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# CHAPTER 4

CLINICAL AND MICROBIOLOGICAL EFFECTS OF INITIAL PERIODONTAL THERAPY IN CONJUNCTION WITH AMOXICIL-LIN AND CLAVULANIC ACID IN PATIENTS WITH ADULT PERIODONTITIS

A randomised double-blind, placebo-controlled study

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# Abstract

The aim of the present study was to investigate the clinical and microbiological effects of initial periodontal therapy in conjunction with systemic amoxicillin plus clavulanic acid in adult periodontitis patients using a double-blind, parallelgroup, and placebo-controlled protocol. Twenty one patients with a clinical diagnosis of generalised adult periodontitis were recruited. Clinical measurements and microbiological assessments were carried out at baseline, 3, and 12 months post-treatment. Approximately 6 weeks after initial periodontal treatment (3-6 hours), patients were randomly assigned to receive coded study medication of 500 mg amoxicillin plus 125 mg clavulanic acid (Augmentin®) or placebo, every 8 hours for 10 days. Patients returned for follow-up visits 3, 6, 9, and 12 months after completion of the medication. The mean plague index (PI) at baseline was 1.1 for the placebo group and 0.9 for the test group. At 3 months, the PI had dropped to 0.3 in both groups, and was maintained during the rest of the study. The changes in bleeding on probing (BOP) and gingival index (GI) in the course of the study were similar in both groups. The mean whole mouth probing pocket depth (PPD) in the placebo group was 3.8 mm at baseline and 3.9 mm in the test group. A mean reduction of 1.0 mm in the placebo group and 0.9 mm in the test group was observed during the first 3 months. No further reduction in PPD was noticed during the study period in either group. There was no statistically significant difference in the PPD reduction between the 2 groups. The change in clinical attachment level (CAL) from baseline to 3 months amounted to 0.5 mm in both groups. Between 3 and 12 months, the CAL changed in neither group. In both groups, treatment resulted in a decrease in the number of spirochetes and motile rods in positive patients, but no significant differences between either group were noted in any of the dark field microscopy observations. At baseline, 1 patient in the placebo group and 2 patients in the test group were culture positive for Actinobacillus actinomycetemcomitans (Aa). After therapy, Aa was not detectable in the placebo group and 1 patient remained positive in the test group. In the placebo group, the number of patients positive for Porphyromonas gingivalis (Pg) decreased from 7 to 2 after therapy. In the test group, the 4 patients positive for Pg at baseline remained positive after therapy. In both groups, all subjects were positive for Prevotella intermedia (Pi) and Fusobacterium nucleatum (Fn) at baseline. At 12 months, all subjects had detectable subgingival Fn. Nine out of the 11 placebo and 8 of the 10 test patients remained positive for Pi. There were no differences in detection frequency of Peptostreptococcus micros (Pm) and Bacteroides forsythus (Bf) in both groups between baseline, 3, and 12 months post-treatment. The findings demonstrated that, in comparison to placebo, systemic amoxicillin plus clavulanic acid provi-

ded no additional clinical and microbiological effects in the treatment of adult periodontitis patients.

#### Introduction

Most forms of periodontitis can successfully be treated by conventional periodontal therapy, which includes, amongst others, mechanical removal of subgingival bacteria. However patients may respond poorly to this treatment. When this occurs in the presence of proper oral hygiene, these patients are referred to as patients with refractory periodontitis. In these patients, additional systemic antibiotic treatment can enhance the effect of mechanical debridement (Slots 1996, Van Winkelhoff et al.1996, Van Winkelhoff & Winkel 1997, Winkel et al. 1997). During recent decades, a number of antibiotics have been used not only in refractory periodontitis. The drugs more extensively investigated for systemic use include tetracycline, clindamycin, ciprofloxacin, metronidazole and amoxicillin (Van Winkelhoff et al. 1996). In the case of amoxicillin, it has been used alone (Slots & Rams 1990, Van Oosten et al.1986) or in combination with metronidazole (Berglundh et al. 1998, Flemmig et al. 1998, Pavičić et al. 1994, Van Winkelhoff et al.1989, Winkel et al. 1998).

Amoxicillin is one of the most frequently prescribed antibiotics by periodontists in the USA (Slots & Rams 1990). By coincidence, Van Oosten et al. (1986) found periodontal improvements and a change of the composition of the subgingival microflora after initial periodontal therapy in a patient treated for otitis media with systemic amoxicillin. The effects of amoxicillin in the treatment of periodontitis have not been very well documented. Amoxicillin has a wide range of activity against subgingival strict and facultative anaerobic bacterial species (Baker et al. 1983, Walker et al. 1985). Recently, Van Winkelhoff et al. (1997) showed that amoxicillin in vitro was able to inhibit the growth of total subgingival plaque of adult periodontitis patients by more than 95%. It has also been shown that the subgingival microflora in adult periodontitis patients displays detectable  $\beta$ -lactamase activity in the majority of the patients (Legg & Wilson 1990, Walker et al. 1989, Van Winkelhoff et al. 1997). These observations suggest a potential rôle of amoxicillin in the treatment of periodontitis provided that the antibiotic is protected against  $\beta$ -lactam degrading enzymes by clavulanic acid. This suggestion was supported by 2 recent placebo-controlled studies (Magnusson et al. 1994, Haffajee et al. 1995). These studies showed an additional effect of amoxicillin plus clavulanic acid (Augmentin®) in patients with evidence of recent disease activity.

The aim of the present study was to investigate the clinical and microbiological

effects of initial periodontal treatment in conjunction with amoxicillin and clavulanic acid in patients with untreated adult periodontitis.

# **Material and Methods**

## Study population

Twenty one patients who were referred to the Academic Centre for Dentistry Amsterdam (ACTA) for diagnosis and treatment of periodontitis were selected. Inclusion criteria to participate in this study were: (1) age 25 years or older, (2)  $\geq$  3 natural teeth in each quadrant, (3) clinical diagnosis of generalised adult periodontitis, characterised by the presence of  $\geq$  1 periodontal site with a probing pocket depth of > 5mm showing bleeding upon probing and radiographic evidence of alveolar bone loss in each quadrant. Patients participated on the basis of a written informed consent. Exclusion criteria to enter the study were hypersensitivity towards  $\beta$ -lactam agents, professional scaling and root planing or surgical periodontal therapy in the past and systemic or topical antibiotic therapy 6 months prior to the initiation of the study, pregnancy, lactating or planning a pregnancy, systemic diseases such as diabetes or HIV, acute necrotising periodontitis, and use of non-steroid anti-inflammatory drugs.

## Study design

This investigation was a randomised, double-blind, placebo-controlled, parallel study with baseline and 3, 6, and 12 months post-treatment clinical measurements. Microbiological assessments were carried out at baseline, 3 and 12 months post-treatment (Table 1). After the baseline visit, patients returned for a full-mouth initial periodontal treatment consisting of subgingival scaling and root planing (S&R) and extensive oral hygiene instructions. S&R was carried out in 3 to 6 sessions of 1 hour, under local anaesthesia on the patient's indication. At each of these sessions, oral hygiene was reinforced. Approximately 6 weeks after the last session of S&R, patients were re-appointed for a full mouth checkup, at which S&R was administered at sites with a probing pocket depth of > 3mm and sites showing bleeding on probing. In addition, oral hygiene was reinforced. On the same day, patients were randomly assigned to receive coded study medication of 500 mg amoxicillin plus 125 mg clavulanic acid (Augmentin®) or placebo, every 8 hours for 10 days. To assess the compliance with the medication, patients were asked to record the time of study medication intake on a diary booklet. Patients were instructed to return all unused study medication at their 1st follow-up visit. Approximately 2 weeks after the end of the medication.

Table 1. Outline of study.

|                          | Pre-trial<br>patient | -<br>-   | Approx.   | 6 weeks after S&R, | 2 weeks | 3 months | 6 months | 9 months | 12 months |
|--------------------------|----------------------|----------|-----------|--------------------|---------|----------|----------|----------|-----------|
|                          | selection            | Baseline | z months  | IU days medication | atter M | alter M  | atter M  | aiter M  | alter M   |
| Treatments:              |                      |          |           |                    |         |          |          |          |           |
| S&R                      |                      |          | 36 visits | loc                |         | loc      | loc      | loc      | loc       |
| ОНІ                      |                      |          | *         | *                  |         | *        | *        | *        | *         |
| Assessments:             |                      |          |           |                    |         |          |          |          |           |
| periodontal chart        | *                    |          |           |                    |         |          |          |          |           |
| clinical measurements    |                      | ¥        |           |                    |         | *        | *        |          | *         |
| selection sample place   | *                    |          |           |                    |         |          |          |          |           |
| microbiological sampling |                      | *        |           |                    |         | *        |          |          | *         |
| bowel habits             |                      |          |           | *                  |         |          |          |          |           |
| adverse effects          |                      |          |           |                    | *       | *        | *        | *        | *         |
| medication compliance    |                      |          |           |                    |         | ÷        |          |          |           |
|                          |                      |          |           |                    |         |          |          |          |           |

S&R: scaling and rootplaning; OHI: oral hygiene instruction; M: medication; loc: S&R locally, i.e., at sites showing bleeding on probing and with a probing pocket depth >3 mm. patients were phoned to check whether they had taken the medication and to elicit information about any adverse experience and/or changes in concomitant medication. Patients returned for follow-up visit approx. 3, 6, 9, and 12 months after completion of the medication treatment phase. At these visits the oral hygiene was re-inforced. Furthermore S&R was administered at sites with a probing pocket depth of > 3 mm and at sites showing bleeding on probing.

## **Clinical measurements**

One investigator carried out all clinical measurements and was unaware of the medication provided. Probing pocket depth and clinical attachment level measurements were performed using a constant force probe (Brodontic<sup>®</sup>, Ash/Dentsply<sup>®</sup>) containing a 0.5 mm diameter tapered tip with Williams mm markings, at a probing force of 0.75 N (probing pressure 382 N/cm<sup>2</sup>). To avoid measurement errors, the same probe was used for both pre- and post-treatment measurements for each patient (Van der Zee et al. 1994).

The plaque index, the gingival index and the bleeding index were recorded at 4 sites (mesio-, mid, disto-buccal and mid-lingual) per tooth. The probing pocket depth and the clinical attachment level were assessed on 6 sites (mesio-, mid-, disto-buccal, and mesio-, mid-, disto-lingual) per tooth. The following clinical variables were assessed: (1) plaque index (PI), according to Silness & Löe (1964); (2) modified gingival index (GI), according to Lobene et al. (1986); (3) probing pocket depth (PPD); sites that could not be measured reliably were excluded; (4) bleeding on probing (BOP), recorded as absent (0) or present (1); (5) clinical attachment level (CAL) was measured from a reference point provided by a custom made acrylic stent.

#### Sampling and bacteriological procedures

At intake (Table 1), the deepest, bleeding pocket in each quadrant was selected for microbiological evaluation (Mombelli et al. 1991, 1994, Müller et al. 1990). Microbiological analyses of the subgingival plaque were performed at baseline and approximately 3 and 12 months after completion of the medication. Microbiological sampling was always carried out after the PI assessments. Supragingival plaque at the selected site was carefully removed with a curette, after which the sample site was isolated with cotton rolls and gently air-dried. A subgingival plaque sample was taken by 2 sterile paper points (Fine, UDM, West Palm Beach, USA) that were consecutively inserted into the periodontal pocket and removed after 10 seconds. Paper points from 4 sample sites were collected in reduced transport fluid (RTF, Syed & Loesche 1972) supplemented with 10% Filders extract (Oxoid, UK) to preserve motility of motile micro-organisms (Petit et al. 1991) and processed within 6 hours (Petit et al. 1991, 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) 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 5 days (Van Steenbergen et al. 1986). Blood agar plates were used for enumeration of total bacterial counts, 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 alucose, 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 morphology, Gram stain and production of specific enzymes (API 32A, Biomerieux, La Balme, Les Grottes, France).

Subgingival plaque samples were examined for the presence and proportions of spirochetes and motile rods using dark-field microscopy (Listgarten & Helldén 1978) at a magnification of x1000.

## Statistical analysis of the data

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. Differences in clinical and microbiological parameters, at baseline, after initial therapy (IT), and after 3, 6, and 12 months between test and placebo group, were analysed using a Mann-Whitney test. A Fisher's exact test was used to analyse differences in the frequency of species after each phase of therapy. Values of p < 0.05 were accepted as statistically significant.

# Results

The placebo group consisted of 4 males and 7 females with a mean age of 39 years (range 28-47). The test group consisted of 2 males and 8 females and had a mean age of 49 years (range 36-66). In both test and placebo group, 5 subjects were current smokers. In both groups, 2 patients experienced mild diarrhoea after medication.

## **Clinical results**

The mean clinical measurements are presented in Table 2. The mean plaque index (PI) at baseline was 1.1 and 0.9 for the placebo (P) and test (T) groups, respectively. At 3 months, the PI had dropped to 0.3 in both groups. A PI score of 0.3 was measured in both groups at the 12- months assessment. The BOP in group P was 0.5 at baseline and dropped to 0.2 at 3 months and remained stable until the end of the study period. The BOP in group T was 0.6 at baseline and dropped to 0.1 at 3 months and did not change significantly till the end of the study period. The change in BOP was comparable in both groups. The baseline scores and the improvement of the gingival index in the course of the study were similar in both groups.

Full-mouth mean PPD was 3.8 mm at the baseline for group P and 3.9 mm for group T. A mean reduction of 1.0 mm in group P and 0.9 mm in group T was observed. No further reduction in PPD was noticed during the following 9 months of the study period. There was no statistically significance difference in the PPD reduction between the 2 groups.

The change in CAL from baseline to 3 months was 0.5 mm in both groups. Between 3 and 12 months, the CAL did not change in both groups. Baseline and

| Table 2. The mean plaque index (PI), bleeding index (BOP), gingival index (GI), probing pocket     |
|--|
| depth (PPD) and clinical attachment level (CAL) of the placebo group (P) and the test group (T) at |
| baseline, and 3, 6 and 12 months post-treatment.   |

| <br>             |       |           |           |           |           |  |
|------------------|-------|-----------|-----------|-----------|-----------|--|
| <i>n</i> =21     | Group | baseline  | 3 months  | 6 months  | 12 months |  |
| PI               | Р     | 1.1 (0.2) | 0.3 (0.1) | 0.2 (0.1) | 0.3 (0.1) |  |
|                  | Т     | 0.9 (0.1) | 0.3 (0.1) | 0.4 (0.2) | 0.3 (0.1) |  |
| BOP              | Р     | 0.5 (0.1) | 0.2 (0.1) | 0.2 (0.1) | 0.2 (0.1) |  |
|                  | Т     | 0.6 (0.1) | 0.1 (0.1) | 0.1 (0.1) | 0.2 (0.1) |  |
| GI               | Р     | 1.3 (0.2) | 0 3 (0.1) | 0.2 (0.1) | 0.3 (0.1) |  |
|                  | Т     | 1.2 (0.2) | 0.3 (0.1) | 0.3 (0.1) | 0.2 (0.1) |  |
| PPD              | Р     | 3.8 (0.5) | 2.8 (0.3) | 2.8 (0.3) | 2.8 (0.4) |  |
|                  | Т     | 3.9 (0.4) | 3.0 (0.2) | 2.8 (0.1) | 2.9 (0.2) |  |
| CAL <sup>1</sup> | Р     | 7.3 (0.3) | 6.8 (0.3) | 6.7 (0.4) | 6.8 (0.4) |  |
|                  | Т     | 7.4 (0.9) | 6.9 (0.8) | 6.8 (0.8) | 6.9 (0.9) |  |
|                  |       |           |           |           |           |  |

(): standard deviation; ' = measured from an acrylic stent as fixed reference point.

post-treatment pocket depths were divided into 4 categories. The mean frequencies per category are summarised in Table 3. At baseline, the proportion of  $\geq$  5 mm pockets was 34% in group P and 36% in group T. After initial treatment, the proportion of > 5 mm pockets had dropped to 10% and 11% in groups P and T, respectively. The changes in all probing pocket depth categories were similar in both groups.

|               | Months   | n   | 1–3 mm<br>(%) | 4 mm<br>(%) | 5–6 mm<br>(%) | ≥7 mm<br>(%) |
|---------------|----------|-----|---------------|-------------|---------------|--------------|
| placebo group | baseline | 155 | 54 (13)       | 12 (5)      | 23 (9)        | 11 (8)       |
|               | 3        | 155 | 78 (13)       | 11 (8)      | 8 (6)         | 2 (3)        |
|               | 6        | 155 | 80 (13)       | 10 (8)      | 8 (6)         | 2 (3)        |
|               | 12       | 155 | 78 (15)       | 9 (7)       | 11 (8)        | 2 (3)        |
| test group    | baseline | 152 | 49 (11)       | 15 (6)      | 26 (9)        | 10 (7)       |
|               | 3        | 152 | 76 (7)        | 13 (4)      | 10 (5)        | 1(1)         |
|               | 6        | 152 | 78 (6)        | 12 (4)      | 9 (4)         | 1 (1)        |
|               | 12       | 152 | 75 (7)        | 12 (4)      | 11 (4)        | 1 (1)        |

*Table 3.* The frequency distribution (%) of 4 different probing pocket depth categories at baseline, and 3, 6 and 12 months post-treatment.

n: mean number of pockets per patient; (): standard deviation.

Table 4 shows the mean changes in probing pocket depth and clinical attachment level in different categories at baseline and at 12 months. The greatest reduction in pocket depth was found in sites with initial PPD of  $\geq$  7mm. In these sites, the mean PPD reduction was 2.7 mm in group P and amounted to 2.4 mm in group T. Furthermore, the improvement in attachment level was most pronounced in pockets  $\geq$  7 mm and amounted to 1.7 mm and 1.1 mm in the P and T groups, respectively. None of the differences between groups T and P were statistically significant.

Table 4. Mean change in probing pocket depth (PPD) and clinical attachment level (CAL) at baseline and 12 months post-treatment in different probing pocket depth categories in the placebo (P) and test group (T).

| Probing<br>pocket depth<br>categories | Group | PPD<br>change<br>(mm) | CAL<br>change<br>(mm) |
|---------------------------------------|-------|-----------------------|-----------------------|
| 0–3 mm                                | Р     | 0.3                   | 0.1                   |
|                                       | Т     | 0.3                   | 0.1                   |
| 4-6 mm                                | Р     | 1.5                   | 0.6                   |
|                                       | Т     | 1.4                   | 0.7                   |
| ≥7 mm                                 | Р     | 2.7                   | 1.7                   |
|                                       | Т     | 2.4                   | 1.1                   |

Table 5 shows the mean clinical parameters of the 4 sample sites. The changes in clinical variables recorded between group P and group T did not reveal any statistically significant difference. The reduction in PPD in group P amounted to 2.6 mm with a gain in CAL of 1.3 mm, and was 2.3 mm and 1.1 mm in group T, respectively.

| n=2 | 1 Group        | Baseline   | 3 months  | 12 months |  |
|-----|----------------|------------|-----------|-----------|--|
| PI  | Р              | 1.4 (0.3)  | 0.6 (0.3) | 0.5 (0.3) |  |
|     | Т              | 1.4 (0.2)  | 0.8 (0.4) | 0.6 (0.3) |  |
| BOP | P              | 0.9 (0.1)  | 0.6 (0.3) | 0.5 (0.2) |  |
|     | Т              | 0.8 (0.2)  | 0.6 (0.2) | 0.5 (0.3) |  |
| GI  | Р              | 1.7 (0.4)  | 0.7 (0.2) | 0.6 (0.2) |  |
|     | Т              | 1.5 (0.4)  | 0.7 (0.2) | 0.4 (0.2) |  |
| PPD | Р              | 7.4 (0.9)  | 4.5 (1.0) | 4.8 (1.0) |  |
|     | Т              | 6.7 (1.2)  | 4.5 (0.8) | 4.4 (0.8) |  |
| CAL | <sup>1</sup> P | 10.3 (1.2) | 8.8 (1.7) | 9.0 (1.5) |  |
|     | Т              | 10.0 (1.0) | 8.4 (1.4) | 8.9 (1.1) |  |

*Table 5*. The mean clinical parameters of the 4 sample sites of the placebo group (P) and the test group (T) at baseline, and 3 and 12 months post-treatment.

PI: plaque index; BOP: bleeding on probing; GI: modified gingival index; PPD: probing pocket depth; CAL: clinical attachment level; (): standard deviation; ': measured from an acrylic stent as fixed reference point.

| Table 6 | 6. Number ( | of positive p | patients (n) | and pro   | portions | (standard   | deviation | on) of sele | cted subg  | gingi- |
|---------|-------------|---------------|--------------|-----------|----------|-------------|-----------|-------------|------------|--------|
| val per | iodontal pa | thogens in    | placebo ai   | nd test g | group at | baseline, 3 | and 12    | 2 months p  | post-treat | ment.  |

|             |   | Place  | bo group ( | n=11)     | Te       | Test group $(n=10)$ |           |  |  |
|-------------|---|--|------------|-----------|----------|---------------------|-----------|--|--|
| n=21        |   | baseline   | 3 months   | 12 months | baseline | 3 months            | 12 months |  |  |
| spirochetes | n | 11   | 7          | 7         | 10       | 3                   | 4         |  |  |
| •           | % | 13 (7)   | 2 (1)      | 2 (1)     | 7 (4)    | 1 (<1)              | 1 (<1)    |  |  |
| motile rods | n | 11   | 9          | 5         | 10       | 7                   | 6         |  |  |
|             | % | 11 (9)   | 2 (2)      | 1(1)      | 11 (10)  | 1 (<1)              | 2 (2)     |  |  |
| Aa          | n | 1  | 2          | ND        | 2        | ND                  | 1         |  |  |
|             | % | <i< td=""><td>1.1 (0)</td><td></td><td>&lt;1 (0)</td><td>0 (0)</td><td>&lt;1 (0)</td></i<> | 1.1 (0)    |           | <1 (0)   | 0 (0)               | <1 (0)    |  |  |
| Pg          | n | 7  | 4          | 2         | 4        | 2                   | 4         |  |  |
| •           | % | 19 (11)  | 6 (6)      | 9 (3)     | 31 (11)  | 12 (0)              | 15 (17)   |  |  |
| Bf          | n | 9  | 8          | 7         | 8        | 7                   | 7         |  |  |
|             | % | 10 (5)   | 12 (10)    | 12 (10)   | 9 (5)    | 11 (11)             | 7 (5)     |  |  |
| Pi          | n | 11   | 7          | 9         | 10       | 8                   | 8         |  |  |
|             | % | 4 (4)  | 5 (6)      | 9 (10)    | 5 (7)    | 6 (3)               | 9 (9)     |  |  |
| Fn          | n | 11   | 10         | 11        | 10       | 9                   | 10        |  |  |
|             | % | 6 (6)  | 5 (6)      | 5 (6)     | 7 (5)    | 7 (11)              | 7 (7)     |  |  |
| Pm          | n | 8  | 9          | 9         | 6        | 9                   | 10        |  |  |
|             | % | 6 (7)  | 7 (5)      | 5 (5)     | 4 (4)    | 9 (14)              | 8 (9)     |  |  |

Aa: Actinobacillus actinomycetemcommitans; Pg: Porphyromonas gingivalis; Bf: Bacteroides forsythus; Pi: Prevotella intermedia; Fn: Fusobacterium nucleatum; Pm: Peptostreptococcus micros;
%: percentage of cultivable microflora.

## Microbiological results

Table 6 summarises the microbiological findings of the patients at baseline, and 3 months and 12 months post-treatment. At baseline, all subjects in both groups were positive for spirochetes and motile rods. In both groups, treatment resulted in a decrease of the number of positive patients. Between groups P and T, no significant differences were noted in any of the dark-field microscopy observations.

At baseline, only 1 patient in the placebo group and 2 patients in the test group were culture positive for *Actinobacillus actinomycetemcomitans* (Aa). After therapy Aa was not detectable in the placebo group and 1 patient remained positive in the test group. Of the 7 *P. gingivalis* (Pg) positive patients at baseline in group P, 2 were still Pg positive at 12 months. In group T, all 4 patients initially Pg positive patients had detectable levels of Pg at 12 months. The mean % of Pg at baseline in group P was 19% and 31% in group T, and decreased from 19 % to 9 % in group P and from 31% to 15 % in group T. In both groups, all subjects were positive for *P. intermedia* (Pi) and *F. nucleatum* (Fn) at baseline. At 12 months, all subjects had detectable subgingival Fn. Nine out of the 11 placebo and 8 of the 10 test patients remained positive for Pi. There were no differences in detection frequency of *P. micros* (Pm) and *B. forsythus* (Bf) in both groups between baseline, 3 and 12 months post-treatment. None of the microbiological changes were statistically significant.

# Discussion

The aim of the present clinical study was to investigate the effects of conventional initial periodontal therapy followed by systemic amoxicillin and clavulanic acid in adult periodontitis patients using a placebo-controlled protocol. Patients received 10 days of systemic antibiotic or placebo after completion of thorough initial periodontal therapy. On the basis of the present findings, it can be concluded that in comparison to placebo, adjunctive amoxicillin plus clavulanic acid does not provide additional clinical and microbiological effects in the treatment of adult periodontitis patients. Twelve months after therapy, the reductions in mean probing pocket depth in the present study were approximately 1 mm in both T and P groups. The P group showed a mean change in probing pocket depth in pockets initially 4-6 mm of 1.5 mm and of 2.7 mm in pockets initially  $\geq$  7 mm. These results correspond to previous findings in our department (Timmerman et al. 1996) in a comparable study population. They found, after 12 months, a mean reduction of 2.6 mm in initially  $\geq$  7mm pockets in their placebo group. Cobb (1996) performed a meta-analysis on the treatment outcome of ini-

tial 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  $\geq$  7mm, was calculated. On the basis of these findings, the treatment result of the present study can be regarded as adequate.

In 4 studies in adult refractory periodontitis patients, an additional effect of Augmentin<sup>®</sup> on initial periodontal therapy was claimed (Collins et al. 1993, Haffajee et al. 1995, Magnusson et al. 1989,1994). Magnusson et al. (1989) observed that the adjunctive use of this antibiotic reduced the incidence of attachment loss for at least 12 months. A mean reduction in probing pocket depth of 2.5 mm was observed in 'active' sites, which is comparable to what was observed in the present study at sites with initial PPD of  $\geq$  7 mm in both test and control group. This raises the question as to whether the interpretation of the positive outcome in the Magnusson study suffers from the lack of a placebo group. In the study of Collins et al. (1993) in refractory periodontitis patients treated with additional Augmentin®, they described successful suppression of P. gingivalis in 10 of 11 patients, which was paralleled with a gain in clinical attachment. However, in this non-placebo controlled study, concomitant intrasulcular delivery of povidone iodine and the use of chlorhexidine mouthwash was provided. This may in part be responsible for the "treatment effects" of the additional Augmentin<sup>®</sup>.

In a later study of Magnusson et al. (1994), 17 patients with "active" disease were treated; 13 patients received adjunctive Augmentin<sup>®</sup> (250/125 mg, TID for 14 days) and 4 patients a placebo medication. After therapy, no significant differences in mean clinical attachment gain were noted between test and placebo groups. Moreover, in the "active" sites, no significant differences in probing pocket depth change were noted in the test group in comparison to placebo patients. Only a significant difference in change of mean probing pocket depth was observed in the "non-active" sites; however, this was probably due to the pocket depth increase in the placebo group after therapy.

In a study of Haffajee et al. (1995), an adult refractory periodontitis patient group was treated with Augmentin<sup>®</sup> (n=10) and the results were compared with a placebo-controlled patient group (n=11). They observed a comparable change in probing pocket depth reduction between test and control groups, which is in accordance with the present study. However, subjects receiving adjunctive antibiotic therapy showed a significantly greater mean gain of clinical attachment level (0.7 mm) post-therapy. The mean gain of attachment in the placebo group of the Haffajee study was < 0.1 mm, which was, in comparison to the present study, marginal and may therefore explain the significant difference between their test and control groups. Haffajee et al. (1995) observed no significant differences in the composition of the subgingival microflora between test and control groups

post-treatment. The lack of the additional microbiological effect of systemic Augmentin<sup>®</sup> in the present study as well as in the study of Haffajee et al. (1995) is difficult to understand given the antimicrobial activity of amoxicillin *in vitro*. Van Winkelhoff et al. (1997) found > 95% of growth inhibition of whole subgingival plaque samples from the patients described in the present study. These observations exemplify the discrepancy between *in vitro* susceptibility and clinical efficacy of a systemic periodontal antimicrobial therapy. The lack of the clinical and microbiological effects of Augmentin<sup>®</sup> in the present study can probably not be explained by insufficient subgingival concentration of the drug (Tenenbaum et al. 1997). Possibly biofilm phenomena, e.g., lack of diffusion of the antibiotic into the subgingival plaque layer, may be responsible for the observed absence of clinical and microbiological effects (Wright et al. 1997).

In summary, in adult periodontitis patients, initial periodontal therapy in conjunction with systemic amoxicillin plus clavulanic acid was no more effective than initial periodontal therapy alone.

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