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Research Article

SYSTEMIC AMOXICILLIN AND METRONIDAZOLE IN NON-SURGICAL TREATMENT OF GENERALIZED AGGRESSIVE PERIODONTITIS: A RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL

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ABSTRACT

Aim:- The objective of this study was to assess the adjunctive clinical effect of the administration of systemic amoxicillin and metronidazole in the non-surgical treatment of generalized aggressive periodontitis (GAP).

Methods: fifty systemically healthy subjects with GAP were included in this 6-month double-blind, placebo-controlled, randomized clinical trial. Patients received a course of full-mouth non-surgical periodontal treatment delivered over a 24 h period using machine-driven and hand instruments. Test subjects received an adjunctive course of systemic antibiotic consisting of 500 mg amoxicillin and 500 mg metronidazole three times a day for 7 days. Clinical parameters were collected at baseline, and at 2 and 6 months post-treatment.

Results: In both the test and the placebo groups, all clinical parameters improved at 2 and 6 months. In deep pockets (≥7 mm), the test treatment resulted in an additional 1.4 mm (95% confidence interval 0.8, 2.0 mm) in full-mouth probing pocket depth (PPD) reduction and 1 mm (0.7, 1.3 mm) of life cumulative attachment loss (LCAL) gain at 6 months. In moderate pockets (4–6 mm), the adjunctive benefit was smaller in magnitude: PPD reduction was 0.4 mm (0.1, 0.7 mm) and LCAL gain was 0.5 mm (0.2, 0.8 mm). In addition, the 6-month data showed LCAL gains ≥2 mm at 25% of sites in test patients compared with 16% in placebo (p = 0.028). Similarly, PPD reductions of 2 mm or more were observed in 30% of sites in test and 21% of sites in placebo patients. Seventy-four percent of pockets with PPD ≥5 mm at baseline were 4 mm or shallower at 6 months in the test group. This compared with 54% in the placebo group (p 5=0.008). Disease progression at 6 months was observed at 1.5% of test and 3.3% of sites in test and placebo, respectively (p = 0.072).

Conclusions: These data indicate that a 7-day adjunctive course of systemic metronidazole and amoxicillin significantly improved the short-term clinical outcomes of full-mouth non-surgical periodontal debridement in subjects with GAP.

INTRODUCTION

Generalized aggressive Periodontitis (GAP) Armitage, G. C. (1999) affects a minority of periodontal patients but is highly significant because it is characterized by severe destruction of the supporting apparatus of the teeth, which may lead to edentulism early in life.

In recent years, two approaches have been introduced to improve the clinical outcomes of cause-related periodontal therapy in chronic periodontitis patients: the use of adjunctive antibiotics, and performing debridement within a 24 h period, the so-called ‘‘full-mouth disinfection’’ approach Quirynen, M *et al* (1995). The adjunctive use of systemic antibiotics is supported by evidence published in systematic reviews of trials assessing the benefit of systemic antibiotics in cases with advanced Periodontitis (Herrera *et al* 2002, Haffajee *et al* 2003). Among the possible regimens, the combination of amoxicillin and metronidazole has gained increasing popularity because of its wide spectrum of activity and effectiveness in terms of suppression of Actinobacillus actinomycetemcomitans, (van Winkelhoff *et al* 1989) possibly because of a synergistic effect of the combination of amoxicillin and metronidazole against A. actinomycetemcomitans that has been demonstrated in vitro. (Pavicic *et al* 1991) In addition, chronic Periodontitis patients

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harbouring subgingival Porphyromonas gingivalis benefit significantly from the combined therapy. (Winkel, E. G *et al* 2001) Randomized-controlled clinical trials have reported clinical and microbiological improvements in chronic periodontitis patients treated with these two antibiotics(Winkel, E. G, Flemmig *et al* 1998, Rooney, J *et al* 2002). However, because of the lack of a control group in these studies the benefits achieved could not be confirmed as attributable to the adjunctive antibiotic. Recent investigations, performed in chronic periodontitis patients, have indicated that full-mouth scaling and root planing within 24 h (FSR) results in different degrees of clinical and microbiological additional benefits(Quirynen, M *et al* 1995, Bollen, C. M *et al* 1996), The benefits of this approach have not been systematically evaluated in aggressive periodontitis patients but initial data in chronic periodontitis patients suggest that the full-mouth scaling within 24 h may perform as well as the conventional treatment, (Apatzidou *et al* 2004, Wennstrom *et al* 2005) In addition, some potential benefits, such as the application of a better understanding of the infectious process, a reduced number of treatment sessions for patients, a more efficient use of treatment time and a reduced cost of therapy, may all be in favour of the FSR (Greenstein, G. 2002). The aim of this double-blind randomized placebo-controlled study was to test the‘‘difference in treatment effect of adjunctive use of systemic amoxicillin plus metronidazole during full-mouth non-surgical cause-related periodontal treatment (FSR) performed within 24 h compared with FSR alone, in patients with GAP patients at 2 and 6 months after the completion of active treatment.

MATERIAL AND METHODS

Experimental design

This study was a randomized placebo controlled, parallel-design, double-blind clinical trial with 6-month follow-up. Ethical approval was obtained from the SKIMS medical college Bemina. Subjects eligible for the study were identified from the population referred to the dental department. A complete periodontal examination was performed including a full medical and dental history, an intra-oral examination and a full-mouth periodontal probing. A radiographic examination was undertaken using either periapicals or a pantomogram. A periodontal diagnosis was made, and subjects who fulfilled the study inclusion/exclusion criteria were provided with a written information sheet, related to the study protocol, and they were invited to participate in the study. The study included subjects with (i) GAP (ii) at least 20 teeth present; (iii) good general health and (iv) age between 16 and 35 when first diagnosed with aggressive periodontal disease.

Subjects were excluded from the study if they: (i) were considered to have a diagnosis of chronic Periodontitis (ii) were pregnant or lactating females; (iii) required antibiotic pre-medication for the performance of periodontal examination and treatment; (iv) suffered from any other systemic diseases (cardiovascular, pulmonary, liver, cerebral, diseases or diabetes); (v) had received antibiotic treatment in the previous 3 months; (vi) were taking long-term anti-inflammatory drugs; (vii) had received a course of periodontal treatment within the last 6 months; (viii) were allergic to penicillin or metronidazole.

All the subjects went through motivation sessions during which oral hygiene instructions were given. Subjects were randomly assigned by a computer-generated table to receive one of the two treatments.

Clinical parameters

Clinical parameters were assessed using a UNC-15 periodontal probe by the calibrated examiner at six sites/tooth excluding third molars. Full-mouth plaque score (FMPS) was recorded by assigning a binary score to each surface (1 for plaque present, 0 for absent) and calculating the percentage of total tooth surfaces that revealed the presence of plaque detected by the use of a periodontal probe as modified by Tonetti *et al*. (2002). Similarly, a full-mouth percentage bleeding score (FMBS) was calculated after assessing the presence of bleeding on probing from the bottom of the pocket when probing with a manual probe with a force of 0.3N (Tonetti *et al*. 2002). Full-mouth PPD and recession of the gingival margin (REC) were recorded at the same time. REC was recorded as a positive value if the free gingival margin (FGM) occurred apical to the cemeno–enamel junction (CEJ), whereas it was recoded as a negative value if it was coronal to the CEJ.

Non-surgical periodontal therapy

Periodontal therapy was initiated within 1 month of the baseline screening examination. If for any reason, the initiation of the therapy was delayed, a new full-mouth periodontal examination was performed. A standard cycle of periodontal therapy consisting of oral hygiene instructions, supra- and sub-gingival mechanical instrumentation of the root surface (scaling and root planing) was performed by a single experienced therapist using a piezoelectric instrument with fine tips (EMS) and hand instruments, as appropriate. Both groups received this treatment in two long appointments during the same day. Test subjects received an adjunctive course of systemic antibiotics consisting of 500 mg of amoxicillin and 500 mg of metronidazole three times a day for 7 days, while control subjects received placebo. Subjects were asked to take the first dose of the medication before mechanical instrumentation had started at the first treatment session. All subjects used a 0.2% chlorhexidine rinse twice a day for 2 weeks post–treatment, and relied on standard oral hygiene methods as instructed at the commencement of the study.

Re-assessment examinations

Re-assessment visits occurred at 2 and 6 months after the completion of the treatment. During these appointments, the examiner recorded any medical history changes, and the clinical periodontal parameters recorded at the baseline visit were repeated. At the end of the appointment, a session of supragingival debridement was performed as necessary. No attempt was made to re-instrument residual periodontal pockets.

Primary and secondary outcome measures

The primary outcome measure of the study was PPD reduction in sites with initial PPD ≥7 mm. Secondary outcomes included differences between groups for the (i) changes in mean full mouth PPD and LCAL (ii) changes in FMPS and FMBS; (iii) description and frequency of adverse events; and (iv) compliance with the systemic medication.

Statistical Analysis

Data were entered into an Excel (Microsoft office 2000) database and were proofed for entry errors. The database was subsequently locked, imported into SPSS for Windows (SPSS Inc. version 11.0) formatted and analyzed.

Mean values for clinical parameters

The baseline examination revealed that the two study groups showed similar plaque levels. Mean full-mouth clinical outcomes and mean clinical outcomes at shallow (≤3 mm), moderate (4–6 mm) and deep (≥7 mm) pocket categories for baseline, and the differences between baseline – 2 months and baseline – 6 months are displayed in Table 1.

LCAL gain at different pocket categories) is displayed in Table 3. Multivariate models based on linear regression ANOVA were constructed taking into account the potential sources of variability such as smoking status and baseline pocket depth. When considering full-mouth mean LCAL, there were no statistically significant differences between test and placebo. Similarly when examining pockets ≤3mm, no differences were observed between test and placebo for either LCAL or PPD. For ease of presentation, these analyses have been omitted from Table 2. There were highly significant treatment effects for full-mouth PPD reduction, PPD reduction at 4–6mm pockets and PPD reduction at ≥7mm pockets at 2 and 6 months, with the outcomes favouring the test treatment.

Table 1 Mean clinical outcome variables at baseline and differences between 0–2 and 0–6 months

Clinical outcomes mean	Group	Baseline 0 months	Difference between 0 and 2 months	Difference between 0 and 6 months	p-value paired t-test	
					difference 0–2 months	difference 0–6 months
Full-mouth mean PPD	Placebo	4.1±0.3	0.8±0.3	0.7±0.4	<0.001	<0.001
	Test	4.1±0.3	1.1±0.3	1.2±0.2	<0.001	<0.001
Mean PPD at pockets ≤3mm	Placebo	2.3±0.3	0.2±0.2	0.1±0.2	0.003	0.052
	Test	2.3±0.3	0.3±0.1	0.0±0.1	<0.001	0.931
Mean PPD at pockets 4–6mm	Placebo	5.0±0.2	1.2±0.5	1.0±0.3	<0.001	<0.001
	Test	5.0±0.2	1.7±02	1.5±02	<0.001	<0.001
Mean PPD at pockets ≥7mm	Placebo	7.7±0.2	2.1±0.3	1.8±0.2	<0.001	<0.001
	Test	7.7±0.3	3.0±0.3	3.1±0.2	<0.001	<0.001
Full-mouth mean LCAL	Placebo	4.8±0.4	0.3±0.2	0.5±0.1	<0.001	<0.001
	Test	4.7±0.3	0.7±0.3	0.8±0.1	<0.001	<0.001
Mean LCAL at sites with initial pockets ≤3mm	Placebo	3.1±0.4	0.0±0.1	0.0±0.2	0.683	0.704
	Test	2.9±0.3	0.0±0.1	0.0±0.2	0.631	0.634
Mean LCAL at sites with initial pockets 4–6mm	Placebo	5.7±0.3	0.8±0.2	0.8±0.2	<0.001	<0.001
	Test	5.7±0.4	1.1±0.2	1.3±0.3	<0.001	<0.001
Mean LCAL at sites with initial pockets ≥7mm	Placebo	8.1±0.6	1.3±0.6	1.3±0.3	<0.001	<0.001
	Test	8.1±0.4	1.8±0.3	2.3±0.1	<0.001	<0.001

PPD, probing pocket depth; LCAL, life cumulative attachment loss.

Table 2 Analysis of covariance for PPD reduction and LCAL gain at 2 and 6 months in different pockets categories

Clinical outcomes mean	Group	Baseline 0 months	Difference between 0 and 2 months	Difference between 0 and 6 months	p-value Wilcoxon's signedranks test	
					difference 0–2 months	difference 0–6 months
Percentage of pockets ≥4mm	Placebo	45.1±10.3	15.3±9.3	14.3±10.3	<0.001	<0.001
	Test	46.1±10.3	19.6±10.3	21.6±10.3	<0.001	<0.001
Percentage of pockets ≥5mm	Placebo	31.3±17.3	17.2±10.2	17.2±10.2	0.003	0.052
	Test	35.5±15.3	22.3±11.1	24.3±11.1	<0.001	0.931
Percentage of pockets ≥6mm	Placebo	18.0±20.2	11.2±7.5	11.9±7.5	<0.001	<0.001
	Test	22.1±8.2	16.4±112	18.4±112	<0.001	<0.001
Percentage of pockets ≥7mm	Placebo	9.0±10.2	6.1±4.3	5.3±4.3	<0.001	<0.001
	Test	12.0±9.3	10.5±6.3	10.8±6.3	<0.001	<0.001

Significant difference between groups favoring test treatment ($p < 0.05$).
Significant difference between groups favoring test treatment ($p < 0.02$).

At baseline, there were no significant differences between test and placebo. All parameters, with the exception of the mean LCAL gain at the initial shallow pockets, showed a statistically significant difference between baseline and 2 months. This was also true between baseline and 6 months except for LCAL gain and PPD reduction at shallow pockets. At 2 months, there were statistically significant differences ($p < 0.02$) between test and placebo in the mean PPD at moderate pockets (4–6 mm) and mean PPD at deep pockets (≥7 mm). At 6 months, statistically significant differences were detected between test and placebo groups in the mean PPD at moderate pockets ($p<0.02$), mean PPD at deep pockets ($p<0.001$) and LCAL at deep pockets ($p<0.05$). The significance of this treatment effect between the groups at 2 and 6 months (difference between the test group and the placebo group in the mean PPD reduction and the mean

For PPD reduction in 4–6mm pockets, the adjusted differences between test and placebo treatment were 0.5mm at 2 months and 0.4mm at 6 months. In the deeper pockets ≥7mm this difference was much larger: 0.9mm at 2 months and 1.4mm at 6 months.

For sites with initial PPD ≥7, LCAL gain was also significantly better in test subjects: an adjunctive benefit of 0.6mm at 2 months and 1.0mm at 6 months was observed. While there was no statistically significant benefit in terms of 2-month LCAL gain ($p=0.650$) at sites with initial PPD 4–6 mm, a highly significant difference of 0.50mm in favour of the test group was observed at 6 months ($p=0.001$).

In addition, the effect of smoking on the primary outcome variable (PPD reduction at ≥7mm pockets) was statistically

significant (p = 0.007), and the difference between a non-smoker and a smoker on PPD reduction at deep pockets was 0.9mm (95% CI 0.3, 1.5) at 2 months and 1.0mm (0.3, 1.7) at 6 months. The corresponding value for the difference between non-smokers and smokers on PPD reduction in initial pockets of 4–6mm was 0.4mm (0.0, 0.8), demonstrating a borderline significance (p=0.050) at 2 months and a non-significant difference of 0.2mm (-0.1, 0.6) at 6 months (p = 0.183), whereas there were no statistically significant differences for LCAL.

Percentage of sites with pockets

The percentage of sites (median and inter-quartile range) with a PPD of a specific threshold at baseline and the reduction in the percentage of pockets within groups (difference between baseline - 2 months and baseline - 6 months) are reported in Table 3

DISCUSSION

This was the first randomized-controlled clinical study (RCT) designed to assess the adjunctive effect of the metronidazole–amoxicillin antibiotic combination, originally proposed by van Winkelhoff *et al*. (1989), in the treatment of GAP. The data indicated that the experimental therapy resulted in clinically significant short-term improvements in clinical parameters. As all patients had pre-treatment sessions of oral hygiene instructions and reinforcement as necessary, FMPS were low from the beginning of the study. There was little additional benefit to plaque reduction from the therapy at 2 an 6 months, and there was no difference between the treatment regimes. Pre-treatment sessions to achieve plaque scores <20% were included in order to reduce the impact of inadequate plaque control in the success of non-surgical treatment (Magnusson *et al*. 1984).

Table 3 Analysis on FMPS and FMBS at baseline (post-oral hygiene instructions) and differences between 0–2 and 0–6 months.

Median (IQ)	Group	Baseline 0 months	Difference between 0 and 2 months	Difference between 0 and 6 months	p-value Wilcoxon's signedranks test	
					difference 0–2 months	difference 0–6 months
Full-mouth plaque score (%)	Placebo	20.1±10.3	3.3±5.3	0.0±8.3	0.029	0.112
	Test	25.1±10.3	6.6±10.3	1.6±15.3	0.038	0.170
Full-mouth bleeding score (%)	Placebo	55.3±17.3	17.2±10.2	21.2±7.2	<0.001	0.001
	Test	61.5±15.3	34.3±11.1	32.3±9.1	<0.001	<0.001

Significant difference between groups favoring test treatment (p<0.02).
FMPS, full-mouth plaque score; FMBS, full-mouth bleeding score.

Table 4 Percentage of sites with clinically relevant changes in test and placebo groups at 2 and 6 months

Median of percentage (IQ)	0–2 months data			0–6 months data		
	test group	placebo group	p-value Mann–Whitney test	test group	placebo group	p-value Mann–Whitney test
Percentage of sites with ≥2mm of LCAL gain at 2 months	19.1±8.3	14.1±8.3	0.047	25.1±10.3	16.1±3.3	0.047
Percentage of sites with ≥2mm of PPD reduction at 2 months	29.3±17.3	20.3±17.3	0.029	30.3±16.3	20.3±12.3	0.029
Percentage of sites with LCAL loss ≥2mm at 2 months	1.3±2.2	3.3±2.2	0.041	1.5±2.1	3.3±4.1	0.041
Percentage of pockets converting from ≥5mm at baseline to ≤4mm after treatment	71.2±8.2	56.2±8.2	0.039	74.2±4.2	54.2±8.2	0.039
Percentage of pockets converting from ≥4mm at baseline to ≤3mm after treatment	49.2±15.2	41.2±15.2	0.112	55.2±10.2	37.2±15.2	0.112

LCAL, life cumulative attachment loss

Oral hygiene and bleeding on probing

FMPS and FMBS at baseline, and the reduction (difference baseline - 2 months and baseline - 6 months) within each group are displayed in Table 4. Plaque scores decreased in both treatments from baseline to 2 months, and the difference was statistically significant for test and placebo groups. However, the 6-month plaque scores values were equal to baseline values. The effects of both treatments had a large impact on bleeding, and these changes were statistically significant at 2 and 6 months (p<0.001). Furthermore, there was a statistically significant difference between test and placebo for the improvement in the percentage of bleeding sites at 2 and 6 months (p<0.02). Percentage of sites with clinically relevant changes A subset analysis was carried out to test the changes of some clinically relevant parameters at 2 and 6 months (Table 4).

This was important because full-mouth instrumentation was performed in two visits, and thus the therapist had fewer opportunities to deliver, check and reinforce the necessary oral hygiene instructions. Our experimental population consisted of subjects with the clinical characteristics of GAP according to the criteria of the 1999 international classification. Our patients were average of 31 years of age, who presented with almost all teeth and with severe widespread disease (an average of 33% of the sites with PPD ≥5mm after probing six sites around each tooth). Patients, however, were not screened or selected based upon a microbiological diagnosis. In this study, we prescribed 500 mg of amoxicillin combined with 500 mg of metronidazole three times a day for 7 days. This dosage has not been reported in previous clinical trials. It aims to provide a wide spectrum of activity and to reach and maintain serum concentrations above the minimum effective concentration. The rationale for the wide spectrum use is based on the reported high prevalence of

A. actinomycetemcomitans and anaerobic pathogens in GAP patients (Sasaki, N *et al* 1989, Listgarten *et al* 1995, Lopez *et al* 1995, Lee *et al* 2003, Tonetti *et al* 1999). The choice of dosage comes from an analysis of previous studies in chronic periodontitis subjects (van Winkelhoff *et al* 1999, Winkel 1997, Palmer 1999). Attention has been drawn recently to the fact that the amount of metronidazole needed for effective concentration in body fluids amounts to 20–25 mg/kg, and that an insufficient antibiotic concentration would turn into a lack of effect on clinical and microbiological parameters(van Winkelhoff 1999). This means that 1400–1750 mg/day of the medication should be taken by a 70 kg adult patient (Winkel 1997). Therefore, in GAP patients with a high prevalence of anaerobic and micro-aerophilic periodontal pathogens, a moderate dose of amoxicillin (375–500 mg) will have synergistic effects with metronidazole and its hydroxymetabolite against A. actinomycetemcomitans(Pavicic *et al* 1992), while a high dose of metronidazole (500 mg) will target the anaerobic microflora. It is clear from other clinical trials that mean full-mouth PPD and LCAL values may not be the best way to describe the data. Shallow sites, which are not expected to change as a result of therapy, are likely to significantly dilute the changes observed at the deeper sites, which are the ones of therapeutic concern. Therefore, the primary outcome variable selected was the difference in PPD reduction between the treatment groups at deep pockets. The mean PPD reduction at 6 months was 1.8mm (95% CI 1.3, 2.3) for the placebo group and 3.1mm (2.7, 3.5) for the test group. A multivariate model (Table 2) determined that the additional benefit for test subjects after taking into account the potential sources of variability was 1.4mm (0.8, 2.0). It should be noted that the results obtained in the control group were within the range expected from non-surgical periodontal treatment in chronic periodontitis patients. Cobb (1996) reviewed the most relevant clinical studies related to PPD reduction after non-surgical therapy alone, and found that at deep pockets (PPD≥ 7 mm), the mean PPD reduction was 2.2 mm. This was in excellent agreement with the results of our placebo group, which exhibited a mean PPD reduction of 2.1mm at 2 months and 1.8mm at 6 months. The results are also comparable with those of the control group in a similar study in aggressive Periodontitis patients treated with the adjunctive use of three different single antibiotic regimens (Sigusch *et al* 2001). They showed that in pockets ≤6 mm, a 2.3mm PPD reduction was achieved 6 months after treatment. The similarity between the outcomes of subgingival instrumentation at deep pockets of chronic and aggressive periodontitis patients is in agreement with reports indicating that aggressive periodontitis patients respond well to mechanical instrumentation alone (Wennstrom *et al* 1986). In contrast, the adjunctive benefits are more difficult to compare with other studies because of the paucity of randomized controlled clinical trial in GAP patients. Recent meta-analyses have suggested that the adjunctive benefit expected from antibiotic usage may be greater in aggressive periodontitis patients. (Quirynen, M *et al* (1995) An additional gain in LCAL of 0.7mm was observed in seven studies including 231 subjects receiving the antibiotic adjunctively to non-surgical or surgical root instrumentation. In the present study, the use of adjunctive antimicrobials resulted in an additional benefit of 0.5mm in LCAL gain in moderate pockets (4–6mm), while a 1.0mm benefit was observed in deeper pockets (≥7 mm) compared with non-surgical root debridement alone. Our test subjects showed a mean PPD reduction of 3.1mm in pockets ≥7 mm at 6 months. These results are slightly inferior but comparable with the 6-month outcomes reported by Sigusch *et al*. (2001) with the use of adjunctive metronidazole or clindamycin. In terms of PPD reduction at 6 months, the added benefit that we observed was 0.4mm for moderate pockets (4–6mm) and 1.4mm for the deep pockets (≥7 mm). This gradient of effect is consistent with the notion that the benefit of the antibiotic is particularly evident at deeper pockets where mechanical debridement is less effective. For most clinicians, results reported as mean full-mouth values offer little insight into the clinical relevance of the findings. To illustrate tangible clinical benefits, after the analysis on the primary outcome variable (PPD reduction in pockets ≥7 mm) and the other parameters based on full-mouth mean or median values, secondary analyses were carried out. Accordingly, the test treatment significantly decreased the percentage of pockets that remained above specific thresholds at 2 and 6 months after subgingival debridement (Table 4). As in previous studies,(Berglundh *et al* 1998) the percentage of all sites that gained ≥2mm in LCAL and the percentage of all sites that had a PPD reduction ≥2mm were statistically significantly higher in the test group at 2 and 6 months. Furthermore, the percentage of sites experiencing disease progression (LCAL loss of 2mm or more over the 6-month observation period) was significantly decreased by the antibiotic combination. However, a critical question at reevaluation 3–6 months after the completion of non-surgical therapy is related to what to do with residual pockets and the need for further treatment beyond maintenance care. This conclusion can be used as a rationale for providing further treatment to patients, e.g. pocket reduction surgery. As reported in other studies (Loesche *et al* 1992, Smith *et al* 2202), we compared the reduction in the frequency of sites in test and control patients who would require surgical intervention for PPD reduction at 2 or 6 months using 5mm as the discriminant value. At 2 months post-therapy, we found that the subjects receiving the test treatment showed a 71% reduction in the number of sites in need of surgical intervention, while the subjects in the placebo group had a reduction of 57% (p = 0.039). These values were maintained at 6 months. Using an even stricter discriminant value (4mm), at 6 months, 55% of the test sites with baseline pockets showed maintainable probing depths (3mm or less) as compared with 37% of the placebo sites (p5 = 0.038). Two subjects in the placebo group and four subjects in the test group did not fully comply with the medication. On the other hand, this fact provides the study with a higher external validity as lack of compliance is a reality in clinical practice (Grob, P. R. (1992). Furthermore, given the fact that some of the observed incomplete compliance can be attributed to the onset of significant side effects, clinicians prescribing this regimen to their patients should expect less than optimal compliance. An additional analysis assessing the impact of incomplete compliance will be presented in a companion paper focused on the microbiological outcomes of the study where an ‘‘on drug’’ analysis gives important additional information.

In conclusion, the findings of the present study have indicated that the adjunctive use of systemic amoxicillin plus metronidazole, during full-mouth non-surgical cause-related periodontal treatment (FSR) performed within 24 h, has

resulted in significant additional improvements in the clinical conditions of GAP patients when compared with FSR alone. These observations are valid for both the 2- and 6-month evaluations after the completion of active treatment.

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