Adjunctive local antibiotic therapy in the treatment of peri-implantitis II: clinical and radiographic outcomes

Giovanni E. Salvi
G. Rutger Persson
Lisa J. A. Heitz-Mayfield
Marc Frei
Niklaus P. Lang

Authors' affiliations:
Giovanni E. Salvi, G. Rutger Persson, Marc Frei, Niklaus P. Lang, School of Dental Medicine, University of Berne, Berne, Switzerland
Lisa J. A. Heitz-Mayfield, University of Western Australia, Perth, Australia

Correspondence to:
Giovanni E. Salvi
Department of Periodontology & Fixed Prosthodontics
School of Dental Medicine
University of Berne
Freiburgstrasse 7
CH-3010 Berne
Switzerland
Tel.: +41 31 632 35 31
Fax: +41 31 632 49 15
E-mail: giovanni.salvi@zmk.unibe.ch

Key words: antibiotics, cumulative interceptive supportive therapy (CIST), inflammation, local drug delivery, oral implants, peri-implantitis

Abstract
Aim: To monitor over 12 months clinical and radiographic changes occurring after adjunctive local delivery of minocycline microspheres for the treatment of peri-implantitis.

Material and methods: In 25 partially edentulous subjects, 31 implants diagnosed with peri-implantitis were treated. Three weeks after oral hygiene instruction, mechanical debridement and local antiseptic cleansing using 0.2% chlorhexidine gel, baseline (Day 0) parameters were recorded. Minocycline microspheres (Arestin®) were locally delivered to each implant site with bone loss and a probing pocket depth (PPD) ≥ 5 mm. Rescue therapy with Arestin® was allowed at Days 180 and 270 at any site exhibiting an increase in PPD ≥ 2 mm from the previous visit. The following clinical parameters were recorded at four sites/implant at Day 0, 10, 30, 60, 90, 180, 270 and 360: PPD, clinical attachment level (CAL), bleeding on probing (BOP) and plaque index (PlI).

Results: Six implants in six subjects were either rescued or exited because of persisting active peri-implantitis. Successful implants showed a statistically significant reduction in both PPD and percentage of sites with BOP between baseline and Day 360 (P < 0.05). At mesial implant sites, the mean PPD reduction amounted to 1.6 mm (95% CI: 0.9–2.2 mm, P < 0.001) and was accompanied by a statistically significant reduction of the BOP value (P < 0.001). Binary regression analysis showed that the clinical parameters and smoking history could not discriminate between successfully treated and rescued or exited implants at any observation time point.

Conclusion: Non-surgical mechanical treatment of peri-implantitis lesions with adjunctive local delivery of microencapsulated minocycline led to positive effects on clinical parameters up to 12 months.

As introduced at the first European Workshop on Periodontology in Ittingen, Switzerland, peri-implant diseases were defined as a collective term for inflammatory processes in the tissues surrounding an osseointegrated implant [Albrektsson & Isidor 1994]. Peri-implant mucositis was defined as a reversible inflammatory process in the soft tissues surrounding a functioning implant, whereas peri-implantitis is an inflammatory process characterized by additional loss of peri-implant bone. The formation of a subgingival biofilm has been shown in animal experiments and clinical studies to be the pivotal etiological factor for the initiation of peri-implant inflammation and subsequent loss of marginal bone [Lindhe et al. 1992; Lang et al. 1993; Schou et al. 1993a, 1993b].

While the incidence of peri-implantitis appears to be low, the increasing use of oral implants in reconstructive dentistry may
in the future lead to a higher prevalence of peri-implantitis lesions. Based on the evidence available for the treatment of periodontitis, similar approaches have been proposed for the management of peri-implant infections. Such therapies include mechanical debridement, the use of antibiotics, systemic administration of local and systemic antibiotics, access flap surgery with or without the use of bone-regenerating procedures and supportive therapy. A cumulative interceptive supportive therapy (CIST) treatment regime for the treatment of peri-implant infections was developed and implemented at the University of Berne, Switzerland (Lang et al. 1997). This systematic approach aims at the reduction of the peri-implant biofilm in order to establish a microbiota conducive to health and may involve the use of antibiotics. There are, however, relatively few studies evaluating treatment outcomes with antibiotics whether administered systemically or locally. Findings from animal experiments have shown that mechanical debridement, combined with systemic administration of amoxicillin and metronidazole, resulted in resolution of ligature-induced peri-implantitis lesions (Ericsson et al. 1996).

In subjects diagnosed with peri-implantitis lesions, mechanical debridement, pocket irrigation with chlorhexidine and adjunctive systemic administration of 1000 mg ornidazole/day for 10 days resulted in improved clinical and microbiological conditions up to 12 months (Mombelli & Lang 1992).

Because peri-implantitis lesions represent well-demarcated saucer-like defects, controlled local delivery devices originally developed for the treatment of localized periodontal lesions have been propagated for the treatment of peri-implant infections. Antimicrobial agents contained in such devices are released over a period of 7–10 days at doses sufficient to kill bacteria protected in a biofilm and incompletely removed by mechanical debridement alone. Findings from a randomized multicenter clinical trial have shown that in patients with chronic periodontitis, scaling and root planing in conjunction with locally delivered minocycline microspheres was more effective than scaling and root planing alone in reducing probing depths (Williams et al. 2001; Paquette et al. 2004).

Clinical, microbiological and radiographic improvements in the treatment of peri-implantitis lesions have been documented after mechanical debridement in conjunction with the use of resorbable or non-resorbable local delivery devices (Mombelli et al. 2001; Buchter et al. 2004; Renvert et al. 2004; Persson et al. 2006). Recent reviews, however, have identified insufficient evidence to recommend a specific protocol for the treatment of peri-implantitis lesions (Klinge et al. 2002; Roos-Jansäker et al. 2003; Heitz-Mayfield & Lang 2004; Schou et al. 2004). The number of clinical longitudinal studies evaluating different treatment protocols for peri-implantitis is limited. Most reports deal with single cases treated by combinations of procedures. Because of ethical considerations, treatment of human peri-implantitis cases generally lack randomization and controls. Owing to the relatively low incidence of peri-implantitis, clinical studies usually involve small sample sizes. The development of resorbable controlled delivery devices in recent years offers an alternative to non-resorbable local delivery systems and systemic antibiotic therapy for treatment of peri-implantitis lesions.

Thus, the aim of this study was to evaluate the clinical and radiographic changes after adjunctive local delivery of microencapsulated minocycline for the treatment of peri-implantitis lesions over an observation period of 12 months.

Material and methods

The study was designed and conducted as a single-center open-label case cohort study. The study protocol was submitted and approved by the Ethical Committee of the Canton of Berne (KEK), Switzerland.

Study population

Partially edentulous subjects were screened from the pool of the Department of Periodontology & Fixed Prosthodontics of the University of Berne. After signing informed consent, subjects meeting the following inclusion criteria were enrolled:

- between the age of 35 and 75 and in good general health,
- completion of non-surgical and surgical periodontal treatment,
- enrollment in a maintenance care program with full-mouth plaque score ≤25% and ≤20% of residual sites with probing pocket depth (PPD) ≥5 mm with concomitant bleeding on probing (BOP),
- peri-implant PPD ≥5 mm with concomitant BOP applying a force of 0.2–0.25 N.

Subjects presenting with the following conditions were excluded:

- pregnant and lactating women,
- chronic medication (i.e., ≥2 weeks) known to affect periodontal status within 1 month of the baseline visit,
- medical requirement of prophylactic antibiotics,
- allergies to tetracyclines and
- use of systemic antibiotics within 6 months before enrollment.

Clinical assessments and procedures

After completion of periodontal treatment and prosthetic rehabilitation including the use of oral implants, all subjects were enrolled in a supportive periodontal therapy (SPT) program. After detection of a peri-implant PPD ≥5 mm with concomitant BOP and radiographic bone loss, the CIST regime was implemented. Three weeks after oral hygiene instruction, mechanical debridement with carbon fiber curettes and local antiseptic cleansing using 0.2% chlorhexidine gel (Plak Out® Gel, Kerr Hawe SA, Bioggio, Switzerland), baseline (Day 0) parameters were recorded. Minocycline HCL microspheres (Arestin®, OrpharPharma, Warminster, PA, USA) were locally delivered to each implant site with a PPD ≥5 mm bleeding on probing and displaying bone loss on radiographs. Rescue therapy with Arestin® was allowed at Days 180 and 270 at any site exhibiting an increase in PPD ≥2 mm from the previous visit. PPD and clinical attachment level (CAL) were recorded using a calibrated periodontal probe with a standardized force set at 0.2 N and reported in millimeters. In order to calculate CAL, the crown margin located at the implant shoulder level was used as a reference line to determine the distance in millimeters to
the soft tissue margin. Peri-implant sites bleeding on probing (BOP) were assessed using a calibrated periodontal probe with a standardized force set at 0.2 N and reported dichotomously. The presence or absence of bacterial deposits was recorded by running a probe along the soft tissue margin. All clinical parameters were recorded at four sites/implant [i.e., mesial, distal, oral, buccal and distal] at Days 0, 10, 30, 60, 90, 180, 270 and 360.

Radiographic assessment

Standardized peri-apical intraoral radiographs [Ultraspeed®, Eastman Kodak Co., Rochester, NY, USA] were taken at baseline (i.e., Day 0) and at the 1-year examination (i.e., Day 360), respectively. A dental X-ray unit [Orthorax® 64S, Gen-dex Dental Systems S.r.l., Milano, Italy] equipped with a long-cone paralleling device was used in conjunction with customized acrylic bite blocks. To assess linear changes at interproximal alveolar crestal bone height, the distance from the implant shoulder to the most coronal bone-to-implant contact (DIB) was determined both at the mesial and distal aspect of each implant and expressed in millimeters.

Primary outcome measures included the assessment of changes in PPD and BOP from Days 0 to 360. Secondary outcome measures included the assessment of changes in marginal soft tissue recession (REC) from the implant shoulder, CAL, percentage of sites covered with plaque (plaque) and interproximal (i.e., mesial and distal) marginal bone level (DIB).

Statistical analysis

Descriptive statistics were used to present the material [Table 1]. The four values [e.g., mesial, distal, oral, buccal] of the clinical parameters PPD, REC, CAL, BOP and plaque recorded around each implant were averaged to obtain a mean implant score ± standard deviation (SD). In addition, clinical parameters were recorded locally at the site with the deepest PPD at baseline.

To assess longitudinal changes of the parameters PPD, REC, CAL, BOP, plaque and DIB, the Wilcoxon-matched pairs signed-rank test adjusted for multiple comparisons was used. The implant was the statistical unit of analysis. A value of mean implant plaque scores (i.e., FMPPD, FMPS, FMBS, FMCAL) were averaged to obtain a mean implant (e.g., mesial, distal, oral, buccal) of the material (Table 1). The four values of these 21 subjects are summarized in Table 1.

### Table 1. Baseline demographic data of the subjects completing the 12-month follow-up visit

<table>
<thead>
<tr>
<th>n (subjects)</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) ± SD</td>
<td>60 ± 10.2</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>40–73</td>
</tr>
<tr>
<td>Males/females</td>
<td>10/11</td>
</tr>
<tr>
<td>Mean FMBS (%) ± SD</td>
<td>19.9 ± 8.3</td>
</tr>
<tr>
<td>Mean FMPS (%) ± SD</td>
<td>13.7 ± 5.5</td>
</tr>
<tr>
<td>Mean FMPPD (mm) ± SD</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Mean FMCAL (mm) ± SD</td>
<td>3.5 ± 0.8</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>8</td>
</tr>
<tr>
<td>Never smokers</td>
<td>4</td>
</tr>
<tr>
<td>Former smokers</td>
<td>9</td>
</tr>
</tbody>
</table>

FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; FMPPD, full-mouth pocket probing depth; FMCAL, full-mouth clinical attachment level.

**P** < 0.05 was considered to be the level of statistical significance.

**Results**

Twenty-five subjects with 31 osseointegrated implants displaying signs of peri-implantitis were enrolled and treated according to the study protocol. Three implants were rescued and retreated with Arestin® at Days 180 or 270. Over the 12-month observation period, six implants in six subjects were exited from the study because of persistent peri-implant inflammation requiring surgical access for mechanical debridement and surface decontamination. Thus, 21 subjects with 25 implants were followed over a period of 12 months. The demographic characteristics of these 21 subjects are summarized in Table 1.

**Clinical outcomes**

The mean and local changes in peri-implant PPD, REC, CAL, BOP and plaque scores of the 25 implants are presented in Table 2. A mean implant score [i.e., I] was calculated by averaging the mesial, distal, buccal and oral sites of each implant with respect to PPD, REC, CAL and percentage of sites bleeding on probing and harboring plaque [i.e., PPD I, REC I, CAL I, BOP I and plaque I]. Moreover, the local changes [i.e., L] in PPD, REC, CAL, BOP and plaque scores are presented for the peri-implant site with the deepest PPD at baseline [i.e., PPD L, REC L, CAL L, BOP L and plaque L]. Statistically significant changes (**P** < 0.05) between baseline and Day 360 were observed for mean PPD I and L scores, respectively. The mean PPD I decreased from 4.5 ± 1.3 mm at baseline to 3.5 ± 0.7 mm at Day 360. Similarly, the mean PPD L decreased from 5.9 ± 0.7 mm at baseline to 4.2 ± 0.6 mm at Day 360. No statistically significant changes (**P** > 0.05) between the implant shoulder and the peri-implant soft tissue margin [i.e., REC] were found over time. The CAL gain, however, showed statistically significant changes over time (**P** < 0.05) at the implant level [i.e., from 3.3 ± 1.1 to 2.2 ± 1 mm] and at the site with the deepest PPD at baseline [i.e., from 4.1 ± 1.1 to 2.3 ± 0.9 mm]. Concomitant with the decrease in PPD scores, the mean BOP L score statistically significantly decreased (**P** < 0.05) from 69 ± 38% at baseline to 19 ± 30% at Day 360, while the mean BOP L score statistically significantly decreased from 92 ± 28% at baseline to 44 ± 51% at Day 360 (**P** > 0.05).

A statistically significant change (**P** < 0.05) in mean implant plaque scores [i.e., plaque I] was only observed between baseline and final examination [i.e., Day 360]. At the peri-implant site with the deepest PPD at baseline, no statistically significant changes (**P** > 0.05) were observed over time with respect to plaque scores [i.e., plaque L]. Smoking status was not significantly associated with PPD, REC, CAL and BOP changes.

**Radiographic outcomes**

Table 3 summarizes the mean linear measurements of the distance from the implant shoulder to the most coronal implant-to-bone contact (DIB). These values were assessed at the mesial and distal aspect of 22 out of the 25 implants followed up for 12 months. Around three implants, radiographic assessment of the landmarks could not be performed and the measurements were excluded from the analysis. At baseline, the mean DIB amounted to 4.17 ± 1.03 mm at the mesial and to 4.45 ± 1.2 mm at the distal aspect of the implant, respectively. After 12 months, the DIB values slightly increased to 4.32 ± 1.16 mm at the mesial and to 4.59 ± 1.47 mm at the distal aspect of the implant, respectively. The differences between baseline and Day 360 did not reach statistical significance (**P** > 0.05). No statistically significant associations (**P** > 0.05) between DIB changes and plaque scores or smoking status were observed.
Table 2. Mean changes ± standard deviation of the parameters pocket probing depth (PPD in mm), bleeding on probing (BOP in %), mucosal recession (REC in mm), clinical attachment level (CAL in mm) and plaque (plaque in %) assessed around 25 implants over the observation period of 12 months

<table>
<thead>
<tr>
<th></th>
<th>n = 25</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 10</td>
<td>Day 30</td>
<td>Day 60</td>
<td>Day 90</td>
<td>Day 180</td>
<td>Day 270</td>
</tr>
<tr>
<td>PPD I</td>
<td>4.5 ± 1.3</td>
<td>4 ± 1*</td>
<td>3.6 ± 0.7*</td>
<td>3.5 ± 0.6*</td>
<td>3.5 ± 0.7*</td>
<td>3.5 ± 0.8*</td>
<td>3.5 ± 0.7*</td>
</tr>
<tr>
<td>PPD L</td>
<td>5.9 ± 0.7</td>
<td>5.1 ± 0.9*</td>
<td>4.4 ± 0.7*</td>
<td>4.2 ± 0.8*</td>
<td>4.3 ± 1*</td>
<td>4.4 ± 0.8*</td>
<td>4.2 ± 0.7*</td>
</tr>
<tr>
<td>REC I</td>
<td>1.3 ± 0.6</td>
<td>1.3 ± 0.8</td>
<td>1.5 ± 0.8</td>
<td>1.4 ± 0.9</td>
<td>1.4 ± 1.1</td>
<td>1.4 ± 1.1</td>
<td>1.3 ± 1.1</td>
</tr>
<tr>
<td>REC L</td>
<td>1.8 ± 1.2</td>
<td>2 ± 1.2</td>
<td>2.2 ± 1.1</td>
<td>2.1 ± 0.9</td>
<td>1.9 ± 0.9</td>
<td>2.1 ± 1.1</td>
<td>1.9 ± 1.1</td>
</tr>
<tr>
<td>CAL I</td>
<td>3.3 ± 1.1</td>
<td>2.7 ± 1.3</td>
<td>2.1 ± 0.8*</td>
<td>2 ± 0.9*</td>
<td>2.2 ± 0.7*</td>
<td>2.2 ± 0.9*</td>
<td>2.2 ± 0.8*</td>
</tr>
<tr>
<td>CAL L</td>
<td>4.1 ± 1.1</td>
<td>3.1 ± 1.3*</td>
<td>2.2 ± 1.1*</td>
<td>2.1 ± 1*</td>
<td>2.4 ± 0.8*</td>
<td>2.3 ± 0.9*</td>
<td>2.3 ± 0.9*</td>
</tr>
<tr>
<td>BOP I</td>
<td>69 ± 37.5</td>
<td>47 ± 46.8*</td>
<td>33.7 ± 39.6*</td>
<td>34.4 ± 35.6*</td>
<td>30 ± 31.5*</td>
<td>34 ± 29.9*</td>
<td>25 ± 35.9*</td>
</tr>
<tr>
<td>BOP L</td>
<td>92 ± 27.7</td>
<td>84 ± 37.4</td>
<td>56.5 ± 50.7*</td>
<td>58.3 ± 50.4*</td>
<td>60 ± 50*</td>
<td>68 ± 47.6*</td>
<td>56 ± 50.7*</td>
</tr>
<tr>
<td>Plaque I</td>
<td>2 ± 2.3</td>
<td>5 ± 15</td>
<td>4.3 ± 19.4</td>
<td>7.3 ± 22.1</td>
<td>7 ± 22.4</td>
<td>3 ± 15</td>
<td>8 ± 23.5</td>
</tr>
<tr>
<td>Plaque L</td>
<td>4 ± 20</td>
<td>8 ± 27.7</td>
<td>4.3 ± 20.9</td>
<td>12.5 ± 33.8</td>
<td>8 ± 27.7</td>
<td>4 ± 20</td>
<td>16 ± 37.4</td>
</tr>
</tbody>
</table>

*Statistically significantly different from baseline, P < 0.05.
I, mean implant score (mesial, distal, buccal and oral sites averaged); L, implant site with deepest PPD at baseline.

Table 3. Mean linear changes ± standard deviation in mm from the implant shoulder to the most coronal bone-to-implant contact (DIB) assessed on standardized radiographs at the mesial and distal aspect

<table>
<thead>
<tr>
<th></th>
<th>n = 22</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 360</td>
<td>Δ DIB (mm)</td>
</tr>
<tr>
<td>DIB mesial (mm)</td>
<td>4.17 ± 1.03</td>
<td>4.32 ± 1.16</td>
<td>-0.15 ± 0.64</td>
</tr>
<tr>
<td>DIB distal (mm)</td>
<td>4.45 ± 1.20</td>
<td>4.59 ± 1.47</td>
<td>-0.14 ± 0.75</td>
</tr>
</tbody>
</table>

Discussion

The findings of this clinical investigation revealed a positive effect of non-surgical mechanical debridement in conjunction with local delivery of minocycline microspheres in the treatment of peri-implant infections. Overall, the clinical benefit obtained by adjunctive local minocycline delivery could be maintained over 12 months and the inflammatory process arrested in the majority of the cases. Furthermore, the positive clinical outcomes of the present study may be partly explained by successful non-surgical, surgical and supportive periodontal therapy before implant placement, as evidenced by the relatively low proportions of mean full-mouth plaque and bleeding scores as well as shallow residual periodontal pockets and limited loss of clinical attachment (Table 1). Surgical therapy including open-flap debridement with regenerative or resective approaches was not deemed necessary for the peri-implant lesions included in the present study. Although it was anticipated that non-surgical mechanical debridement in conjunction with local antibiotic delivery should yield adequate clinical improvements, in six patients meeting the inclusion criteria the extension of the peri-implant lesion was underestimated at baseline and the patients were prematurely excluded from the study. In such cases, additional surgical interventions were performed in order to gain access to the contaminated implant surface and achieve resolution of the peri-implant bony defect by means of regenerative or resective approaches. Although pocket depth reduction was observed throughout the study period, the level of the implant shoulder remained on average 2 mm below the peri-implant soft tissue margin, indicating that CAL gain was mainly the result of probing depth reduction. Reduced probe penetration into peri-implant tissues could be attributed to increased soft tissue tonus after resolution of soft tissue inflammations. This observation is supported by findings comparing tissue resistance with probing and the accuracy of depth measurement at different force levels (e.g., 0.25, 0.5, 0.75, 1 and 1.25 N) around non-submerged ITI* dental implants and teeth [Mombelli et al. 1997]. These authors concluded that peri-implant probing depth measurements were more sensitive to force variation than the corresponding measurements around teeth. Although peri-implant probing was shown to disrupt the epithelial attachment to an implant surface, it did not cause permanent damage to the transmucosal seal and complete new epithelial attachment was re-established 5 days following peri-implant probing [Etter et al. 2002].

Improvements of soft tissue inflammation and probing depth of peri-implant lesions following mechanical or combined mechanical and local antimicrobial therapy have been documented in case report [Ciancio et al. 1995; Mombelli et al. 2001] and comparative [Schenk et al. 1997; Porras et al. 2002; Buchter et al. 2004; Renvert et al. 2004] studies. The results of the present study compare favorably and extend the short-term findings (i.e., 3 months) of treatment of incipient peri-implant infections using local delivery of minocycline microspheres [Renvert et al. 2004]. In this study [Renvert et al. 2004], the use of adjunctive minocycline microspheres resulted in improvements of both probing depth and bleeding on probing scores. At the deepest peri-implant site, the mean probing depth decreased from 5 ± 0.9 to 4.1 ± 0.8 mm and bleeding on probing scores were reduced from 100 ± 0% to 57 ± 35% after an observation period of 3 months (Renvert et al. 2004). In the present study, after an observation period of 12 months, the mean probing depth decreased from 5.9 ± 0.7 to 4.2 ± 0.6 mm and BOP scores were reduced from 92 ± 28% to 44 ± 51% at sites with the deepest PPD at baseline. Comparable results were achieved in the treatment of peri-implant lesions by adjunctive local delivery of tetracycline-impregnated fibers [Actisite®] [Mombelli et al. 2001]. In this study [Mombelli et al. 2001], at sites with the deepest PPD at baseline, pocket depth was reduced from...
6.03 ± 1.54 to 3.85 ± 1.49 mm after an observation period of 12 months.

In conclusion, non-surgical mechanical treatment of peri-implantitis lesions with adjunctive local delivery of microencapsulated minocycline yielded positive effects on clinical parameters up to 12 months. Hence, such an approach may be recommended for the treatment of peri-implant infections. It should be noted, however, that treatment outcomes were pronounced in lesions of medium-size probing depth [i.e., 5–6 mm].

Acknowledgements: This study was supported by the Clinical Research Foundation (CRF), University of Berne, Switzerland and by OraPharma Inc., Warminster, PA, USA.

References