Systemic antibiotic therapy in periodontics
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CHAPTER 5

AMOXICILLIN PLUS METRONIDAZOLE IN THE TREATMENT OF ADULT PERIODONTITIS PATIENTS

A double-blind placebo-controlled study

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Amoxicillin and metronidazole in adult periodontitis treatment

Abstract

The aim of this double-blind, parallel study was to evaluate the adjunctive effects of systemically administered amoxicillin and metronidazole in a group of adult periodontitis patients who also received supra- and subgingival debridement. Forty-nine patients with a diagnosis of generalised severe periodontitis participated in the study. Random assignment resulted in 26 patients in the placebo (P) group with a mean age of 40 years and 23 patients in the test (T) group with a mean age of 45 years. Clinical measurements and microbiological assessments were taken at baseline and 3 months after completion of the initial periodontal therapy with additional placebo or antibiotic treatment. Patients received coded study medication of either 375 mg amoxicillin in combination with 250 mg metronidazole or identical placebo tablets, every 8 hours for the following 7 days. At baseline, no statistically significant differences between groups were found for any of the clinical parameters. Except for the plaque index, there was a significantly larger change in the bleeding, probing pocket depth (PPD) and clinical attachment level (CAL) in the T-group as compared to the P-group after therapy. The greatest reduction in PPD was found at sites with initial PPD of ≥ 7 mm, 2.5 mm in the P-group and 3.2 mm in the T-group. The improvement in CAL was most pronounced in the PPD category ≥ 7 mm and amounted to 1.5 mm and 2.0 mm in the P- and T-groups, respectively. No significant decrease was found in the number of patients positive for any of the test species in the P-group. The number of patients positive for Porphyromonas gingivalis, Bacteroides forsythus and Prevotella intermedia in the T-group showed a significant decrease. After therapy there was a significant difference between the P- and the T-group in the remaining number of patients positive for P. gingivalis, B. forsythus and Peptostreptococcus micros. Four subgroups were created on the basis of the initial microbiological status for P. gingivalis positive (Pg-pos) and negative patients (Pg-neg) in the P- and the T-groups. The difference in reduction of PPD between Pg-pos and Pg-neg patients was particularly evident with respect to the changes in % of sites with a probing pocket depth ≥ 5 mm. This % decreased from 45% at baseline to 23% after treatment in the Pg-pos-placebo subgroup and decreased from 46% to 11% in the Pg-pos-test subgroup (p ≤ 0.005). In contrast, the changes in the proportion of sites with a probing pocket depth ≥ 5 mm in the Pg-neg-placebo and Pg-neg-test subgroup were similar, from 43% at baseline to 18% after treatment versus 40 % to 12 %, respectively. In conclusion this study has shown that systemic usage of metronidazole and amoxicillin, when used in conjunction with initial periodontal treatment in adult periodontitis patients, achieves significantly better clinical and microbiological results than initial periodontal treatment alone.
Moreover, this research suggests that especially patients diagnosed with *P. gingivalis* benefit from antibiotic treatment.

**Introduction**

Treatment of periodontitis aims at reducing supra- and subgingival plaque and calculus by the institution of proper daily oral hygiene measures and meticulous scaling and rootplaning. However, despite this therapy, some patients may experience ongoing periodontal attachment loss. One possible factor responsible for post-treatment progression of disease is the inability of therapy to suppress periodontal pathogens to levels that are compatible with periodontal health. Presence of periodontal pathogens such as *Porphyromonas gingivalis*, *Bacteroides forsythus* and *Actinobacillus actinomycetemcomitans* has been linked to ongoing periodontal destruction by several authors (Bragd et al. 1987; Carlos et al. 1988; Christersson et al. 1985; Dzink et al. 1985; Grossi et al. 1994; Haffajee et al. 1991; Haffajee & Socransky 1994; Macht ei et al. 1997). Moreover, absence of specific periodontal pathogens seems to have a negative predictive value for further attachment loss (Dahlén et al. 1996; Wennström et al. 1987). Therefore, one objective of periodontal treatment might be to suppress or eliminate certain subgingival periodontal pathogens. A number of studies have shown that the adjunctive use of systemic antibiotics can improve the results of the initial periodontal treatment and can more predictably suppress periodontal pathogens in juvenile and adult periodontitis patients (Van Winkelhoff et al. 1996). In adult periodontitis, systemic metronidazole has been shown to improve clinical and microbiological treatment outcomes (Elter et al. 1997; Lindhe et al. 1983; Loesche et al. 1992a; Winkel et al. 1997). However, not all antibiotic regimes achieve a favourable clinical and microbiological result. In a randomized double-blind, placebo-controlled study in adult periodontitis patients, initial periodontal therapy in conjunction with systemic amoxicillin plus clavulanic acid was no more effective than initial periodontal therapy by itself (Winkel et al. 1999). Since the subgingival microflora in adult periodontitis contains various putative pathogens that may differ in antimicrobial susceptibility, several investigators have used a combination of 2 antibiotics to provide more effective therapy (Van Winkelhoff et al. 1996). Metronidazole and amoxicillin have been used successfully in the treatment of advanced periodontitis, especially in cases that were associated with *A. actinomycetemcomitans* (Berglundh et al. 1998; Pavićić et al. 1994; Van Winkelhoff et al. 1989; Van Winkelhoff et al. 1992; Winkel et al. 1998). Elimination of this putative periodontal pathogen has been associated with long-term periodontal stability (Pavićić et al. 1994). Recently, Berglundh et al. (1998) confirmed this observation. These authors showed that
scaling and root planing in combination with systemic metronidazole plus amoxicillin improved clinical parameters significantly better than scaling alone. The present study describes the 3 months' post treatment results of a phase III type clinical trial, performed in 2 separate periodontal clinics. Thus, the purpose of the present double-blind, parallel study was to evaluate the adjunctive effects of systemically administered amoxicillin and metronidazole in a group of adult periodontitis subjects who also received initial supra- and subgingival debridement.

Material and Methods

Study population

A total of 54 volunteers were selected for this study. Patients were referred to the Clinic for Periodontology Amsterdam (N=26) and the Clinic for Periodontology Utrecht (N=28) for diagnosis and treatment of periodontitis. Inclusion criteria were: 1) ≥ 3 natural teeth in each quadrant, 2) clinical diagnosis of generalised severe periodontitis, characterised by the presence of ≥ 1 site in at least 3 of 4 quadrants of the dentition with a probing pocket depth of > 6 mm with interproximal clinical attachment loss of ≥ 3 mm, showing bleeding upon probing and radiographic evidence of alveolar bone loss. Exclusion criteria were: professional scaling and root planing or surgical periodontal therapy in the past, systemic or topical periodontal antibiotic therapy 6 months prior to the initiation of the study; pregnancy, lactating or planning a pregnancy; systemic diseases such as diabetes; known HIV infection; acute necrotising periodontitis; use of non-steroid anti-inflammatory drugs and use of mouthrinses. The patients' smoking status was recorded. Subjects were considered smokers if they were currently smoking or had stopped smoking within the last year.

Study design

This clinical trial was a randomised double-blind, placebo-controlled, parallel study and extended between baseline and end-trial over a 6 months period (Fig.1). This study was carried out with the approval of the medical ethical committee of the University of Amsterdam. Prior to participation, the purpose and procedures were fully explained to all patients. Patients were entered into the study only after having given written consent. Clinical measurements and microbiological assessments were taken at baseline (day 0) and 3 months after completion of the initial periodontal therapy with additional placebo or antibiotic treatment. After the baseline visit, patients returned for full-mouth scaling and root planing (S&R), which was carried out in 3 to 6 sessions of 1 hour, under local
anaesthesia if requested by the patient. At each of these sessions oral hygiene measures were re-inforced. Approximately 6 weeks after the last session of S&R, patients were recalled for a full-mouth check-up, at which S&R was administered at sites with a probing pocket depth of > 3 mm and sites showing bleeding on probing. In addition, oral hygiene measures were re-inforced. On the same day, patients were randomly assigned to receive coded study medication of either 375 mg amoxicillin in combination with 250 mg metronidazole or identical placebo tablets, to be taken every 8 hours for the following 7 days. Patients were informed not to use alcohol during medication. They returned for a follow-up visit approx. 3 months after completion of the medication treatment phase. To check compliance patients were asked to return any medication tablets that remained after 7 days.

**Clinical measurements**

At each clinic location, one examiner (GAW, EGW) was responsible for all clinical measurements and microbiological sampling at baseline as well as the re-examination. Records of earlier examinations were not available to the investigator at the time of re-evaluation. The clinical investigator was unaware of the treatment and the results of the microbiological analyses at any time point of the study. Probing pocket depth and clinical attachment level measurements were performed using a constant force probe (Brodontic®, Ash, Dentsply, England). The probe tips had a diameter of 0.5 mm and the probing force was set at 0.75 N (probing pressure 382 N/cm²). The tips were tapered and had Williams millimeter markings. Individual probes were assigned to each patient throughout the
study to reduce variability (Van der Zee et al. 1991).
The following clinical parameters were assessed on six sites (mesio-, mid-, distobuccal, and mesio-, mid-, distolingual) of each tooth:
- Plaque Index (PI), according to Silness & Löe (1964)
- Probing pocket depth (PPD)
- Bleeding Index (BI), bleeding on pocket probing recorded as present within 30 seconds (1) or absent (0)
- Clinical attachment level (CAL) using the cemento-ename1 junction as a reference.

**Sampling and bacteriological procedures**

At baseline, the deepest bleeding pocket in each quadrant was selected for microbiological evaluation (Mombelli et al. 1991; Mombelli et al. 1994) based on the probing pocket chart, which had been used to screen patients for this study. Microbiological analyses of the subgingival plaque were performed at baseline and approximately 3 months after completion of the medication. Subgingival sampling was carried out after the PI assessments and before PPD, BI and CAL assessment. At the selected sites, supragingival plaque was carefully removed with a curette, after which the sample sites were isolated with cotton rolls and gently air-dried. The subgingival plaque sample was taken by inserting 2 sterile paper points (Fine, UDM, West Palm Beach, USA) consecutively into the periodontal pocket for 10 seconds each. Paper points from all 4 sample sites were collected in reduced transport fluid (RTF) (Syed & Loesch 1972) and processed within 24 hours (Van Steenbergen et al. 1993). Tenfold serial dilutions were prepared in RTF and aliquots of 0.1 ml were plated onto 5% horse-blood agar plates (Oxoid no. 2, Basingstoke, England) supplemented with haemin (5 mg/l) and menadione (1 mg/l) for isolation and growth of obligately anaerobic bacteria, and on TSBV for selective isolation and growth of *A. actinomycetemcomitans* (Slots 1982). Blood agar plates were incubated anaerobically in 80% N₂, 10% H₂ and 10% CO₂ for up to 14 days and TSBV plates were incubated in air + 5% CO₂ for five days (Van Steenbergen et al. 1986). Blood agar plates were used for total bacterial counts and to determine proportions of dark-pigmented colonies, *Bacteroides forsythus*, *Fusobacterium nucleatum* and *Peptostreptococcus micros*. Representative dark-pigmented colonies were purified and identified using standard techniques (Van Winkelhoff et al. 1985), including Gram-stain, hemagglutination of 3% sheep erythrocytes, fermentation of glucose, production of indole from tryptophan and production of specific enzymes (Van Winkelhoff et al. 1986). *B. forsythus* was identified on the basis of the typical colony morphology, Gram-stain and production of a trypsin-like enzyme (Braham & Moncla 1992). *F. nucleatum* and *P. micros* were identified on the basis of colony morp-
hology, Gram stain and production of specific enzymes (API 32A, Biomerieux, La Balme, Les Grottes, France).

**Statistical analysis**

For analyses of the clinical and microbiological data, a patient level response variable was calculated for each parameter by computing the full-mouth mean value of the scores, at baseline and after therapy. The number of pockets \( \geq 5 \) mm was enumerated and calculated in terms of percentage. A small, but significant effect between the 2 centres was found for PPD and CAL. This effect did not interact with results regarding therapy, smoking or microbiological treatment results. All analyses were corrected for the centre effect by using the centre as a co-variate.

Plaque scores at baseline and after therapy were initially entered as co-variates in the analyses concerning probing pocket depth and clinical attachment level, but could be removed since they had no significant influence on test results. \( P \)-values were accepted after normal distribution of residuals was established. Post-testing on clinical parameters for differences between test and placebo group at baseline and after therapy was performed using a Mann-Whitney test. The Mantel-Haenszel Exact test was used to examine the prevalence of the different micro-organisms before and after treatment in the 2 groups. An analysis of variance was performed using the different clinical parameters as dependent variables. Treatment modalities were entered as the group effect. Therapy response with respect to presence or absence of \( P. \) gingivalis was entered as a co-variate. This was not performed for other micro-organisms since the number of culture positive and negative patients at baseline was not equally distributed within the test and placebo groups. To establish the effect of cigarette smoking on therapy outcome, the smoking status was entered into the analyses of variance as a co-variate. To further investigate the trends concerning probing pocket depth (\( p=0.09 \) for both \( P. \) gingivalis and smoking) as found in these analyses, post-testing was performed by dividing the study population in \( P. \) gingivalis negative and positive patient subgroups and smokers and non-smokers. For each subgroup analyses of variance were performed on clinical parameters as described above. Values of \( p < 0.05 \) were accepted as statistically significant.
Results

Four of 54 patients in the test group exited the study due to cessation of medication because of 1) severe headache and 2) severe diarrhoea, 3) refusal to take medication because of the size of the tablets and 4) unwillingness to avoid alcohol consumption during medication. One patient in the placebo group left the study due to pregnancy. Thus, a total of 49 volunteers with a mean age of 42 years (range 28-63) completed the study. Random assignment resulted in 26 patients (10 males, 16 females) in the placebo (P) group with a mean age of 40 years (range 28-55) and 23 patients (11 males, 12 females) in the test (T) group which had a mean age of 45 years (range 32-63). There were 18 current smokers in the P-group and 14 in the T-group.

Clinical results

The mean number of sites evaluated per patient was $157\pm12$ (range 129-173) in the P-group and $154\pm18$ (range 118-180) in the T-group. At baseline, no statistically significant differences between groups were found for any of the clinical parameters (Table 1). After therapy, the periodontal condition in both groups had improved, as was deduced from changes in all clinical parameters. In both groups a PI reduction of 0.6 was found. The BI decreased by 0.4 in the P-group and 0.6 in the T-group. Clinical attachment gain was 0.4 mm in the P-group versus 0.7 mm in the T-group. Reduction of probing pocket depth after therapy amounted to 1.0 mm in the P-group and 1.4 mm in the T-group. The % of sites with a probing pocket depth $\geq 5$ mm reduced with 24.3% in the P-group and 31.8% in the T-group. The % of sites that gained clinical attachment of $\geq 2$ mm amounted to 20.2 % in the P-group and 25.1 % in the T-group. The % of sites that lost clinical attachment $\geq 2$ mm was 7.0 % and 5.5 % for the P- and T-group respectively. Except for the PI, there was a significantly larger change of all clinical parameters in the T-group as compared to the P-group after therapy. Table 2 shows the changes in probing pocket depth and clinical attachment level in different probing pocket depth categories after therapy. In all probing pocket depth categories the T-group showed more PPD reduction than the P-group. The greatest change in pocket depth was found in sites with initial PPD of $\geq 7$ mm. At these sites, the mean PPD reduction was 2.5 mm in the P-group and 3.2 mm in the T-group. In the PPD category 0-3 mm, both the P- and T-group lost clinical attachment level. However, this was more pronounced in the P-group. The gain of attachment in the PPD category 4-6 mm was similar for both groups. The improvement in attachment level was most noticeable in the PPD category $\geq 7$ mm and
amounted to 1.5 mm and 2.0 mm in the P- and T-groups, respectively. The differences between the P- and the T-group in each probing pocket depth category were statistically significant with the exception of the CAL in pockets from 4-6 mm at baseline. Table 3 presents the mean clinical parameters of the 4 sampled sites in each subject. With the exception of CAL, changes between the P- and the T-groups were similar to those observed for the full mouth values (Table 1).

**Microbiological observations**

At baseline there was no significant difference in the number of culture positive patients for any of the selected periodontal pathogens between the P- and the T-group (Table 4). In the P-group, no significant decrease in the number of positive patients was found after therapy for any of the test species. Some patients who were culture negative for a bacterium at baseline became positive after treatment. This occurred in 8 patients for *P. micros* and in 4 patients for *F. nucleatum*. The number of patients positive for *P. gingivalis*, *B. forsythus* and *P. intermedia* in the T-group showed a significant decrease after therapy. After therapy there was a significant difference between the P- and the T-group in the remaining number of patients positive for *P. gingivalis*, *B. forsythus* and *P. micros*. Further analysis was carried out with regard to *P. gingivalis*. Four subgroups were created on the basis of presence or absence of *P. gingivalis* at baseline i.e. for the P-group a *P. gingivalis* positive (Pg-pos/P) and a *P. gingivalis* negative (Pg-neg/P) subgroup as well as for the T-group a Pg-pos/T and a Pg-pos/T subgroup (Fig. 2,3). The reduction of the full mouth mean PPD was most pronounced in the Pg-pos/T subgroup. A statistically significant change in PPD of 1.01 mm in the Pg-pos/P subgroup (n=13) versus 1.52 mm in the Pg-pos/T subgroup (n=13) was observed. No difference was seen in the PPD reduction between the Pg-neg/P (n=13) and Pg-neg/T (n=10) subgroup, 1.11 mm versus 1.13 respectively. The difference in reduction of PPD between Pg-pos and Pg-neg patients was particularly evident with respect to the changes in % of sites with a probing pocket depth ≥ 5 mm (Fig. 4). This % was reduced from 45% at baseline to 23% after treatment in the Pg-pos/P-group and from 46% to 11% into the Pg-pos/T subgroup (p ≤ 0.005). In contrast, the changes at sites with a probing pocket depth ≥ 5 mm in the Pg-neg/P and Pg-neg/T subgroups were similar, 43% to 18% versus 40% to 12%, respectively.
Table 1. Full-mouth mean plaque index (PI), bleeding index (BI), clinical attachment level (CAL), probing pocket depth (PPD) and mean frequency distribution (%) of sites with a probing pocket depth (PPB) ≥ 5 mm of the placebo group and the test group at baseline and after therapy (AT).

<table>
<thead>
<tr>
<th>N=49</th>
<th>n</th>
<th>PI baseline</th>
<th>AT</th>
<th>BI baseline</th>
<th>AT</th>
<th>CAL baseline</th>
<th>AT</th>
<th>PPD baseline</th>
<th>AT</th>
<th>% of sites PPD &gt; 5mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>0.9(0.4)</td>
<td>0.3(0.2)*</td>
<td>0.8(0.2)</td>
<td>0.4(0.1)*</td>
<td>4.0(1.3)</td>
<td>3.6(1.1)</td>
<td>4.4(0.5)</td>
<td>3.4(0.5)*</td>
<td>44.6(11.4)</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>**</td>
<td></td>
<td>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>23</td>
<td>1.0(0.4)</td>
<td>0.4(0.3)*</td>
<td>0.8(0.2)</td>
<td>0.2(0.1)*</td>
<td>3.9(1.1)</td>
<td>3.2(1.0)</td>
<td>4.4(0.6)</td>
<td>3.0(0.4)*</td>
<td>43.8(16.8)</td>
</tr>
</tbody>
</table>

N,n: number of patients; (): standard deviation; *: significant change from baseline (p < 0.05); **: significant difference between groups after therapy (p < 0.05).
NS: not significant.

Table 2. Mean change in probing pocket depth (PPD) and clinical attachment level (CAL) in different initial probing pocket depth categories in the placebo and test group after therapy (AT).

<table>
<thead>
<tr>
<th>N=49</th>
<th>initial PPD</th>
<th>Therapy effect on PPD</th>
<th>Therapy effect on CAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td>0-3 mm</td>
<td>4-6 mm</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>0.11 (0.19)</td>
<td>1.37 (0.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.002*</td>
<td>p=0.005*</td>
</tr>
<tr>
<td>Test</td>
<td>23</td>
<td>0.27 (0.14)</td>
<td>1.72 (0.42)</td>
</tr>
</tbody>
</table>

*: significant difference between P- and T-group (Mann-Whitney U test).
Table 3. Mean plaque index (PI), bleeding index (BI), clinical attachment level (CAL), probing pocket depth (PPD) and mean frequency distribution (%) of sites with a probing pocket depth ≥ 5 mm of the placebo group and the test group at baseline and after therapy (AT) at the 4 sample sites.

<table>
<thead>
<tr>
<th>N=49</th>
<th>n</th>
<th>PI</th>
<th>BI</th>
<th>CAL</th>
<th>PPD</th>
<th>% of sites</th>
<th>PPD &gt; 5mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td></td>
<td>baseline</td>
<td>AT</td>
<td>baseline</td>
<td>AT</td>
<td>baseline</td>
<td>AT</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>1.0 (0.5)</td>
<td>0.4 (0.4)*</td>
<td>2.0 (0.1)</td>
<td>1.4 (0.6)*</td>
<td>7.7 (1.8)</td>
<td>5.8 (1.5)*</td>
</tr>
<tr>
<td>Test</td>
<td>23</td>
<td>1.1 (0.6)</td>
<td>0.4 (0.4)*</td>
<td>1.8 (0.4)</td>
<td>0.9 (0.8)*</td>
<td>7.4 (1.1)</td>
<td>5.1 (1.4)*</td>
</tr>
</tbody>
</table>

N, n : number of patients; () : standard deviation; * : significant change from baseline (p < 0.05); ** : significant difference between groups after therapy (p < 0.05).
NS : not significant.

Table 4. Number of culture positive patients (n) of selected subgingival periodontal pathogens and mean percentage (%) and standard deviation () in culture positive patients in placebo and test group at baseline and after therapy (AT).

<table>
<thead>
<tr>
<th>N=49</th>
<th>Aa</th>
<th>Pg</th>
<th>Bf</th>
<th>Pi</th>
<th>Pm</th>
<th>Fn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>baseline</td>
<td>AT</td>
<td>baseline</td>
<td>AT</td>
<td>baseline</td>
<td>AT</td>
</tr>
<tr>
<td>Placebo</td>
<td>%</td>
<td>0.8 (1.0)</td>
<td>0.3 (0.4)</td>
<td>39.9 (24.4)</td>
<td>18.6 (14.4)</td>
<td>10.4 (9.4)</td>
</tr>
<tr>
<td>Test</td>
<td>%</td>
<td>0.6 (0.4)</td>
<td>3 (3*)</td>
<td>19</td>
<td>3(1)*</td>
<td>19</td>
</tr>
</tbody>
</table>

Aa: Actinobacillus actinomycetemcomitans; Pg: Porphyromonas gingivalis; Bf: Bacteroides forsythus; Pi: Prevotella intermedia; Pm: Peptostreptococcus micros; Fn: Fusobacterium nucleatum.

N, n : number of patients
[] : number of patients culture negative at baseline and positive after therapy
* : significant change from baseline (p < 0.05)
** : significant difference between groups after therapy (p < 0.05).
Fig. 2. Full-mouth mean plaque index (PI), bleeding index (BI) and standard deviation at baseline (before) and after therapy (after) of the placebo group and the test group classified on the basis of presence (pos) or absence (neg) of cultivable Porphyromonas gingivalis (Pg) at baseline. (**: significant difference between placebo and test group after therapy (p <0.001).
Fig. 3. Full-mouth mean probing pocket depth (PPD), clinical attachment level (CAL) and standard deviation at baseline (before) and after therapy (after) of the placebo group and the test group classified on the basis of presence (pos) or absence (neg) of cultivable Porphyromonas gingivalis (Pg) at baseline (*: significant difference between placebo and test group after therapy \( p < 0.05 \), **: significant difference between placebo and test group after therapy \( p <0.001 \)).
Fig. 4. Mean percentage of sites (%) with a probing pocket depth of $\geq 5$ mm and standard deviation at baseline (before) and after therapy (after) of the placebo group and the test group classified on the basis of presence (pos) or absence (neg) of cultivable *Porphyromonas gingivalis* (Pg) at baseline (**: significant difference between placebo and test group after therapy ($p < 0.001$).
Fig. 5. Full-mouth mean plaque index (PI), bleeding index (BI) and standard deviation at baseline (before) and after therapy (after) of the placebo group and the test group classified on the basis of smoking (S) and non smoking (NS) patients ("*" : significant difference between placebo and test group after therapy ($p < 0.001$)).
Fig. 6. Full mouth mean probing pocket depth (PPD), clinical attachment level (CAL) and standard deviation at baseline (before) and after therapy (after) of the placebo group and the test group classified on the basis of smoking and non-smoking patients (*: significant difference between placebo and test group after therapy ($p < 0.05$).
Chapter 5

Smoking

Subjects in the P- and T-groups were subset into non-smokers and smokers (Fig. 5, 6). All patients in the smokers group were current smokers and none had stopped within the last year. The baseline clinical data for these subgroups was similar, with the exception of the CAL. At baseline the mean loss of clinical attachment in the smokers ($n=32$) was significantly higher than in the non-smoker group ($n=17$), $4.3 \pm 1.1 \text{ mm}$ versus $3.4 \pm 1.2 \text{ mm}$ respectively ($p<0.05$).

In the 4 subgroups, the PI before and after therapy was comparable. However, the reduction in PPD and gain of CAL was significantly less in the placebo/smokers subgroup compared to the test/smokers subgroup ($p \leq 0.05$).

Adverse effects

Reported adverse effects of the 49 patients complying with the study protocol and completing the study are shown in Table 5. In the P-group, 24 of 26 patients reported no adverse effects, while 9 of 23 patients in the T-group reported gastrointestinal intolerance during and/or after the prescribed medication. One patient in each of the P- and T-groups reported a rash on the face and 1 patient in the T-group reported a rash on the neck.

Table 5. Diagram stool changes in the placebo group ($n=26$) and the test group ($n=23$).

<table>
<thead>
<tr>
<th>consistency</th>
<th>constipation</th>
<th>normal</th>
<th>softened</th>
<th>watery</th>
<th>diarrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequency</td>
<td>Placebo</td>
<td>Test</td>
<td>Placebo</td>
<td>Test</td>
<td>Placebo</td>
</tr>
<tr>
<td>normal</td>
<td>-</td>
<td>1</td>
<td>24</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>increased</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>very high</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(1) drop out patient due to diarrhoea.

Remarks

In the T-group, 2 patients noticed that the gingiva had become tighter around the teeth after medication and 1 patient reported nausea after the use of alcohol. None of the patients returned any of their medication tablets and one patient complained about missing 1 tablet.

Discussion

The aim of the study was to investigate the effect of initial periodontal treatment in conjunction with systemic ally administered amoxicillin plus metronidazole in a double-blind, placebo-controlled, randomised parallel study in adult periodontitis patients. The results of this study showed that the use of these antibiotics
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as an adjunct to supra- and subgingival debridement in adult periodontitis patients provided a better clinical outcome than scaling and root planning alone. In particular, a significant decrease in bleeding index, clinical attachment level and probing pocket depth was seen in the antibiotic subjects compared with those receiving a placebo. The length of the evaluation period was chosen based on studies that have shown that most of the clinical improvement can be expected within the first 3 months after initial periodontal treatment (Badersten et al. 1984) and 3 months after systemic antibiotic therapy (Berglundh et al. 1998; Pavičić et al. 1994). Regular evaluation of results of initial periodontal treatment in daily practice is often performed 3 months after treatment, suggesting that this period of evaluation is suitable for a phase III-type clinical study.

In a meta-analysis of the treatment outcome of initial periodontal therapy, a mean reduction in probing pocket depth of 1.3 mm in pockets initially 4-6 mm, and 2.2 mm in pockets initially ≥ 7 mm was calculated (Cobb 1996). In this respect, the quality of the initial therapy is shown to be by the clinical improvement in the placebo group (1.4 mm in 4-6 mm pockets; 2.5 mm in pockets ≥ 7 mm).

A number of studies have suggested that a microbiological goal of periodontal treatment might be the elimination of certain periodontal pathogens, such as A. actinomycetemcomitans and P. gingivalis, from the periodontal pockets as well as suppression of other periodontal pathogens below certain threshold levels (Bragd et al. 1987; Dahlén et al. 1996; Rams et al. 1996; Renvert et al. 1990; Wennström et al. 1987). The results of the present study showed that this treatment goal was more predictably achieved in the patients treated with adjunctive metronidazole and amoxicillin than in patients that had received placebo medication. In addition, besides short-term outcome of periodontal treatment, absence of key pathogens such as A. actinomycetemcomitans and P. gingivalis seems to have an impact on the long-term periodontal stability and is probably a prerequisite for long-term clinical improvement (Berglundh et al. 1998; Dahlén et al. 1996; Pavičić et al. 1994). The present findings confirm previous observations that the use of systemic amoxicillin and metronidazole is effective in suppressing A. actinomycetemcomitans below cultivable levels and in reducing the number of patients culture positive for P. gingivalis, B. forsythus, P. micros (Berglundh et al. 1998; Goené et al. 1990; Müller et al. 1998; Pavičić et al. 1994; Van Winkelhoff et al. 1989; Van Winkelhoff et al. 1992; Winkel et al. 1998). By contrast, in the placebo group 4 patients were culture positive for A. actinomycetemcomitans 6 months after initial periodontal therapy, although 2 patients became culture negative. This observation has already been reported by several other authors and confirms that periodontal scaling and root planing alone cannot predictably suppress subgingival presence of A. actinomycetemcomitans (Christersson et al. 1985; Mombelli et al. 1994; Müller et al. 1998; Renvert et al. 1990; Winkel et al.
1998). It should be noted that in this study at baseline the prevalence of *Actinomyces actinomyces* (18%) was rather low compared to other studies in the same age group of untreated periodontitis patients (Rodenburg et al. 1990 (40%), Van der Weijden et al. 1994 (33%)).

In this test group 3 patients remained positive for *P. gingivalis* post-treatment, and this concurs with similar reported findings (Flemming et al. 1998; Winkel et al. 1998). One explanation could be inadequate compliance with the test medication (Loesche et al. 1993). Another possible reason could be insufficient sub- and supragingival debridement. The essential role of meticulous scaling and root planing to eliminate *P. gingivalis* has recently been shown by López & Gamonal 1998. In that study patients suffering from moderate to advanced progressive periodontitis treated with systemic amoxicillin and metronidazole without scaling and root planing harbored moderate to high levels of *P. gingivalis* post-treatment. Berglundh et al (1998) also found that sites not receiving scaling and root planing, in patients that had received systemic metronidazole and amoxicillin, still had detectable *P. gingivalis*.

In contrast to previous studies (Van Winkelhoff et al. 1989; Van Winkelhoff et al. 1992; Winkel et al. 1998), baseline microbiological findings were not used to select patients for adjunctive systemic anti-microbial therapy. The analyses of the present study indicate that not all patients have benefitted equally from the additional antibiotic therapy. Patients with *P. gingivalis* at baseline in the test group showed significantly more pocket depth reduction in comparison to patients treated with placebo. In patients with no detectable levels of *P. gingivalis* at baseline, no difference in probing pocket depth reduction was observed between placebo and test patients. In addition, the greatest change in percentage of sites with pockets ≥ 5 mm was found in the patients in the test group who were positive for *P. gingivalis* at baseline. One important clinical finding was the observation that patients with subgingival *P. gingivalis* at baseline who were treated with antibiotics showed approximately half the number of ≥ 5 mm pockets after therapy compared with *P. gingivalis* positive patients treated with placebo. This implies that patients culture positive for *P. gingivalis* the antibiotic therapy had significantly reduced the number of teeth in need of subsequent surgical treatment. By contrast, no significant difference in reduction of percentage of sites with probing pocket depth of 5 mm or more was noted between placebo and test patients who were culture negative for *P. gingivalis* at baseline. Any decision to use amoxicillin and metronidazole in this group of patients must be taken with caution. Although, on average the entire test group benefitted from the antibiotic treatment, the response of *P. gingivalis* positive subjects seems largely responsible for this result. This finding suggests that microbiological testing of periodontitis patients prior to prescribing antibiotics is warranted. It may also
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indicate a more rational application of antibiotics in periodontics. The effects of the different treatment regimes were also analysed with respect to the smoking habits of the patients. With the exception of the mean plaque index, the change in clinical variables was least marked in the smoking group that had received the placebo. By contrast, the greatest reductions in bleeding index, probing pocket depth and gain of attachment was noted in the smoker group treated with antibiotics. On the basis of these observations one may speculate that smoking, among other factors may be important in the decision to treat severe periodontitis patients with systemic antibiotics.

In conclusion this study has shown that the systemic use of metronidazole and amoxicillin, when used in conjunction with initial periodontal treatment in adult periodontitis patients, achieves significantly better clinical and microbiological results than initial periodontal treatment alone. Moreover, this research suggests that patients harboring \textit{P. gingivalis} and those who smoke benefit from antibiotic treatment.

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References


Chapter 5


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Chapter 5


