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Control of periodontal infections: A randomized controlled trial I. The primary outcome attachment gain and pocket depth reduction at treated sites

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Abstract

Objective: To compare the treatment outcome of scaling and root planing (SRP) in combination with systemic antibiotics, local antibiotic therapy and/or periodontal surgery.

Material and Methods: One hundred and eighty-seven patients were assigned to eight groups treated by SRP plus none, one, two or three adjunctive treatments and monitored for 24 months in a randomized controlled clinical trial using a $2 \times 2 \times 2$ factorial design. Systemic amoxicillin + metronidazole (SMA), local tetracycline delivery (LTC) and periodontal surgery (SURG) were evaluated as adjuncts. Changes in clinical attachment level (CAL) and probing pocket depth (PPD) were statistically evaluated by ANCOVA of main effects.

Results: Effects of adjunctive therapy to SRP were minimal at 3 months. Between 3 and 6 months PPD reduction occurred particularly in patients receiving periodontal surgery. After 6 months, both CAL gain and PPD reduction reached a plateau that was maintained at 24 months in all groups. The 24-month CAL gain was improved by SMA (0.50 mm) while PPD was reduced by SMA (0.51 mm) and SURG (0.36 mm). Smoking reduced CAL gain and PPD reduction.

Conclusion: Patients receiving adjunctive therapies generally exhibited improved CAL gain and/or PPD reduction when compared with the outcome of SRP alone. Only additive, not synergistic effects of the various adjunctive therapies were observed.

Key words: antibiotics; periodontal disease; periodontal surgery; randomized controlled trial

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Conflict of interest and sources of funding statement

J. M. Goodson developed the tetracycline fiber used in this study between 1976 and 1994 when it was introduced. It has not been on the market since 2003. No other participants have any conflict of interest with any of the products tested in this study. This research was supported by the National Institute of Dental and Craniofacial Research grants DE12861 and RR025771, and GCRC funding from RR00533 and RR01032.

Scaling and root planing (SRP) has been and continues to be the most commonly employed professionally administered form of periodontal therapy (Haffajee et al. 1997, Cugini et al. 2000, Van der Weijden & Timmerman 2002). Surgical proce-

dures have been shown to augment many of the effects of SRP, such as reduction in gingival inflammation, probing pocket depth (PPD) and gain of clinical attachment level (CAL), particularly in sites with deeper periodontal pockets (Antczak-Bouckoms et al. 1993, Levy et al. 1999, 2002, Heitz-Mayfield et al. 2002).

Tested SRP adjuncts included systemic antibiotics (Haffajee et al. 1995, 2006, Berglundh et al. 1998, Feres et al. 1999, 2001, Palmer et al. 1999, Ramberg et al. 2001, Winkel et al. 2001, Rooney et al. 2002, Smith et al. 2002, Guerrero et al. 2005, Xajigeorgiou et al. 2006) and low dose antimicrobial agents (Caton et al. 2000, Emingil et al. 2004a,b, Gurkan et al. 2005). Most studies indicated that patients receiving SRP plus adjunctive therapy showed better clinical outcomes than patients receiving SRP alone. Local drug delivery has also been employed as an adjunct to SRP, particularly in sites with deeper periodontal pockets. In most studies, an improved clinical response was reported when compared with SRP alone (Goodson et al. 1991, Newman et al. 1994, Kinane & Radvar 1999, Hanes & Purvis 2003, Pavia et al. 2003, Bonito et al. 2005, Paolantonio et al. 2008).

In these studies, we compare responses to three adjunctive therapies with SRP; systemically administered amoxicillin plus metronidazole, locally delivered tetracycline and modified Widman flap surgery. A factorial design which tests the eight possible combinations of these therapeutic adjuncts was selected to focus on differences with sufficient statistical power to identify superior treatments. The tested hypothesis was that adjunctive therapy will result in statistically significant changes in clinical measures of periodontal health. This study presents the experimental design and the main effects of the adjunctive therapies on CAL gain and PPD reduction.

The amount of data collected in this study required segmenting into multiple reports. In this report, (1) we evaluate changes in the primary (CAL gain) and secondary (PPD reduction) outcome variables. In subsequent reports we will describe, (2) responses at deep, intermediate and shallow sites, (3) changes in the associated measures of bleeding, redness, plaque and suppuration, (4) bacterial changes and (5) Changes in local and systemic inflammatory mediators.

Material and Methods

Patient population

Two hundred and thirty-one patients from two geographic locations Boston (USA) and Goteborg (Sweden) were selected to participate in a therapeutic trial (Fig. 1).

Inclusion criteria

All patients were more than 20 years of age, had at least 15 natural teeth, and were in good general health. Patients had at least four teeth with pockets > 5 mm and $\geq$ 8 teeth with CAL > 3 mm. Both males and females, and patients of any racial group were accepted into the study.

Exclusion criteria

Patients were excluded if they were pregnant or nursing, received antibiotic or periodontal therapy in the previous 3 months, had any systemic condition that would affect the course of periodontal disease (e.g. diabetes, AIDS), had any systemic condition that required antibiotic coverage during periodontal therapy (e.g. certain heart conditions, joint replacements), or had allergy to amoxicillin, metronidazole, tetracycline, lidocaine or chlorhexidine.

Periodontal treatments

Self-administered home-care procedures

Each patient in the study was provided a powered toothbrush (3D; Oral B; Boston, MA) and a triclosan-containing toothpaste (Total®; Colgate; Piscataway, NJ, USA), and appropriate devices for approximal tooth cleaning. Patients were instructed to perform the oral hygiene procedures twice daily.

Scaling and root planing

All patients received SRP, which was performed under local anaesthesia and usually completed in four weekly visits. During SRP treatment, patients rinsed twice daily with a 0.12% chlorhexidine mouth rinse (Peridex®; Proctor & Gamble Co., Cincinnati, OH, USA).

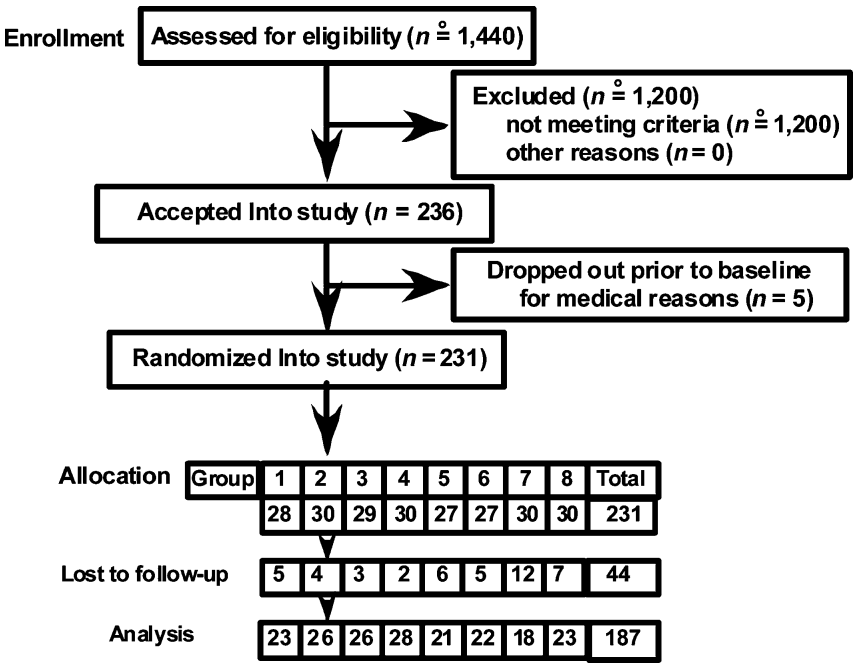

Fig. 1. Flow chart of patient recruitment, randomization and retention. The total number of patients screened (1440) is approximate. Typically, about six potential patients were screened to fit the inclusion and exclusion criteria for moderate to severe periodontitis. A total of 231 patients were randomized and 187 completed the study. Group numbers are defined in Table 1.

Systemic antibiotic administration

The patients randomized into groups that received systemic antibiotics (SMA) were given 14 days of medication with instructions to take 250 mg metronidazole morning, noon and night along with 500 mg of amoxicillin to be taken morning and evening (total dose: 14 g amoxicillin, 10.5 g metronidazole). This was started immediately after the first session of SRP. Compliance was self-reported to the dental examiner and was not placebo controlled.

Local antibiotic administration

Tetracycline fibres (Actisite®; Proctor and Gamble, Cincinnati, OH, USA) create a sustained concentration of approximately 1590 mg/ml in the periodontal pocket by releasing approximately 1.7 mg/tooth (Tonetti et al. 1990). The fibres (LTC) were placed immediately following SRP of a jaw quadrant and only in periodontal pockets ≥ 5 mm and were removed after 7 days.

Periodontal surgery

At the 3-month monitoring visit following SRP, patients assigned to SURG that had residual sites with PPD ≥ 5 mm that bled on probing were scheduled for modified Widman flap surgery performed at weekly intervals, as needed. The use of a 0.12% chlorhexidine mouth rinse for 1 min. twice daily was prescribed during the surgical phase and 2 weeks following the last surgical session.

Post-treatment phase

At each follow-up visit (3, 6, 12, 18 and 24 months) the patients' oral hygiene standard was checked and reinforced when indicated. Furthermore, at the 12-month recall, all sites with PPD ≥ 5 mm and BOP positive were subjected to SRP.

Trial design

Patients were stratified into current smokers and non-smokers, and then randomly assigned in computer generated permuted randomized blocks of eight to the treatments: (1) SRP alone, (2) SRP + LTC, (3) SRP + SMA, (4) SRP + LTC + SMA, (5) SRP + SURG, (6) SRP + LTC + SURG, (7) SRP + SMA + SURG and (8) SRP + LTC + SMA + SURG (Table 1).

At each centre, at least two therapists and two clinical examiners were identified. Designated clinical examiners were masked to the therapies administered. Only therapists were given the treatment identity. As errors in inappropriate groupings of treatments for evaluation were considered to be substantial, statistical personnel were not blinded. Also patients were not blinded because of the obvious impact of surgery and unavailability of a placebo local delivery system.

All probe measurements were taken twice at each visit. Examiners from each centre participated in calibration studies, involving probing the same half mouth of each of four patients twice within 1 week. The average standard deviation of PPD measurement was 0.53 mm and of CAL measurement was 0.65 mm. The standard deviation of differences between the first and second measurement for PPD was 0.41 mm and for CAL was 0.55 mm. Repetitive differences between the first and second measurement made over a period of 2 years averaged 0.53 mm for PPD and 0.53 mm for CAL. As a practical matter, all accepted examiners were tested and required to achieve a precision of 0.6 mm as a standard deviation of duplicate differences in PPD and 0.8 mm for CAL. Examiner calibration took place prior to study initiation and repeated annually or at each time a new examiner was added throughout the trial.

Clinical measurement

Probing pocket depth (PPD) and the distance from the cemento-enamel junction to the gingival margin (gingival recession) were measured to the nearest millimetre using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA), at four sites per tooth (mesiobuccal, distobuccal, distolingual and mesiolingual) at all teeth, except third molars. The order of measurement was: gingival redness (RED, 0 or 1), suppuration (SUP, 0 or 1), PPD (mm), gingival recession (mm), bleeding on probing (BOP, 0 or 1)

Table 1. Numbers, percentage and baseline mean values of patients in the study and in each treatment group

Groups and Treatments	Major effects			No. of patients (%)	Sweden (%)	Smoke (%)	Age (y) ± SE	CAL (mm) ± SE	PPD (mm) ± SE	BOP (%) ± SE	Patients with missing teeth (%)
Total study	SURG	LTC	SMA	187 (100)	90 (48)	75 (40)	48 ± 0.8	6.02 ± 0.09	6.09 ± 0.04	77 ± 1	150 (80)
1. SRP alone	–	–	–	23 (12)	10 (43)	7 (30)	47 ± 2.6	5.84 ± 0.32	6.17 ± 0.17	83 ± 3	14 (61)
2. SRP + LTC	–	+	–	26 (14)	11 (42)	7 (27)	46 ± 2.0	5.98 ± 0.19	6.15 ± 0.12	75 ± 4	22 (85)
3. SRP + SMA	–	–	+	26 (14)	11 (42)	9 (35)	47 ± 2.0	6.35 ± 0.27	6.01 ± 0.09	70 ± 3	17 (65)
4. SRP + SMA + LTC	–	+	+	28 (15)	12 (43)	15 (54)	48 ± 1.4	6.57 ± 0.19	6.19 ± 0.13	69 ± 4	23 (82)
5. SRP + SURG	+	–	–	21 (11)	10 (48)	8 (38)	48 ± 1.9	5.88 ± 0.30	6.17 ± 0.12	84 ± 4	18 (86)
6. SRP + LTC + SURG	+	+	–	22 (12)	12 (55)	10 (45)	51 ± 2.2	5.76 ± 0.24	5.94 ± 0.09	77 ± 5	20 (91)
7. SRP + SMA + SURG	+	–	+	18 (10)	12 (67)	8 (44)	51 ± 2.8	5.37 ± 0.21	6.02 ± 0.12	83 ± 4	18 (100)
8. SRP + SMA + LTC + SURG	+	+	+	23 (12)	12 (52)	11 (48)	51 ± 2.5	6.07 ± 0.31	6.03 ± 0.14	79 ± 4	18 (78)

SRP, scaling and root planing; SURG, periodontal surgery; SMA, systemic antibiotics (amoxicillin + metronidazole); LTC, local antibiotics (tetracycline fibres); Sweden, number of Swedish patients (%); Smoke, number of patients currently smoking (%); CAL, baseline clinical attachment level; PPD, baseline probing pocket depth; BOP, baseline percentage of periodontal sites bleeding on probing; SE, standard error of the mean.

and plaque accumulation (PLA, 0 or 1). PPD and gingival recession were measured twice at each visit (Haffajee et al. 1983). Although multiple examiners were used, a single examiner made all clinical measurements at all visits for any given patient. Measurements were recorded on forms that were scanned, interpreted, verified (Teleform®; Autonomy Cardiff, Vista, CA, USA) and recorded in a Structured Query Language database.

Data analysis

Clinical attachment level gain was selected as the primary outcome variable, as it is widely recognized as the "gold standard" in clinical trials of periodontal disease therapy (Page & DeRouen 1992). PPD reduction was included as a secondary outcome because of its common clinical use.

Statistical power

Considering the smallest effect that would be of clinical significance to be 0.5 mm and within group standard deviations of about 1 mm, the effect size for power calculation would be 0.5. With 187 patients, a nominal cell size of 96 cases two-tailed alpha of 0.05, the power of this study to evaluate the three major effects (SURG, SMA and LTC) is greater than 90%.

Data preparation

All analyses were based on the patient as the unit of measure. Full-mouth computations included only inter-proximal sites measuring $\geq$ 5 mm at baseline (target treatment sites). Tabular results were reported as mean and standard error of the mean.

Analysis of CAL gain and PPD reduction

The magnitude of therapeutic response was evaluated by millimetre change. The mean value of duplicate probe measurements was used to determine PPD and CAL (Haffajee et al. 1983).

Analysis by factorial ANCOVA for CAL gain and PPD reduction

Using the 2 × 2 × 2 factorial design of the study, main effects for LTC, SMA and SURG were examined for a target 96 patients per group as the primary statistical analysis. Main effects and interactions were evaluated by ANCOVA for CAL gain and PPD reduction at 24 months for 187 patients using surgery, systemic antibiotics, local antibiotics centre and current smoking as independent categorical variables with baseline CAL (CAL1) or baseline PPD (PPD1) along with baseline bleeding on probing (BOP1) as covariates. Gender, baseline plaque, baseline redness and age were tested as covariates, but omitted as they did not contribute significantly to the model.

Analysis by treatment ANCOVA

Values for CAL gain and PPD reduction at each site averaged for each patient for each treatment group in the study were analysed by ANCOVA as a secondary statistical analysis. The significance of differences over time in each group for each parameter was sought in a model adjusting for the same covariates plus 24 month plaque reduction. Significance of differences between pairs of treatments was sought using Fisher's protected least significant difference. Values calculated in Table 4 are provided for comparison with the results obtained by factorial ANCOVA (Table 3).

Bonferroni corrections were applied in all statistical tests to compensate for multiple testing. Chi-square analysis was used to examine differences in 2 × 2 comparisons.

Results

This study was conducted between March 1999 and January 2004. The baseline clinical and demographic features are presented in Table 1. There were no significant differences among treatment groups for mean PPD, mean CAL, % of patients with missing teeth, % of Swedes, % of males, % of current smokers and age. The mean age of the total patient sample was 48 years, 48% were from Sweden and 40% were current smokers. The average baseline CAL and PPD was 6.02 and 6.09 mm respectively. There were significant differences among groups in the percentage of sites with plaque, gingival redness, BOP and suppuration. In general, patients in groups 1, 2, 4 and 5 had higher mean values for these parameters at baseline. In each treatment group 18–28 patients were evaluated. All patients provided systemic antibiotics reported that they were taken as prescribed.

Adverse events

No serious adverse events were associated with any of the treatments. In the course of the study, two patients developed type 2 diabetes. Five patients dropped out because of medical conditions (high blood pressure (n = 3), coronary bypass surgery (n = 1) and coronary heart disease fatality (n = 1)). Of the 95 patients receiving systemic antibiotics, one dropped out because of nausea and vomiting and one developed candidiasis that responded to oral miconazole.

Patient retention

One hundred and eighty-seven patients completed and 44 dropped out of the study (Fig. 1, Table 2a); seven Swedish and 37 US patients. Analysis by major effect revealed that the periodontal surgery group was associated with a significantly higher dropout rate than non-surgical therapies. Reasons for dropout included fear of surgery (n = 5), fear of periodontal therapy (n = 5), loss of interest or unable to continue in the study (n = 5), altered medical status (n = 5) and moved (n = 4). The remaining 20 patients could not be contacted and therefore the reason for dropout could not be determined.

A total of 170 of 231 patients had clinical data for all six monitoring visits. 44 patients had data for three or less visits and were excluded from the analyses. 17 patients with at least four monitoring visits had their data carried forward to provide a total of 187 patients for the analyses. Considering that 68% of the dropouts were scheduled to receive surgery, an intent-to-treat analysis (Table S2) including all 231 patients analysed by last value carried forward, produced results comparable to that of Table 3. Similarly, a comparison of baseline clinical values (Table S3) demonstrated that patients who dropped out were not clinically

Table 2. Patient dropouts and extracted teeth. (a) Patient dropouts by centre and by treatment. FI, Forsyth Institute; BU, Boston University; UG, University of Gothenburg. Patients more frequently dropped out in the US (FI and BU) or when assigned to a periodontal surgery treatment group. (b) Numbers of extracted teeth during the active therapy phase (0–6 months) and the post-therapy monitoring phase (12–24 months), in each treatment group. (c) Tooth counts excluding third molars. Significance relative to each main effect was computed by chi-square analysis

(a)

Centre	Completed	Dropout	*p*
FI	56	26	
BU	41	11	
UG	90	7	<0.001
	187	44	
FI *versus* UG			<0.001
BU *versus* UG			0.01
FI *versus* BU			0.2
Adjunct	Without	With	*p*
SURG	14	30	0.005
SMA	20	24	0.7

(b)

Treatment	Baseline	Active therapy			Post-therapy				Total
		3 months	6 months	Patients	12 months	18 months	24 months	Patients	
SRP + SMA + LTC + SURG	120	0	3	3	4	1	0	5	8
SRP + SMA + SURG	82	1	0	1	2	0	0	2	3
SRP + LTC + SURG	93	1	5	6	1	0	2	3	9
SRP + SURG	72	0	6	6	1	2	5	8	14
SRP + All	106	1	1	2	3	1	3	7	9
SRP + SMA + LTC	78	1	0	1	0	1	4	5	6
SRP + LTC	99	2	1	3	2	2	2	6	9
SRP alone	62	1	2	3	3	2	0	5	8
All treatments	712	7	18	25	16	9	16	41	66

(c)

Main Effect	Maintained		Extracted		*p*
	With	Without	With	Without	
SURG	1969	2530	16	9	0.04
SMA	2267	2232	7	18	0.03
LTC	2340	2159	14	11	0.69
Post-therapy					
SURG	1951	2507	18	23	0.99
SMA	2248	2210	19	22	0.60
LTC	2319	2139	21	20	0.92

different in initial disease severity (PPD, CAL and BOP) from the 187 that were included in analysis.

Teeth extracted during the study

At baseline, the 187 patients had 4524 teeth. During the 2-year period of the study, 66 teeth were extracted, 25 during the active treatment phase and 41 during the post-therapy monitoring phase (Table 2b). No significant association with major effects was found with regard to tooth extraction during the post-treatment phase (6–24 months). For the purpose of analysis, the last recorded value of each extracted tooth site was carried forward.

Mean change in PPD and CAL over time

Figure 2 presents PPD reduction and attachment level gain following the SRP treatment phase (3 months), the surgical phase (6 months) and the maintenance phase (24 months), in the eight treatment groups. Marked improvement was observed 3 months after the SRP treatment phase for both PPD and CAL, without significant additive effect of adjunctive systemic and/or local antibiotic therapy (Fig. 2). Virtually, all CAL gain observed during the 24-month study interval was established already after 3 months. There was a further notable reduction in mean PPD from 3 to 6 months particularly in patients receiving periodontal surgery. After 6 months, both CAL gain and PPD reduction reached a plateau. Thus, the values achieved following the active treatment phases (baseline 6 months) were maintained for 24 months for all treatment groups.

Table 3. Factorial ANCOVA of main effects, interactions and least squares means at 24 months. Responses of periodontal surgery (SURG), systemically administered amoxicillin and metronidazole (SMA) and locally delivered tetracycline (LTC) on probe measurement change at sites with pockets ≥ 5 mm from baseline to 24 months. CAL1, PPD1 and BOP1 are baseline values of clinical attachment level (CAL) , probing pocket depth and bleeding on probing respectively

(a) Clinical Attachment Gain

Source	Sum-of-Squares	df	Mean-Square	*F*-ratio	*p*
SURG	1.049	1	1.049	1.478	0.2
SMA	11.395	1	11.395	16.058	0.00009*
LTC	3.679	1	3.679	5.185	0.02
Current smoke	4.683	1	4.683	6.599	0.01*
Centre	0.126	2	0.063	0.089	0.9
CAL1	9.840	1	9.840	13.866	0.0003
BOP1	3.256	1	3.256	4.588	0.03
SURG*SMA	0.674	1	0.674	0.950	0.3
SURG*LTC	0.013	1	0.013	0.018	0.9
LTC*SMA	1.359	1	1.359	1.915	0.2
SURG*SMA*LTC	0.126	1	0.126	0.178	0.7
Error	123.477	174	0.710		
Least squares means					
Factor	Level	LS mean	SEM	*N*	
SURG	Without	1.275	0.089	103	
SURG	With	1.119	0.100	84	
SMA	Without	0.941	0.096	92	
SMA	With	1.452	0.093	95	
LTC	Without	1.053	0.098	88	
LTC	With	1.341	0.090	99	

(b) Probing Pocket Depth Reduction

Source	Sum-of-Squares	df	Mean-Square	*F*-ratio	*p*
SURG	5.46	1	5.46	11.882	0.0007*
SMA	11.457	1	11.457	24.933	0.000001*
LTC	1.765	1	1.765	3.841	0.05
Current smoke	3.976	1	3.976	8.651	0.004*
Centre	3.955	2	1.978	4.304	0.02
PPD1	13.373	1	13.373	29.102	0.0000002
BOP1	9.876	1	9.876	21.492	0.00001
SURG*SMA	0.346	1	0.346	0.752	0.4
SURG*LTC	0.043	1	0.043	0.094	0.8
LTC*SMA	0.432	1	0.432	0.940	0.3
SURG*SMA*LTC	0.661	1	0.661	1.438	0.2
Error	79.956	174	0.460		
Least squares means					
Factor	Level	LS mean	SEM	*N*	
SURG	Without	2.044	0.072	103	
SURG	With	2.396	0.079	84	
SMA	Without	1.965	0.076	92	
SMA	With	2.475	0.075	95	
LTC	Without	2.121	0.078	88	
LTC	With	2.320	0.073	99	

*Statistically significant $p \leq 0.05$, after applying a Bonferroni correction of $p \leq 0.01$ for the six comparisons (SURG, SMA, LTC, for CAL gain and PDD reduction) made in this study.

CAL gain and PPD reduction at 24 months-analysis by main effect

The greatest differences between presence and absence of a main effect (Fig. 3) were seen in the CAL gain, with regard to systemic antibiotics (SMA). Using this adjunctive treatment, a significant difference was established at 6 months and an improved CAL gain of 0.5 mm was maintained at 24 months ($p < 0.001$). PPD reduction was similarly affected by this therapy. The additive effects of locally delivered tetracycline (LTC) were in the same direction, but markedly less.

Treatment by periodontal surgery did not improve CAL gain ($p = 0.2$). The main effect of periodontal surgery was to establish a significant level of PPD reduction that was maintained at 24 months ($p = 0.001$).

Current smoking decreased both CAL gain (NS, $p = 0.01$) and PPD reduction (S, $p = 0.004$). The magnitude of inhibition by current smoking approached a magnitude that would negate the effectiveness of the best adjunctive therapy.

Analysis of main effects and interactions at 24 months (Table 3a) revealed that a significant increase in CAL gain occurred only with systemic antibiotic therapy. Local antibiotic therapy increased CAL gain and periodontal surgery and current smoking reduced CAL gain, but these changes were statistically non-significant after adjusting for multiple testing.

Probing pocket depth (PPD) was significantly reduced by both periodontal surgery and systemic antibiotic therapy in 24 months (Table 3b). Current smoking also significantly affected PPD. Although centre differences appeared to affect PPD reduction, after adjustment for multiple testing this was not found to be statistically significant. None of the interactions between therapies were statistically significant.

Swedish patients exhibited far less plaque accumulation than U.S. patients (Table S1). These differences, however, did not result in significant centre differences by factorial ANCOVA (Table 3) and did not significantly contribute when introduced into treatment ANCOVA models (Table 4b).

CAL gain and PPD reduction at 24 months-analysis by treatment group

Applying the Bonferroni correction for multiple testing of these 56 comparisons, statistical significance at the $p < 0.05$ level could be claimed only for comparisons with a p-value < 0.0009. Comparisons meeting this criterion in CAL gain were groups SRP + SMA, SRP + SMA + LTC and SRP + SMA + LTC + SURG compared with group SRP + SURG (Table 4a). Comparisons in PPD reduction meeting this criterion were groups SRP + SMA, SRP + SMA + LTC, SRP + LTC + SURG, SRP + SMA + SURG and SRP +

SMA + LTC + SURG compared with SRP alone and the group SRP + SMA + LTC + SURG compared with SRP + LTC.

Discussion

The present investigation demonstrated that SRP performed in patients with moderate periodontitis resulted in pronounced reduction in PPD at sites with initially deep pockets and some CAL gain. In agreement with others (Cobb 1996, Heitz-Mayfield et al. 2002), this shows the importance of root debridement in the treatment of diseased sites. The 3-month examination furthermore disclosed that adjunctive measures including the use of systemic antibiotics or locally delivered tetracycline (or a combination of the two), during the SRP phase of therapy provided no additional benefit with respect to PPD reduction or CAL gain. This is in agreement with investigators who observed that systemic amoxicillin and metronidazole had no influence on the overall outcome (PPD reduction and CAL gain) of non-surgical therapy as evaluated after 2 and 12 months (Berglundh et al. 1998).

In the present multicentre trial, it was also observed that surgical access therapy (modified Widman flap procedure), performed after the 3-month examination interval, resulted in a marked further overall reduction of the PPD values. This observation is in agreement with findings described by others (Westfelt et al. 1985, Ramfjord et al. 1987, Becker et al. 1988), who reported that various surgical procedures increased the percentage of shallow and decreased or even eliminated sites with deep pockets. The effect of surgical treatment in this Swedish and US patient sample had, however, only a modest, if any, influence on CAL. This outcome is corroborated by observations of various treatment modalities provided patients with moderately advanced periodontitis (Ramfjord et al. 1987). In these studies, all patients first received a comprehensive non-surgical therapy (Morrison et al. 1980). After a healing period of 3 months additional therapy was provided including (i) curretage, (ii) resective surgery, (iii) modified Widman flap surgery or repeated and (iv)

Table 4. (a) Attachment level gain and pocket depth reduction analysis by treatment ANCOVA. Values are computed from baseline to 24 months in patients randomized to eight treatment groups at sites with pocket depth >5 mm at baseline. Significant pairwise differences were determined by post hoc analysis using Fisher's Protected LSD. Values with the same superscript letter within each column differed at $p < 0.0009$ (Bonferroni correction for 56 comparisons to maintain $p < 0.05$). Tabulated values are adjusted mean (mm) ± SEM. (b) Treatment ANCOVA and Matrix of 56 pairwise comparison probabilities. Numbers in boldface represent $p < 0.0009$. DPLA6 is plaque reduction at visit six (24 months), which did not significantly contribute to either model

Group	*N* patients	CAL gain (mm)	PPD reduction (mm)
1. SRP alone	23	0.92 ± 0.21	1.81 ± 0.23^{abcde}
2. SRP + LTC	26	1.42 ± 0.22	2.11 ± 0.14^{f}
3. SRP + SMA	26	1.53 ± 0.16^{a}	2.36 ± 0.20^{a}
4. SRP + SMA + LTC	28	1.50 ± 0.15^{b}	2.24 ± 0.13^{b}
5. SRP + SURG	21	0.64 ± 0.19^{abc}	2.30 ± 0.15
6 SRP + LTC + SURG	22	0.96 ± 0.21	2.26 ± 0.14^{c}
7. SRP + SMA + SURG	18	1.27 ± 0.16	2.63 ± 0.22^{d}
8. SRP + SMA + LTC + SURG	23	1.54 ± 0.15^{c}	2.77 ± 0.15^{ef}

(a) Clinical Attachment Gain

Source	Sum-of-Squares	df	Mean-square	*F*-ratio	*p*
GROUP	18.758	7	2.680	3.793	0.0007
CAL1	10.677	1	10.677	15.115	0.0001
BOP1	2.317	1	2.317	3.280	0.07
Centre	0.526	2	0.263	0.372	0.7
Current smoke	4.172	1	4.172	5.906	0.02
DPLA6	1.269	1	1.269	1.796	0.2
Error	122.208	173	0.706		

Group	Matrix of pairwise comparison probabilities							
	1	2	3	4	5	6	7	8
1	1							
2	0.030646	1						
3	0.009655	0.616006	1					
4	0.006686	0.52755	0.89375	1				
5	0.321827	0.002042	**0.000501**	**0.000299**	1			
6	0.361993	0.233514	0.097446	0.073947	0.065181	1		
7	0.045267	0.955281	0.699835	0.617187	0.004255	0.25274	1	
8	0.003660	0.364939	0.671561	0.764508	**0.000168**	0.04189	0.44489	1

(b) Probing Pocket Depth Reduction

Source	Sum-of-Squares	df	Mean-square	*F*-ratio	*p*
GROUP	20.278	7	2.897	6.298	0.000001
PPD1	13.257	1	13.257	28.822	< 0.000001
BOP1	8.537	1	8.537	18.560	0.00003
CENTRE	3.249	2	1.625	3.532	0.03
CURRENT SMOKE	3.773	1	3.773	8.202	0.005
DPLA6	0.383	1	0.383	0.832	0.4
Error	79.573	173	0.460		

Group	Matrix of pairwise comparison probabilities							
	1	2	3	4	5	6	7	8
1	1							
2	0.040620	1						
3	**0.000042**	0.023363	1					
4	**0.000119**	0.048121	0.759795	1				
5	0.011249	0.548914	0.127613	0.20819	1			
6	**0.000315**	0.072455	0.711573	0.934608	0.262051	1		
7	**0.000023**	0.011485	0.61707	0.441852	0.059711	0.40922	1	
8	**0.000000**	**0.000061**	0.056728	0.026867	0.001297	0.02854	0.2148	1

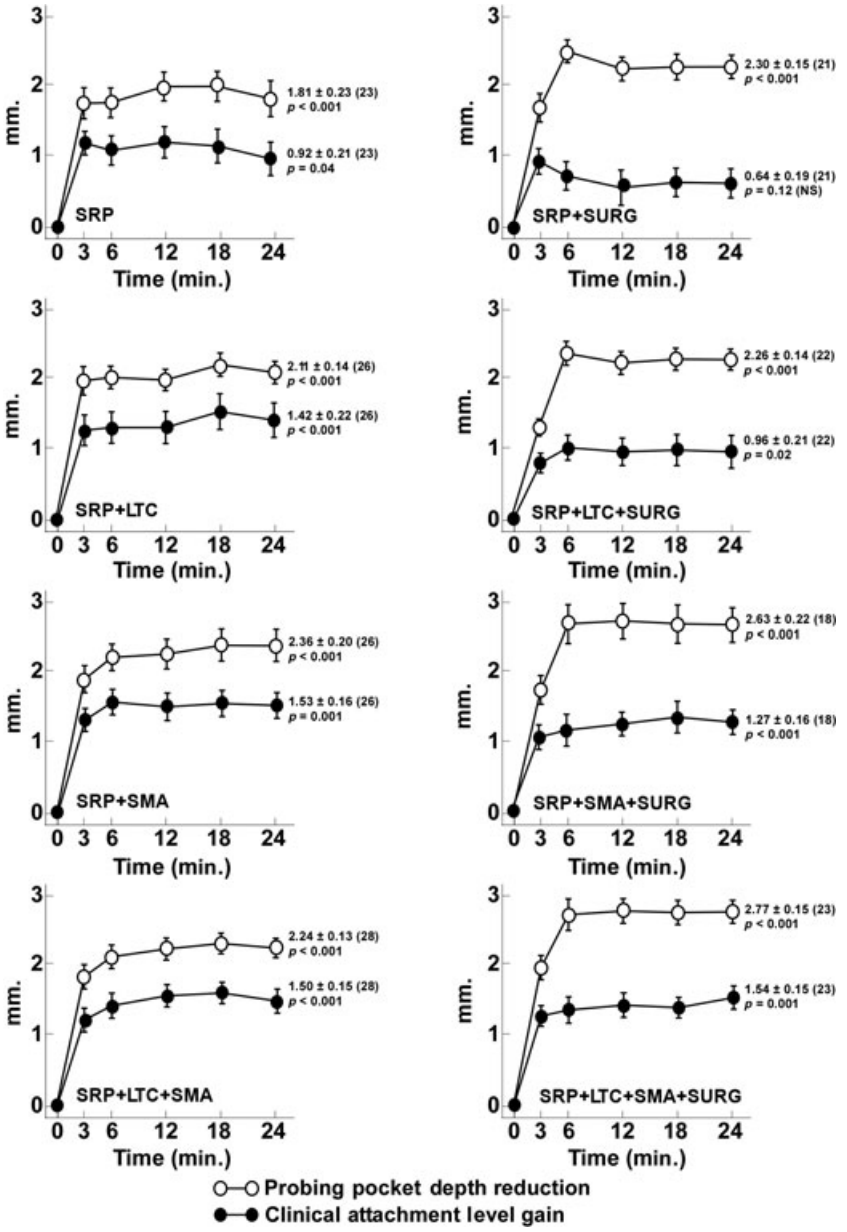

Fig. 2. Mean values for probing pocket depth reduction and clinical attachment level (CAL) gain computed as a full-mouth average of inter-proximal sites with a baseline PPD $\geq$ 5 mm. Values were computed as differences from baseline to 3, 6, 12, 18 and 24 months in 187 patients, randomly assigned to one of eight treatment groups that did or did not receive: modified Widman flap surgery (SURG), systemically administered amoxicillin + metronidazole (SMA) or treated with tetracycline fibres (LTC). Mean values ± SEM (number of patients) are listed for 24-month observations. Significance of differences between baseline and 24 months for each treatment determined by paired *t*-test are listed below the mean values.

SRP. These additional measures, however, failed to further improve CAL above and beyond that obtained by initial SRP at sites with pockets in the 4– > 6 mm category (Hill et al. 1981).

In the current study surgical treatment, evaluated at the 6-month examination interval was more effective (CAL change) in patients that had received systemic antibiotic therapy (SMA). The reason for this may be related to a more comprehensive reduction of putative pathogens in the SMA group during SRP and that this reduction persisted through the 6-month examination. This hypothesis is in part supported by findings presented by Berglundh et al. (1998). They found that in patients who following a baseline examination had received adjunctive SMA (to SRP) the subgingival microbiota sampled after 12 months contained virtually no *P. gingivalis* or *A. Actinomycetemcomitans*. The findings of improved outcomes in the treatment groups that received adjunctive SMA corroborate the observations by Berglundh et al. (1998). In this context, however, findings by Serino et al. (2001) must be considered. They demonstrated that 2-year benefits of SMA were not maintained for 5 years.

During the maintenance phase the patients in the present clinical

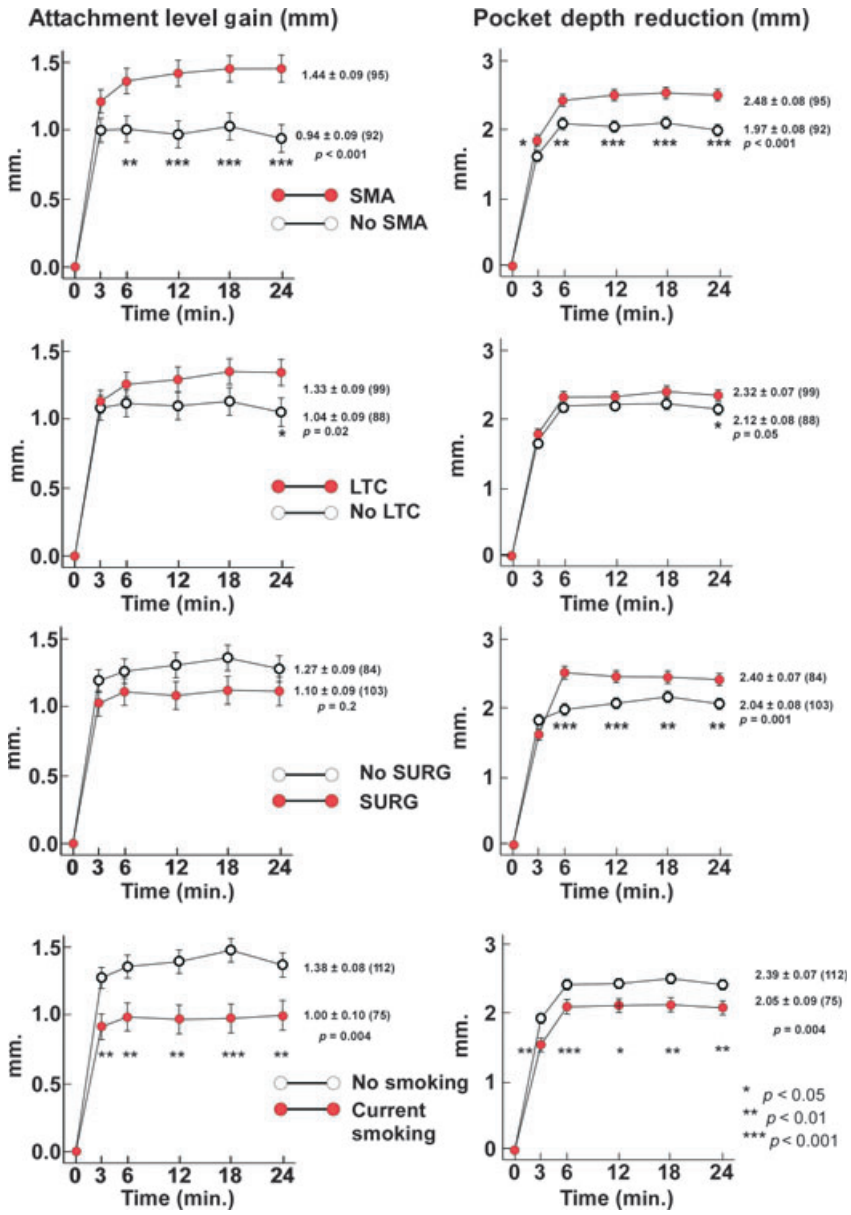

Fig. 3. Factorial ANCOVA of clinical attachment level (CAL) gain and probing pocket depth reduction at inter-proximal sites with baseline PPD ≥ 5 mm. Values and significant differences between presence (coloured circles) and absence (clear circles) of systemic antibiotic (SMA), local antibiotic (LTC), periodontal surgery (SURG) and current smoking at each monitoring visit. Adjusted mean values ± SEM (number of patients) are tabulated for the 24 month visit.

trial upheld their PPD and CAL values more or less unaltered. This indicates that the supportive therapy that was provided between 3/6 and 24 months was effective and prevented disease recurrence. The importance of proper supportive therapy in the overall treatment is in agreement with findings documented in previous studies (Rosling et al. 1976, Axelsson & Lindhe 1981).

Significant additive effects on CAL gain and reduced PPD were not observed for locally delivered tetracycline. This finding suggests that local antibiotic therapy may be less adapted to initial treatment of diseased periodontal sites.

A major reason for conducting studies with a factorial design is to test whether or not treatments interact with each other (Piantadosi 2008). The test of interaction between therapies (cross products) for 24-month CAL gain and PPD reduction revealed no statistical significance. We therefore conclude that only additive effects occurred among adjunctive therapies, with no evidence of synergism or antagonism.

The high prevalence of currently smoking patients (40%) and the balanced distribution of smokers across groups permitted analysis of current smoking as an independent categorical variable. Reduced CAL gain and PPD reduction (Fig. 3, Table 3) was observed for smokers at all examination intervals. This observation adds to previous evidence for supporting the inclusion

of smoking cessation as an integral part of periodontal therapy (Warnakulasuriya et al. 2010). In this study, no smoking intervention effort was made.

Conclusions

The purpose of this study was to compare the effects of different combinations of adjunctive periodontal therapies with SRP on changes in CAL and PPD. We found that patients receiving these therapies generally exhibited improved CAL gain and/or PPD reduction when compared with the effects of SRP alone. We also found that smoking was detrimental to treatment irrespective of treatment group.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Percentage (±SEM) of sites with visible plaque from American and Swedish patients averaging across all treatment groups. All differences were statistically significant.

Table S2. Intent-to-treat analysis (n = 231). Factorial analysis of main effects, interactions and least squares means at 24 months of an intent-to-treat sample created by the principle of last value carried forward. Responses of periodontal surgery (SURG), systemically administered amoxicillin and metronidazole (SMA) and locally delivered tetracycline (LTC) on probe measurement change at sites with pockets $\geq$5 mm from baseline to 24 months. CAL1, PPD1 and BOP1 are baseline values of CAL, probing pocket depth and bleeding on probing respectively. Compared with the analysis of Table 3, the error terms are larger and the p-values of significant differences were smaller. The interpretation of results are comparable considering that 68% (30/44) of dropouts were scheduled to receive surgery, but did not.

Table S3. Baseline differences of clinical parameters between subjects who dropped out of the study (n = 44) and those included in analysis (n = 187). Mean values and standard deviations are in millimetres (mm) and percentage of sites (%). No differences were statistically significant except for baseline redness which was found in 66.2% of included subjects and 84.4% of subjects that dropped out.

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Clinical Relevance

Scientific rationale for the study: Many adjuncts appear to benefit periodontal therapy, but have not been compared under common protocol.
Principal findings: Amoxicillin + metronidazole provided CAL gain and PPD reduction. Locally delivered tetracycline had no statistically significant effects. Periodontal surgery provided PPD reduction, but was not associated with CAL gain.
Practical implications: Treatment of periodontitis may be improved by systemic antibiotic inclusion, but potential benefits have to be weighed in relation to the risks of potential adverse events and antimicrobial resistance. Smoking reduced clinical responses to all therapies.