0.5%), and the control group (14 patients) received a placebo gel. The study was performed double blind. After 4 weeks, patients were instructed to discontinue using the gel and to continue with routine oral hygiene at the implant sites. Baseline parameters were repeated at 1 and 3 months.

Results: At 1 month, there was a statistically significant reduction in the mean number of sites with BOP and mean probing depth measurements at implants in both groups. There were also some statistically significant changes in these parameters from 1 to 3 months. However, there were no statistically significant differences between test and control groups. One month following treatment, 76% of implants had a reduction in BOP. Complete resolution of BOP at 3 months was achieved in 38% of the treated implants. The presence of a submucosal restoration margin resulted in significantly lower reductions in probing depth following treatment.

Conclusions: Non-surgical debridement and oral hygiene were effective in reducing peri-implant mucositis, but did not always result in complete resolution of inflammation. Adjunctive chlorhexidine gel application did not enhance the results compared with mechanical cleansing alone. Implants with supramucosal restoration margins showed greater therapeutic improvement compared with those with submucosal restoration margins.

Implant Complication Research Group [ICRG]: Andrea Botticelli, Geneva, Switzerland; Daniele Botticelli, Rimini, Italy; Malcolm Faddy, Perth, WA, Australia; Mary Cullinan, Dunedin, New Zealand; Niklaus P. Lang, Hong Kong, Hon Kong SAR, China

Authors' affiliations:
Lisa J. A. Heitz-Mayfield, Centre for Rural and Remote Oral Health, The University of Western Australia, Crawley, WA, Australia
Giovanni E. Salvi, School of Dental Medicine, University of Bern, Bern, Switzerland
Daniele Botticelli, Ariminum Odontologica s.r.l., Rimini, Italy
Andrea Mombelli, Department of Periodontology, University of Geneva, Geneva, Switzerland
Malcolm Faddy, Queensland University of Technology, Brisbane, Qld, Australia
Niklaus P. Lang, Faculty of Dentistry, The University of Hong Kong, Hon Kong SAR, China

Corresponding author:
Prof. Lisa J. A. Heitz-Mayfield
Centre for Rural and Remote Oral Health
The University of Western Australia
Crawley
WA
Australia
Tel.: +61 89 321 7581
Fax: +61 89 321 2741
e-mail: heitz.mayfield@iinet.net.au

© 2011 John Wiley & Sons A/S
Therefore, peri-implant mucositis appears to represent the host response to the bacterial challenge as the counterpart to gingivitis at tooth sites [Heitz-Mayfield & Lang 2010]. It is assumed that peri-implant mucositis is the precursor for peri-implantitis, as gingivitis is the precursor for periodontitis [N. P. Lang, D. D. Bosshardt, M. Lulic, unpublished data].

Protocols similar to those used to treat gingivitis have been adopted to treat peri-implant mucositis. However, few studies are available evaluating anti-infective protocols for the treatment of peri-implant mucositis [Heitz-Mayfield & Lang 2004; Renvert et al. 2008; Maximo et al. 2009; Ramberg et al. 2009; Thöne-Mühling et al. 2010]. As peri-implant mucositis may progress to peri-implantitis, an effective treatment resulting in resolution of inflammation would be the prerequisite for the prevention of peri-implantitis.

Thus, the aim of this study was to evaluate the effectiveness of two anti-infective protocols for the treatment of peri-implant mucositis.

Material and methods

Patient selection

Patients were recruited from four clinical and university centres [West Perth Periodontics, Western Australia, Australia; University of Bern, Switzerland; University of Geneva, Switzerland; Arminum Odontologica, Rimini, Italy]. In total, 49 patients with one implant diagnosed with peri-implant mucositis (bleeding on light probing [0.2–0.3 N], with no loss of supporting bone) were included in the study.

An investigator meeting was held before the commencement of the study to standardise the examination and treatment protocols and to calibrate for the parameters assessed.

Power calculation

The sample size of (at least) 14 patients in each group resulted in a power of 80% to detect a mean difference of 1.1 mm in probing depths between groups.

Exclusion criteria

Patients who smoked >20 cigarettes/day (self-reported) were excluded as well as patients with uncontrolled diabetes. A full-mouth plaque score (FMPS) was obtained at baseline and patients with inadequate oral hygiene (FMPS >2.5%) or untreated periodontitis were excluded.

Baseline measurements

Baseline clinical measurements including probing depths, presence or absence of plaque, BOP and/or suppuration, were obtained at four sites (mesial, distal, facial and oral) per implant. Probing depth measurements were made using a graduated periodontal probe with a light probing force (approximately 0.2–0.3 N) [Gerber et al. 2009]. Radiographs were taken to confirm that there was no loss of supporting bone. Restorative margins were classified as supramucosal or submucosal.

Submucosal plaque samples, at the deepest implant site, were obtained using a single paper point, which was transferred to a sterile Eppendorf tube containing TE buffer. One-hundred microlitres of sodium hydroxide was added to each sample tube and the samples were sent to the Oral Microbiology Laboratory at the University of Bern, Bern, Switzerland, where they were analysed using the checkerboard DNA–DNA hybridization technique [Socransky et al. 1994]. The presence and levels of the 40 subgingival species [Socransky et al. 1998] with the addition of Staphylococcus aureus were evaluated.

Treatment protocol

Following baseline measurements, the implants diagnosed with peri-implant mucositis were mechanically debrided using titanium-coated Gracey curettes [HuFriedy, Chicago, IL, USA] or carbon fibre curettes [KerrHawe SA, Bioggio, TI, Switzerland] followed by prophylaxis with a rubber cup and polishing paste. Patients were instructed to brush around the implant twice daily using 1 cm of the gel provided for a period of 4 weeks.

Test group

Patients in the test group received a plastic bottle containing 100 ml of 0.5% chlorhexidine gel [Plak-Out® Gel, KerrHawe SA, Bioggio, TI, Switzerland].

Control group

Patients in the control group received an identical plastic bottle containing placebo gel (without chlorhexidine). The placebo gel was prepared to the same consistency, appearance and taste as the active chlorhexidine gel. Placebo and chlorhexidine gels were prepared in a pharmaceutical laboratory (Compounding on Oxford, Leederville, WA, Australia) and distributed to the participating centres.

Randomisation

Randomisation was performed for each centre separately using randomisation tables with permuted blocks of four.

Allocation concealment

Examiners and patients were unaware of the allocation to test and control for the duration of the study.

1- and 3-month re-evaluation

Clinical parameters (probing depth measurements, presence or absence BOP and/or suppuration and plaque) were recorded and plaque samples were taken at 1 and 3 months following treatment. Any adverse events were recorded.

Ethics approval

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

Statistical analysis

The outcome variables of interest following treatment in either the test or control group were (i) number of sites with BOP at the treated implant, (ii) sum of probing depths at the treated implant (four sites measured) and (iii) the total DNA count at the deepest implant site. These variables were measured at baseline, 1 and 3 months after treatment.

The following possible confounding covariates were also recorded:

1. Smoking history [non-smoker, former smoker; current smoker [<20 cigarettes/day]]
2. History of treated periodontitis [yes or no]
3. FMPS at baseline (<12% or ≥12%)
4. FMBS at baseline (<12% or ≥12%)
5. Submucosal restoration margin at baseline (yes or no)
6. Number of sites with plaque at the treated implant at baseline (for 1-month treatment outcome) and at 1 month (for 3-month treatment outcome)

The following possible microbial confounding covariates were measured at the deepest implant site at baseline (for 1-month treatment outcomes) and at 1 month (for 3-month treatment outcomes):

1. Proportions of the total DNA count of red complex species [Socransky et al. 1998] (0: ≤4%, 1: >4–10%, 2: >10%)
2. Proportions of the total DNA count of orange complex species [Socransky et al. 1998] (0: <10%, 1: 10–30%, 2: >30%)
3. Level of Staphylococcus aureus (0: <10⁴, 1: 10⁴–10⁵, 2: 10⁵–10⁶, 3: ≥10⁶)
4. Level of Aggregatibacter actinomycetemcomitans (0: <10⁴, 1: 10⁴–10⁵, 2: 10⁵–10⁶, 3: ≥10⁶)

In addition to simple pair-wise comparisons, multiple regression analysis was used to quantify the treatment outcomes, with the mean outcome being a function of the above covariates, including test and control groups, and the outcome of the earlier examination. Only statistically significant covariates were retained, using a backward clim-
Table 1. Baseline patient demographics for control and test group

<table>
<thead>
<tr>
<th></th>
<th>Test group (N=14)</th>
<th>Control group (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Current smokers</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Former smokers</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>History of treated periodontitis</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Submucosal restoration margin</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2. Mean number of BOP-positive sites at treated implants

<table>
<thead>
<tr>
<th>BOP</th>
<th>Test</th>
<th>Control</th>
<th>Significance of difference between test and control means (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>1 month</td>
<td>1.2†</td>
<td>0.9</td>
<td>1.0†</td>
</tr>
<tr>
<td>3 months</td>
<td>1.1</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

†Statistically significant reduction from baseline to 1 month.
SD, standard deviation; BOP, bleeding on probing.

Results

Twenty-nine patients with one implant diagnosed as peri-implant mucositis participated in the study, 15 in the test and 14 in the control group. There were 17 non-smokers, eight former smokers and four smokers (≤20 cigarettes/day). All patients were re-examined at 1 and 3 months. No adverse events were reported at any observation time. Baseline demographics including age, gender, number of smokers, former smokers and non-smokers, history of treated periodontitis and presence of a submucosal restoration margin for test and control groups are presented in Table 1.

BOP

Data on numbers of sites with BOP at the treated implants (total four sites evaluated) at baseline, 1 and 3 months are summarised in Table 2.

Simple pair-wise comparisons showed that there were significant reductions in the number of sites with BOP from baseline to 1 month for both test and control groups (P-values < 0.05), with little apparent change between 1 and 3 months (P-values > 0.1). There was no statistically significant difference in the changes in BOP between the test and control groups at 1 month or at 3 months (P-values > 0.1).

The multiple regression analysis showed that, not surprisingly, greater reductions in BOP occurred at implants with higher BOP scores initially (P-values < 0.01), and this corresponded to significant reductions in BOP between baseline and 1 month, and between 1 and 3 months. None of the other covariates had any significant effect on the changes in BOP (P-values > 0.05).

The following estimates of BOP were obtained from the multiple regression analysis:

Mean number of sites BOP at 1 month

\[ \text{Mean number of sites BOP at 1 month} = 0.74 + 0.15 \times \text{number of sites BOP at baseline} \]

and

Mean number of sites BOP at 3 months

\[ \text{Mean number of sites BOP at 3 months} = 0.31 + 0.57 \times \text{number of sites BOP at 1 month} \]

In other words, there were up to 67% reductions in mean BOP from baseline to 1 month and further reductions of up to 33% from 1 to 3 months. Higher plaque scores did tend to reduce these improvements, but such effects did not reach statistical significance (P-values > 0.05).

The number of patients with a reduction, no change or increase in the number of BOP-positive sites at the treated implants at 1 and 3 months is described in Fig. 1. Table 3 shows the number of patients with sites BOP at baseline, 1 and 3 months. At 3 months, 11 patients (38%) had complete resolution of inflammation (absence of BOP at all four sites).

Probing depth changes

Data on probing depths in millimetres (four sites measured) at baseline, 1 and 3 months are summarised in Table 4.

Simple pair-wise comparisons showed that there were significant reductions in mean probing depth from baseline to 1 month (≥0.5 mm) for both test and control groups (P-values < 0.01), with little apparent change between 1 and 3 months (P-values > 0.1). There were no statistically significant differences in mean probing depth reductions between the test and control groups at 1 or 3 months (P-values > 0.1).

The multiple regression analysis showed that a submucosal restorative margin at baseline had a significant negative effect on the probing depth reduction at 1 month (P-value < 0.01), but no significant effect between 1 and 3 months (P-value > 0.1).

The following estimated probing depth reductions were obtained from the multiple regression analysis:

Mean change in sum of probing depths from baseline to 1 month = –4.1 if restoration margin at baseline was supramucosal, or –1.8 if restoration margin at baseline was submucosal

An unexpected finding was a significant effect of the proportion of orange complex species, whereby individuals with higher levels of these species at 1 month experienced further reductions in mean probing depth at 3 months, while those with lower levels experienced some increase (P-value < 0.05).
Regression analysis showed that there were significant

months. Despite this difference, there was no significant
difference between 1 and 3 months were dependent on the total DNA count at 1 month.

a significant reduction in mean DNA counts

months are summarised in Table 5.

Table 4. The sum of probing depths (mm) ± standard deviation (SD) at baseline, 1 and 3 months in test and control group

<table>
<thead>
<tr>
<th>Sum of probing depths mm (mesial, distal, oral, facial)</th>
<th>Test</th>
<th>Control</th>
<th>Significance of difference between test and control means (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline</td>
<td>14.7</td>
<td>3.7</td>
<td>14.4</td>
</tr>
<tr>
<td>1 month</td>
<td>12.5†</td>
<td>4.0</td>
<td>11.7†</td>
</tr>
<tr>
<td>3 months</td>
<td>12.5</td>
<td>3.7</td>
<td>11.9</td>
</tr>
</tbody>
</table>

†Statistically significant reduction from baseline to 1 month.

Table 5. Mean total DNA count ± standard deviation (SD) at baseline, 1 and 3 months in control and test groups

<table>
<thead>
<tr>
<th>Log (total DNA count)</th>
<th>Test</th>
<th>Control</th>
<th>Significance of difference between test and control means (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.24</td>
<td>0.5</td>
<td>5.44</td>
</tr>
<tr>
<td>1 month</td>
<td>5.07†</td>
<td>0.56</td>
<td>5.21†</td>
</tr>
<tr>
<td>3 months</td>
<td>5.31</td>
<td>0.48</td>
<td>5.09</td>
</tr>
</tbody>
</table>

†Statistically significant reduction from baseline to 1 month.

None of the other covariates had any significant
effects on mean probing depth (P-values > 0.1).

The following estimated mean probing depth
reductions were obtained from the multiple
regression analysis:

Mean change in sum of probing depths
from 1 to 3 months = +1.2 if orange complex
proportion at 1 month ≤ 30%, or −0.9 if
orange complex proportion at
1 month > 30%

Total DNA count

Data on total DNA counts at baseline, 1 and 3
months are summarised in Table 5. Simple pairwise comparisons showed that there were no significant differences in mean total DNA counts between test and control groups (P-values > 0.1), a significant reduction in mean DNA counts between baseline and 1 month (P-value < 0.05) and no significant difference between 1 and 3 months (P-value > 0.1). However, the multiple regression analysis showed that there were significant (P-value < 0.05) changes in mean total DNA count between 1 and 3 months, which
were dependent on the total DNA count at 1 month.

Estimated changes were

Mean total DNA count at 1 month

= 0.6 × total DNA count at baseline

Mean total DNA count at 3 months

= 7.4 × 10^4 if total count = 10^4

1.5 × 10^5 if total DNA count at 1 month = 10^5

2.9 × 10^5 if total count at 1 month = 10^6

In other words, there was some further reduction in mean total DNA count between 1 and 3 months, but only if the total DNA count at 1 month was sufficiently high (> 1.7 × 10^4).

The multiple regression analysis also showed that there was a tendency for patients who were smokers and/or had a history of periodontitis to have higher mean total DNA counts at 3 months, but these effects did not reach statistical significance (P-values > 0.05).

Discussion

This randomised placebo-controlled double-blind study found that mechanical debridement with and without the application of antiseptics resulted in a reduction in BOP and probing depths throughout the 3-month period of the study, with most of the improvement occurring in the first month. However, there was no added benefit in the adjunctive use of chlorhexidine gel indicating that mechanical debridement in conjunction with oral hygiene alone is effective in reducing peri-implant soft tissue inflammation.

In a similar recent clinical study involving 13 partially dentate patients with 36 implants diagnosed with peri-implant mucositis, no advantage of adjunctive chlorhexidine (0.12%), applied as a mouth rinse, compared with mechanical debridement alone was found (Thöne-Mühling et al. 2010).

These results confirm the findings of an experimental peri-implant mucositis study, in cynomolgus monkeys, comparing mechanical debridement and mechanical debridement with chlorhexidine (0.12%) application. No statistically significant differences in clinical or histological signs of inflammation between the two treatment groups were identified. Both mechanical therapy alone and combined with chlorhexidine irrigation resulted in minimal inflammation compatible with clinical health (Trejo et al. 2006).

Nevertheless, as there were no adverse effects reported in the present study, adjunctive chlorhexidine gel may also be recommended.

While there was a significant reduction in BOP in the present study, only 38% of the implants diagnosed with peri-implant mucositis had complete resolution of BOP at 3 months. At 3 months, 38% of the implants had one BOP-positive site, 17% had two BOP-positive sites and 7% had three BOP-positive sites.

Other clinical studies evaluating treatment of peri-implant mucositis using adjunctive antiseptic agents including essential oils (Ciancio et al. 1995), chlorhexidine rinsing (Felo et al. 1997), chlorhexidine rinsing plus chlorhexidine gel application (Porras et al. 2002) and 0.3% triclosan dentifrice use (Ramberg et al. 2009) or mechanical debridement alone (Maximo et al. 2009) have reported similar reductions in BOP following treatment. None of the treatment protocols tested have reported complete resolution of inflammation at all implant sites.

In the present study, microbiological changes following treatment did not show any significant differences between test and control groups. Overall, there was some reduction in the total DNA count at 1 month following treatment. Then, further reductions were only found if the count at 1 month was sufficiently high. Increases occurred if the total count at 1 month was low, suggesting the establishment of an equilibrium. Similarly, in another clinical study evaluating treatment of peri-implant mucositis, an initial reduction in bacterial load was followed with bacterial counts after 8 months comparable with baseline (Thöne-Mühling et al. 2010).
When the proportion of the total DNA counts of orange complex species was >30% at 1 month, there was an unexpected decrease in mean probing depth at 3 months, while it was <30% there was an increase in the mean probing depth at 3 months. One explanation of this observation may be that changes in proportions of specific bacterial species or complexes did not play as important a role as the reduction in total bacterial counts in peri-implant mucositis treatment.

In this study, smoking did not have any significant effect on the treatment outcomes [P-values > 0.1]. There were no statistically significant differences between non-smokers and former smokers in reduction in BOP or probing depth reductions. The lack of significant effects of smoking could be explained by the small number (four) of smokers in the study and the exclusion of heavy smokers (>20 cigarettes/day) in the recruitment of the study population.

An important finding in this study was the negative effect of a submucosal restorative margin on the treatment outcome. Implants with submucosal restoration margins had statistically significantly less reduction in probing depth following treatment than those with supramucosal margins. This finding is perhaps not surprising considering the association between subgingival restoration margins at teeth and periodontal inflammation and loss of attachment (Strub & Belser 1978; Lang et al. 1983, Felton et al. 1991, Schätzle et al. 2001). A quantitative relationship between marginal discrepancy and periodontal tissue inflammation was reported for subgingivally located crown margins (Felton et al. 1991). Furthermore, an association between inadequate access for oral hygiene and peri-implantitis has been reported recently (Serino & Ström 2009).

The negative influence of a submucosal restorative margin shown in the present study may have implications for placement protocols of implants. Therefore, where possible, implant restoration margins should be positioned at or above the mucosal margin in order to facilitate access for biofilm control.

In conclusion, this study showed that non-surgical debridement and oral hygiene with and without adjunctive chlorhexidine gel were effective in the treatment of peri-implant mucositis. However, the study has also documented that this successful anti-infective protocol did not always result in complete resolution of inflammation. Implants with supramucosal restoration margins showed greater improvement following the treatment of peri-implant mucositis compared with those with submucosal restoration margins.

Acknowledgements: The authors acknowledge the assistance of Regula Hirschi, Marianne Weibel and Prof. G. Rutger Persson from the Oral Microbiology Laboratory, School of Dental Medicine, University of Bern, Switzerland. This study was supported by an research grant of the International Team of Implantology (ITI) [341–2004] and the Clinical Research Foundation (CRF) for the Promotion of Oral Health, CH-3855 Brienz, Switzerland.

Conflict of interest: There is no conflict of interest.

References


