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Controlled-delivery chlorhexidine chip *versus* amoxicillin/metronidazole as adjunctive antimicrobial therapy for generalized aggressive periodontitis: a randomized controlled clinical trial

Doğan Kaner[1], Jean-Pierre Bernimoulin[1], Werner Hopfenmüller[2], Bernd-Michael Kleber[1] and Anton Friedmann[1]

[1]Institute for Periodontology and Synoptic Dentistry; [2]Institute for Medical Informatics, Biometrics and Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany

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Abstract

Background: Subgingival application of chlorhexidine via a controlled-delivery device (CHX chip) improves the clinical outcome of scaling/root planing (SRP) in therapy for chronic periodontitis. Generalized aggressive periodontitis (GAP) is commonly treated with SRP and adjunctive antimicrobial medication. To date, the efficacy of CHX chips in GAP therapy has not been evaluated.

Aim: To compare SRP plus adjunctive CHX chip placement with SRP plus adjunctive systemic amoxicillin/metronidazole with regard to clinical efficacy in first-line therapy for GAP.

Material and Methods: Thirty-six GAP patients were treated with SRP and randomly with either placement of CHX chips or systemic amoxicillin/metronidazole. Clinical attachment level (CAL), probing depth (PD), bleeding on probing (BoP) and suppuration (Pus) were measured at baseline, 3 and 6 months after therapy.

Results: CAL, PD, BoP and Pus were significantly reduced in both groups after 3 months. In the CHX chip group, PD significantly increased again between 3 and 6 months. Finally, amoxicillin/metronidazole patients presented significantly more CAL ''gain'', PD reduction and less remaining deep sites after 6 months. Pus remained detectable in CHX chip patients only.

Conclusions: In first-line non-surgical therapy for GAP, SRP plus adjunctive systemic amoxicillin/metronidazole was more efficacious in clinically relevant measures of outcome than SRP plus adjunctive placement of CHX chips.

Key words: amoxicillin/metronidazole; chlorhexidine; controlled-delivery device; generalized aggressive periodontitis; scaling/root planing

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Generalized aggressive periodontitis (GAP), a distinct clinical entity of periodontal disease, is characterized by a pronounced episodic and rapid destruction of periodontal tissues and may result in rapid and early loss of teeth (AAP 2000). Depending on the ethnic and population investigated, GAP shows a prevalence of 0.2–3.6% (Papapanou & Lindhe 1997). GAP patients display an inadequate host response to periodontopathogenic bacteria, which is due to

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increased expression of a wide variety of immunological and genetic risk factors (Takahashi et al. 2001, Kinane & Hart 2003, Meng et al. 2007). The complex interplay between these host risk factors and the periodontal microflora induces a high susceptibility to periodontal disease; yet, GAP patients appear healthy otherwise (Tonetti & Mombelli 1999, Nibali et al. 2007). Viral–bacterial interactions and environmental factors such as psychosocial stress and smoking may further promote the development of aggressive periodontal disease (Kamma & Slots 2003, Kamma et al. 2004). Loss of periodontal attachment may occur even within several weeks or months and is characterized by typical clusters of horizontal bone loss combined with deep vertical defects (Page et al. 1983).

Owing to the high susceptibility of the host, the standard therapy for GAP consists of mechanical treatment [scaling/root planing (SRP), and/or periodontal surgery] and adjunctive antimicrobial medications, followed by rigorous supportive periodontal therapy (SPT) (Tonetti & Mombelli 1997, AAP 2000). SRP combined with administration of systemic antibiotics as adjunctive antimicrobial therapy has shown a favourable clinical and microbiological outcome in GAP patients, when compared with SRP alone (Sigusch et al. 2001). In general, it is assumed that patients exhibiting aggressive periodontitis in particular benefit from adjunctive systemic antibiotic therapy (Herrera et al. 2002, Haffajee et al. 2003). Especially, the combination of mechanical therapy and systemic application of amoxicillin and metronidazole combined has been shown to resolve periodontal inflammation effectively in GAP patients (Guerrero et al. 2005), with stability of the improved clinical attachment documented for up to 5 years (Buchmann et al. 2002). Primarily, amoxicillin/metronidazole had been introduced as a specific treatment for periodontal infections with a detected presence of the periodontal pathogen *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*) (van Winkelhoff et al. 1989). However, this drug regimen is more efficacious than the respective single drugs or placebo, even if empirically prescribed without diagnostic identification of detectable pathogens in patients exhibiting advanced periodontal disease (Rooney et al. 2002). Accordingly, amoxicillin/metronidazole is considered to be an antibiotic regimen of first choice and is used widely (Slots & Ting 2002, Addy & Martin 2003).

Despite the proven clinical efficacy of adjunctive systemic antibiotics in GAP therapy, some critical issues regarding the use of antibiotics remain in general. The widespread use of antibiotics in medicine – often without a rational base – together with the massive abuse of antibiotics in food production has led to an increasing prevalence of bacterial resistances (Quirynen et al. 2003). Likewise, patients from countries with high prescription rates and low compliance exhibit more resistant bacteria than patients from countries with a low antibiotic consumption (Voss et al. 1994, Pradier et al. 1997), a finding that has also been obtained for periodontal bacteria (Herrera et al. 2000, van Winkelhoff et al. 2000). Unsure patient compliance and a variety of interactions and side effects, ranging from uncomfortable but harmless disturbances of physiology to life-threatening manifestations of hypersensitivity and allergies, further advocate a limitation of the use of antibiotics and the consideration of alternative strategies (Addy & Martin 2003).

Chlorhexidine is an antiseptic agent with antimicrobial properties against a broad spectrum of oral bacteria (Stanley et al. 1989). Chlorhexidine digluconate shows a high clinical efficacy in supragingival plaque control and is generally considered to be safe (Addy 1997). Although some bacteria have acquired mechanisms for elimination of various biocides (Levy 2002), there is – to our knowledge – no clinical evidence for increasing resistance or change of susceptibility of periodontal bacteria to chlorhexidine.

For subgingival application of chlorhexidine as an adjunct to SRP, a biodegradable controlled-delivery device is available. After placement, the chip establishes a subgingival antibacterial concentration of chlorhexidine for at least 7 days with a peak of 2007 μg/ml chlorhexidine in gingival crevicular fluid after 2 h and still more than 125 μg/ml after 1 week (Soskolne et al. 1998), which is above the known minimal inhibitory concentrations (MIC 90) of various pathogenic periodontal bacteria in planktonic culture (Stanley et al. 1989).

In therapy for chronic periodontitis, the treatment effect of SRP is significantly enhanced by additional subgingival chlorhexidine chip placement. Randomized controlled clinical studies demonstrated at sites with chlorhexidine chip placement significantly more probing depth (PD) reduction and ''gain'' of clinical attachment maintained up to 9 months after SRP (Soskolne et al. 1997, Jeffcoat et al. 1998). Continuous significant reduction of PDs was found over a 2-year observation period as a result of repeated chip application in supportive periodontal care, indicating that adjunctive use of the chlorhexidine chip may be an effective treatment option for long-term management of chronic periodontitis (Soskolne et al. 2003).

With regard to the efficacy of local adjunctive antimicrobial therapy in general, it has been recognized that a variety of local delivery devices, irrespective of the incorporated antimicrobial agent, can offer an additional clinical benefit over SRP alone (Greenstein & Tonetti 2000). However, it is still left to clarify whether local or systemic drug delivery should be selected, whenever adjunctive antimicrobial therapy is indicated (Tonetti 1997, Greenstein 2006). Interestingly, local application of a tetracycline-loaded fibre as an adjunct to SRP has shown clinical efficacy similar to SRP combined with systemic administration of amoxicillin/clavulanic acid in GAP patients (Purucker et al. 2001). Hence, both local and systemic drug delivery can be effective in patients exhibiting severe generalized periodontal disease. This finding, paired with the goal of restricted antibiotics consumption, indicates that antimicrobial treatment of GAP with the chlorhexidine chip may be of clinical interest. Likewise, the efficacy of systemic amoxicillin/metronidazole has not yet been compared with application of antimicrobial drugs by means of local drug delivery with controlled-delivery devices. Thus, the aim of this study was to compare SRP plus adjunctive controlled-delivery chlorhexidine chip with SRP plus adjunctive systemic amoxicillin/metronidazole,

with regard to clinical efficacy in the first-line therapy for GAP.

For scientific purposes, a ''negative control'' group treated merely with SRP, but without antimicrobial medication, may appear to be desirable. The superiority of adjunctive antimicrobial therapy over ''SRP alone'' is, however, well documented for severe GAP and is clinically relevant to these patients (Sigusch et al. 2001, Guerrero et al. 2005). A less effective treatment should not be carried out in a clinical trial, as withholding a superior treatment may raise problems of ethics, acceptability and feasibility (ICH 2000). Therefore, a ''negative control'' group without adjunctive antimicrobial therapy has not been included in the protocol.

Material and Methods

Experimental design

This study was a randomized controlled, parallel-design, single-blinded clinical trial with an observation period of 6 months. The study protocol was approved by the Institutional Ethics Committee of the Charité – Universitätsmedizin Berlin. Written informed consent was obtained from each patient. The study was conducted in accordance with the guidelines of Good Clinical Practice (GCP-ICH) and the principles of the Declaration of Helsinki.

Study patients

Patients with previously untreated advanced GAP were recruited from patients referred to the Institute for Periodontology and Synoptic Dentistry, Charité – Universitätsmedizin Berlin. Patients were included if they were between 18 and 40 years of age, presented at least 20 teeth and showed clinical attachment loss and PD of at least 6 mm at least at two sites of a minimum of 12 teeth at the screening examination. At least three teeth apart from first molars and incisors had to be involved. Exclusion criteria included pregnancy, lactation period, allergy to medications used in the study, intake of antibiotics or anti-inflammatory drugs in the previous 6 months, a history of systematic periodontal therapy and any condition requiring premedication before dental treatment. Patients were recruited between May 2001 and January 2003. The follow-up was completed in October 2003.

Hygiene phase

After recruitment, all patients passed a hygiene phase with detailed case presentation, supragingival scaling, polishing and repeated oral hygiene instructions. These sessions were repeated until sufficient plaque control, indicated by an approximal space plaque index (API, Lange et al. 1977) of $<30\%$, had been established and the patient qualified for the baseline examination.

Clinical measurements

Clinical parameters were measured at baseline, 3 and 6 months after therapy at all present teeth. PD and recession were measured at six sites per tooth to the nearest 0.2 mm by means of an automated periodontal probe equipped with a handpiece to detect the cemento-enamel junction and a constant probing force of 0.2 N (Florida Probe with ''PASHA'' probe (Pressure-controlled, Automated, Standardised Handpiece), Florida Probe Corporation, Gainesville, FL, USA). PD was automatically measured as the distance from the probe tip inserted into the bottom of the ''pocket'' to the probe flange gently touching the gingival margin. Gingival recession was measured as the distance from the gingival margin to a reference point (cemento-enamel junction or restoration margin, when appropriate) after the probe flange had been drawn back to the reference point. The clinical attachment level (CAL) of each site was calculated as the sum of PD and recession.

Bleeding on probing (BoP) and suppuration (Pus) were recorded dichotomously as present or absent for each site after probing of the respective quadrant. Oral hygiene performance was measured by recording of the API.

Investigator calibration

For exercising reliable use of the automated probe, the single designated examiner (D.K., study investigator) measured full-mouth PD and gingival recession of five non-study subjects exhibiting chronic periodontitis (2), GAP (2) and localized aggressive periodontitis (1). CAL was calculated as the sum of PD and recession after measurements. For assessment of intra-examiner reproducibility, a periodontal status with subsequent calculation of CAL was measured on a manikin used for periodontal education (Periodontology Model A-PB, Frasaco, Tettnang, Germany) on two consecutive days. The percentage of agreement $\pm$ 1 mm between repeated measurements at single sites was 92% for PD and 81% for calculated CAL.

Scaling/root planing

Following the baseline examination, SRP was performed quadrant per quadrant under local anaesthesia in four visits at all sites exhibiting a PD $\geqslant$ 4 mm. SRP was completed within at most 10 days. Freshly sharpened Gracey curettes (A. Deppeler, Geneva, Switzerland) and a piezo-magnetic ultrasonic scaler (Piezon Master 400, EMS, Nyon, Switzerland) were used in combination and without a time limit until the root surface felt smooth and clean to an explorer tip (EXD 11/12, Hu-Friedy, Leimen, Germany). During SRP, sites were repeatedly irrigated with H_2O_2 (3%) to reduce bleeding and to wash out debris. Finally, the gingiva was compressed with moistened cotton rolls to minimize the coagulum. The treatment of a quadrant lasted between 75 and 90 min. During the SRP phase, the patients were advised to rinse two times daily for one minute with 15 ml of a 0.2% chlorhexidine digluconate solution (Chlorhexamed forte, GSK, Munich, Germany). Ibuprofen 400 mg (ratiopharm, Ulm, Germany) was prescribed as an analgesic. At the post-treatment control 1 week after conclusion of SRP, teeth were supragingivally scaled and polished and patients received oral hygiene instructions again. Subsequently, the patients were allocated either to the chlorhexidine chip group (test) or the amoxicillin/metronidazole group (control).

Randomization, allocation concealment and study medication

A randomization table was generated with block randomization (four-unit block size). Using the table, treatment assignments were distributed to numbered opaque envelopes before commencement of the study. Subject numbers were assigned in ascending order at completion of SRP. The envelope containing the treatment allocation was opened by the study coordinator after transfer of the patient with the corresponding number by the blinded study investigator at the conclusion of

the 1 week post-treatment control visit. Control patients received amoxicillin/metronidazole combined (amoxicillin 500 mg, metronidazole 250 mg, one of each every 8 h for 10 days). In test patients, the study coordinator inserted chlorhexidine chips (PerioChip, Perio Products Ltd., Jerusalem, Israel) into every site with a baseline PD $\geqslant$ 5 mm (but at most two per tooth): quadrant after quadrant was isolated with cotton rolls and dried with suction. The chosen site was air-dried with the dental unit's syringe and a chlorhexidine chip was inserted into the dried ''pocket'' with a forceps and gently pushed to the bottom of the ''pocket''. The chip was adjusted to size with a scalpel, if necessary.

All treatment procedures and measurements were performed by the same calibrated, trained and blinded study investigator (D.K.) in a standardized manner. The study coordinator (A.F.) was not involved in the course of treatment. All issues regarding study medications including application of the chlorhexidine chip, administration of amoxicillin/metronidazole and survey of adverse events were solely managed by the study coordinator. In advance of each visit, patients were advised to respect the investigator's blinding.

SPT

At the control visits 3 and 6 months after SRP and medication, patients received routine SPT consisting of clinical measurements, supragingival scaling, polishing of all teeth and oral hygiene instructions. Root planing was performed at BoP-positive sites with a PD of 4 mm and at sites exhibiting a PD $\geqslant$ 5 mm. Anaesthesia was used, when demanded. After completion of the 3-month SPT visit, patients were again consigned to the study investigator. In test patients, insertion of the chlorhexidine chip was repeated at sites with remaining PD $\geqslant$ 5 mm. SPT after 6 months was performed without chip placement, as the observation period was completed. One week before both 3-month and 6-month SPT visits, supragingival scaling, polishing of all teeth and oral hygiene instructions were carried out to minimize measurement errors due to newly formed calculus and to avoid false-positive BoP results due to sole sulcular bleeding.

Evaluation of Adverse Events and Compliance

Adverse events in both groups and the compliance of control patients were evaluated by the study coordinator by telephone. Appointments were scheduled only in case of a need for an intervention.

Data presentation and statistical analysis

Probing data were exported from the database of the electronic probe to Excel (MS Excel 2000, Microsoft Corporation, Redmond, WA, USA) by means of an export software program (Data Downloader, Florida Probe Corporation, Gainesville, FL, USA). After other data had been added, the database was imported into a statistical software program, locked and analysed (SPSS 12.0 for Windows, SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used for evaluation of data distribution. According to the non-normal distribution found (data not shown), non-parametric statistics were performed. Medians and inter-quartile ranges (IQ) were calculated for full-mouth PD and CAL (mm) as well as for API, BoP and Pus (%). Additionally, medians for PD and CAL were calculated for all single-rooted teeth (incisors, lower premolars and upper second premolars) and all multi-rooted teeth (upper first premolars and molars) of the subject, respectively. Within patients, sites were grouped into three categories according to their baseline PD: shallow (0–3.4 mm), moderate (3.6–5.4 mm) and deep (5.6 mm and more). For longitudinal comparisons within groups, Wilcoxon's signed rank test was used. The Mann–Whitney U test was applied for comparisons of variables and their changes between treatment groups. Statistical significance was defined as a $p < 0.05$. The primary outcome measure was PD-reduction/subject. Secondary outcomes included ''gain'' of CAL; reductions of API, BoP and Pus; change of proportions of shallow, moderate and deep sites; differential outcome of single-rooted and multi-rooted teeth; and evaluation of adverse events.

Sample size calculation

According to a systematic review (Herrera et al. 2002), adjunctive systemic antibiotics may result in an additional reduction of approximately 0.5 mm (range of 0.06–0.6 mm) for mean full-mouth PD, when compared with SRP alone. For this reason, a difference of 0.5 mm between groups for mean full-mouth PD reduction after 6 months was considered to be clinically relevant. Assuming 0.5 mm as the common standard deviation of full-mouth PD change within both groups, 16 patients per treatment group would provide 80% power to detect a true difference. To compensate for eventual drop-outs, 18 patients were recruited per treatment group.

Results

Patients

Forty-one subjects were recruited into the study. Five patients had to be excluded after enrolment while passing the hygiene phase (one subject: insufficient oral hygiene performance; four subjects: intake of antibiotics for other medical reasons). Random assignment resulted in 18 patients with a median age of 37 years (range 21–39 years) in the test group and 18 patients with a median age of 38 years (range 21–39 years) in the control group. Detailed patient characteristics are shown in Table 1. Figure 1 shows the course of patients through the study protocol.

In the test group, 29 chlorhexidine chips per patient (range from 16 to 47) were placed after SRP. At the SPT visit after 3 months, a significantly lower number of chlorhexidine chips was applied (10 chips per patient, range from 2 to 26, $p \leqslant 0.001$, Wilcoxon's signed rank test).

Full-mouth median values for clinical parameters

The changes of clinical parameters throughout the study period are shown in Table 2 for full-mouth PD and, separately, for PD of single-rooted and multi-rooted teeth, respectively. Changes of full-mouth CAL and of CAL of single-rooted and multi-rooted teeth, respectively, are presented in Table 3. At baseline, similarly elevated values/patient for CAL and PD were found in both groups. Three months after SRP and medication, both the test and control group showed markedly improved periodontal conditions as revealed by significant reductions of full-mouth PD and full-mouth CAL. At 6 months, the difference to baseline was

Table 1. Patient characteristics at baseline

Parameter	Test group ($n = 18$)	Control group ($n = 18$)	p-value (Mann–Whitney U test)
Age (median)	37	38	0.389
Range	21–39	21–39	
Females (%)	61	56	0.791
Smokers (%)	39	61	0.265
Number of teeth (median)	26.5	27	0.501
Range	20–28	20–28	
Full-mouth PD (median)	3.71	4.13	0.279
Inter-quartile range	3.20, 4.30	3.46, 4.83	
Full-mouth CAL (median)	4.57	4.52	0.443
Inter-quartile range	3.82, 5.29	4.06, 5.72	
API (median %)	27	23	0.134
Inter-quartile range	21–30	18–27	
BoP (median %)	48	46	0.988
Inter-quartile range	32, 55	30, 56	
Pus (median %)	10	4	0.097
Inter-quartile range	4–13	1–8	

PD, probing depth; CAL, clinical attachment level; API, approximal space plaque index; BoP, bleeding on probing.

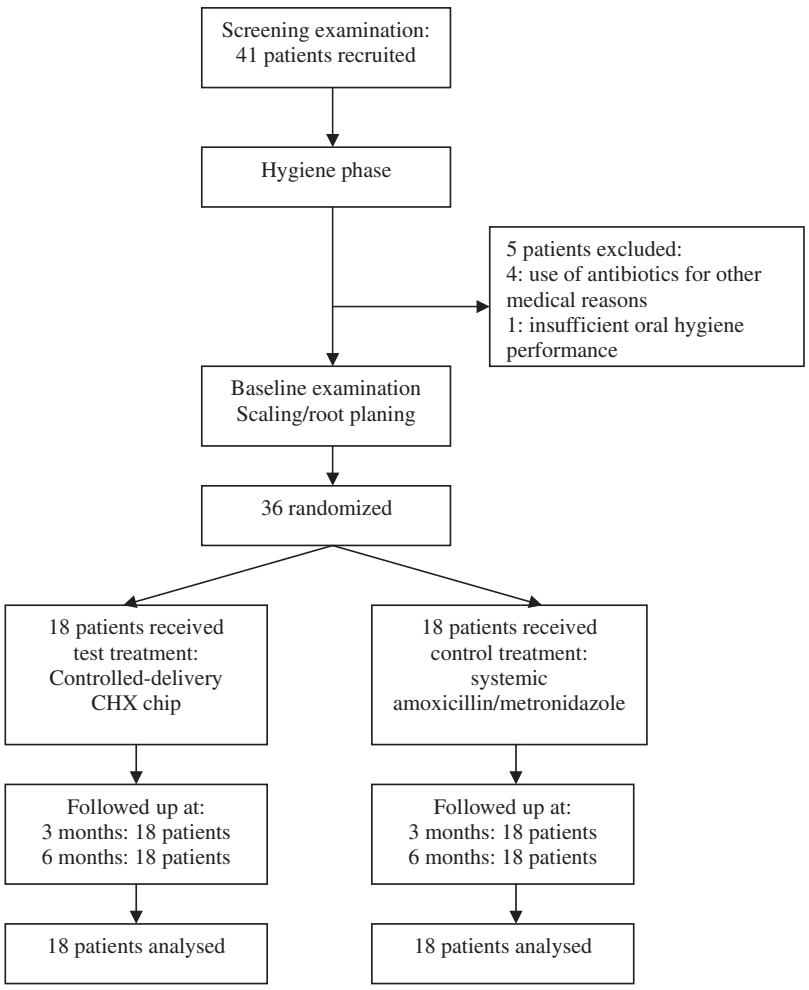

Fig. 1. Flow diagram of study outline.

also significant within both groups. After 3 months, change of full-mouth PD did not differ significantly between the two groups ($p > 0.05$). However, at that time change of full-mouth CAL was significantly higher in the control group (difference between groups: 0.23 mm; $p < 0.05$). Between 3 and 6 months, full-mouth PD significantly increased again in the test group (0.10 mm, IQ 0.0, 0.12; $p = 0.013$). A concomitant significant decrease of full-mouth PD was observed in control patients (– 0.06 mm; IQ – 0.20, – 0.01; $p = 0.021$), finally yielding in 0.66 mm greater reduction of full-mouth PD in the control group at the end of the observation period ($p < 0.001$, Table 2). Regarding full-mouth CAL, no further significant changes were observed within the treatment groups between months 3 and 6. Six months after SRP and medication, the test group presented 0.34 mm less ''gain'' of full-mouth CAL than the control group ($p < 0.01$, Table 3).

Proportions of shallow, moderate, and deep sites

Table 4 displays the proportions of different PD categories (median percentage and IQ) at baseline and their changes after 3 and 6 months. At baseline, all sites were similarly distributed among shallow, moderate and deep categories in both groups. The increase of shallow sites and the decrease of moderate and deep sites between baseline and 3 months were similar in both groups and not significantly different. However, between three and 6 months, a significant decrease of shallow sites was found within the test group (– 2.3%; IQ – 5.6, 0.1; $p = 0.014$), making the change between 3 and 6 months significantly different, favouring the control group ($p < 0.01$). Furthermore, test patients exhibited significantly higher proportions of deep sites after 6 months ($p < 0.05$).

Single-rooted *versus* multi-rooted teeth

A separate analysis of single-rooted and multi-rooted teeth was performed (Tables 2 and 3). Within the treatment groups, significant PD and CAL changes were found for baseline and 3 months as well as for baseline and 6 months for both single-rooted and multi-rooted teeth. For single-rooted teeth, PD reduction was similar in both groups, when

Table 2. Probing depth and probing depth (PD) changes (Medians and inter-quartile ranges)

Variable	Group	Baseline (0 months)	Difference between 0 and 3 months	Difference between 3 and 6 months	Difference between 0 and 6 months	*p*-value Wilcoxon's signed rank test		
						change 0–3 months	change 3–6 months	change 0–6 months
Full-mouth median PD	Test	3.71 (3.20, 4.30)	−1.30 (−1.61, −0.90)	0.10 (0.0, 0.12)	−1.25 (−1.51, −0.68)	<0.001	0.013	<0.001
	Control	4.13 (3.46, 4.83)	−1.92 (−2.10, −1.07)	−0.06 (−0.20, −0.01)	−1.91 (−2.17, −1.24)	<0.001	0.021	<0.001
Difference between groups			0.62	0.16**	0.66***			
Median PD of single-rooted teeth	Test	3.57 (3.14, 4.20)	−1.40 (−1.61, −0.92)	0.02 (−0.06, 0.08)	−1.42 (−1.42, −0.77)	<0.001	0.446	<0.001
	Control	3.86 (3.17, 4.91)	−1.78 (−2.25, −0.99)	−0.07 (−0.31, −0.02)	−1.84 (−2.57, −1.13)	<0.001	0.010	<0.001
Difference between groups			0.38	0.09**	0.42*			
Median PD of multi-rooted teeth	Test	3.97 (3.55, 4.73)	−1.31 (−1.56, −0.80)	0.20 (0.04, 0.39)	−1.12 (−1.38, −0.66)	<0.001	0.001	<0.001
	Control	4.39 (3.77, 4.92)	−1.45 (−2.19, −1.20)	−0.04 (−0.13, 0.04)	−1.69 (−2.22, −1.29)	<0.001	0.134	<0.001
Difference between groups			0.14	0.24***	0.57**			

*Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.05$).
**Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.01$).
***Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.001$).

Table 3. Clinical attachment level and clinical attachment level (CAL) changes (Medians and inter-quartile ranges)

Variable	Group	Baseline (0 months)	Difference between 0 and 3 months	Difference between 3 and 6 months	Difference between 0 and 6 months	*p*-value Wilcoxon's signed rank test		
						change 0–3 months	change 3–6 months	change 0–6 months
Full-mouth median CAL	Test	4.57 (3.82, 5.29)	−0.61 (−0.80, −0.32)	0.02 (−0.08, 0.31)	−0.45 (−0.84, −0.11)	<0.001	0.223	0.001
	Control	4.52 (4.06, 5.72)	−0.84 (−1.38, −0.59)	−0.02 (−0.21, 0.12)	−0.79 (−1.29, −0.67)	<0.001	0.760	<0.001
Difference between groups			0.23*	0.04	0.34**			
Median CAL of single-rooted teeth	Test	4.43 (3.63, 5.47)	−0.44 (−0.89, −0.19)	0.05 (−0.08, 0.42)	−0.41 (−0.88, −0.07)	<0.001	0.184	0.003
	Control	4.49 (3.73, 5.86)	−0.83 (−1.24, −0.48)	0.12 (−0.09, 0.29)	−0.72 (−0.97, −0.49)	<0.001	0.344	<0.001
Difference between groups			0.39*	0.07	0.31*			
Median CAL of multi-rooted teeth	Test	4.91 (3.98, 5.32)	−0.45 (−0.91, −0.15)	0.13 (−0.07, 0.53)	−0.30 (−0.65, −0.14)	0.001	0.068	0.006
	Control	4.94 (4.04, 6.05)	−0.87 (−1.21, −0.60)	−0.02 (−0.21, 0.14)	−0.82 (−1.28, −0.67)	<0.001	0.811	<0.001
Difference between groups			0.42**	0.15	0.52***			

*Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.05$).
**Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.01$).
***Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p<0.001$).

Table 4. Proportions of probing depth (PD) categories and their changes at baseline and 3 and 6 months after therapy (Medians of percentage and inter-quartile ranges)

	Group	Proportions at baseline	Difference between 0 and 3 months	Difference between 3 and 6 months	Difference between 0 and 6 months	Proportions after 6 months	*p*-value Wilcoxon's signed rank test		
							difference between 0 and 3 months	difference between 3 and 6 months	difference between 0 and 6 months
Shallow (PD ⩽ 3.4 mm)	Test	49.8 (33.8, 64.5)	30.2 (19.6, − 39.2)	− 2.3** (− 5.6, 0.1)	26.2* (19.2, 35.3)	77.2 (71.5, 89.5)	< 0.001	0.014	< 0.001
	Control	44.8 (26.6, 60.1)	35.6 (26.4, 48.0)	0.3** (− 0.8, 6.0)	41.8* (27.2, 50.2)	87.8 (75.1, 93.3)	< 0.001	0.164	< 0.001
Moderate (PD 3.6–5.4 mm)	Test	24.5 (19.2, 38.2)	− 9.9 (− 18.7, 0.2)	0.6 (− 1.8, 5.7)	− 9.0 (− 14.8, − 1.0)	19.2 (10.5, 24.3)	0.005	0.125	0.004
	Control	26.7 (21.5, 37.1)	− 10.4 (− 21.1, − 1.7)	− 0.4 (− 5.1, 1.8)	− 11.9 (− 19.1, − 1.8)	11.6 (6.7, 24.7)	0.003	0.099	0.001
Deep (PD ⩾ 5.6 mm)	Test	20.8 (12.8, 29.7)	− 19.2 (− 26.7, − 12.5)	0.7 (− 0.6, 1.5)	− 18.3 (− 24.5, − 11.6)	2.6* (0.6, 5.2)	< 0.001	0.066	< 0.001
	Control	22.7 (16.4, 44.3)	− 21.8 (− 38.4, − 15.9)	0.0 (− 0.75, 0.15)	− 22.4 (− 42.1, − 15.5)	0.6* (0, 1.8)	< 0.001	0.442	< 0.001

*Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p < 0.05$).
**Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p < 0.01$).

Table 5. Approximal space plaque index, bleeding on probing (BoP) and suppuration (Pus) at baseline and their changes (Medians and inter-quartile ranges)

Variable	Group	Baseline (0 months)	3 months	6 months	*p*-value Wilcoxon's signed rank test		
					change 0–3 months	change 3–6 months	change 0–6 months
Approximal space plaque index (API, %)	Test	27 (21, 30)	35* (24–38)	30** (22–36)	0.043	0.184	0.036
	Control	23 (18–27)	18* (9–35)	18** (10–25)	0.527	0.043	0.024
Bleeding on probing (BoP, %)	Test	48 (32–55)	23 (19–43)	24 (17–34)	0.001	0.077	< 0.001
	Control	46 (30–56)	22 (17–29)	19 (16–23)	< 0.001	0.097	0.097
Suppuration (Pus, %)	Test	10 (4, 13)	0 (0, 1)	1** (0, 1)	0.001	0.070	0.001
	Control	4 (1, 8)	0 (0, 0)	0** (0, 0)	0.001	1	0.001

*Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p < 0.05$).
**Significant difference between groups favouring control treatment (Mann–Whitney *U* test, $p < 0.01$).

compared after 3 months. While, in the test group, no further change was observed for single-rooted teeth, control patients presented an ongoing PD reduction between 3 and 6 months ($p = 0.01$). This change significantly favoured the control group ($p < 0.01$). Therefore, a significant difference of 0.42 more PD reduction at single-rooted teeth of control patients was noted at the end of the study ($p < 0.05$). Regarding CAL changes, differences between treatment groups were significant already after 3 months at both single-rooted and multi-rooted teeth and favoured the control group (Table 3). Between 3 and 6 months, no further CAL changes were found for single-rooted teeth of both groups and for multi-rooted teeth of control subjects. There was a trend for multi-rooted teeth of test patients to loose some clinical attachment again ($p = 0.068$). Finally, the CAL ''gain'' of the control group after 6 months was significantly higher for both single-rooted and multi-rooted teeth, the latter showing a highly significant difference of 0.52 mm ($p < 0.001$). An analogous difference was detected regarding PD reduction at multi-rooted teeth. Between 3 and 6 months, no further PD change occurred within the control group ($p = 0.134$). However, a highly significant increase of PD of multi-rooted teeth was found in the test patients (0.20 mm; IQ 0.04, 0.34; $p < 0.001$), yielding in 0.57 mm greater PD reduction for control patients after 6 months ($p < 0.001$).

Oral hygiene, BoP and suppuration

After completion of the hygiene phase, both groups presented similarly low plaque levels (API) at baseline (Tables 1 and 5). Test group patients maintained their oral hygiene performance without significant changes throughout the observation period. An additional significant improvement of API was found in the control group only. After 6 months, the control group showed a significantly decreased API level compared with the test group (Table 5, $p = 0.002$).

Alterations of bleeding score (BoP) and suppuration (Pus) are shown in Table 5. Reduction of BoP frequency was similar in both groups (Table 5). Some sites with remaining suppuration were found in test patients, whereas suppuration was completely eliminated in the control group ($p = 0.018$, Table 5).

Smoking

Analysis with regard to antimicrobial treatment did not reveal any significant differences between smokers and non-smokers, apparently because the number of smoking and non-smoking patients per treatment group was too low (data not shown). Analysis of pooled data of both groups revealed significantly greater full-mouth PD reduction in non-smokers after 6 months (0.11 mm, $p < 0.001$, Mann–Whitney *U* test). Full-mouth ''gain'' of CAL was not significantly different between non-smokers and smokers at any point in time (data not shown). After 6 months, non-smokers presented significantly higher proportions of shallow sites (91.4%, IQ 84.8, 94.6 *versus* 75.3%, IQ 65.5, 78.3; $p < 0.001$, Mann–Whitney *U* test). In smokers, significantly higher proportions of moderate sites (22.2%, IQ 18.0, 30.7 *versus* 8.7%, IQ 4.9, 14.3; $p < 0.001$, Mann–Whitney *U* test) and deep sites (2.5%, IQ 1.2, 4.0 *versus* 0.6%, IQ 0.0, 0.83; $p = 0.008$, Mann–Whitney *U* test) were found after 6 months.

Adverse events and compliance

Five patients (27.8%) of the control group complained about gastrointestinal disturbances (diarrhoea) during or following the study drug regimen, but none had to stop the intake of medication. No other side effects were noted for the control group. One control patient declared leftover of four pills of each amoxicillin and metronidazole, whereas 17 subjects reported full completion of the antibiotic regimen.

Local adverse events occurred in the test group only. Nine patients (50%) complained about discomfort, soreness of gingival tissues and pain after the insertion of chlorhexidine chips at first medication. Gingival swelling, redness and gingival exudation were noted, but disappeared after 3–7 days without therapeutic intervention. Symptomatic treatment consisted of prescription of an analgesic (Ibuprofen). Following SPT after 3 months, one periodontal abscess occurred 5 days after the repeated application of a chlorhexidine chip. Treatment consisted of scaling/root planing under local anaesthesia and concomitant subgingival irrigation with H_2O_2 (3%).

Discussion

The aim of this controlled, randomized and single-blinded clinical study was to compare the clinical effects of a controlled-delivery chlorhexidine chip and systemic amoxicillin/metronidazole, respectively, as adjuncts to non-surgical therapy in generalized aggressive periodontitis patients. Three months after SRP, marked and significant improvements in PD, CAL, BoP and Pus were noted in both groups. PD changes and reductions of bleeding sites of test and control patients were similar, whereas CAL ''gain'' was significantly better for the control group already at that time. Pus was completely eliminated in control patients, but test patients still exhibited suppurating sites.

Although the maximum benefits of SRP with or without adjunctive antimicrobials are generally expected to occur within the first 3 months after treatment (Badersten et al. 1984, Pavicic et al. 1994, Berglundh et al. 1998), a continuous improvement in full-mouth PD over the whole observation period of 6 months was found in the amoxicillin/metronidazole group. Differentiation according to root morphology type revealed a substantial contribution of single-rooted teeth to the ongoing PD reduction in the control group, whereas the clinical parameters in multi-rooted teeth remained unchanged between months 3 and 6. In contrast to the control patients, full-mouth PD increased significantly between 3 and 6 months in the test group, and this was particularly caused by the highly significant deterioration noted at multi-rooted teeth (Table 2). Difficult access and complex root topography can limit the efficacy of SRP in furcation areas (Fleischer et al. 1989). Furcation sites respond less favourably to SRP, when compared with molar flat surface sites or non-molar sites (Nordland et al. 1987, Loos et al. 1989) and show a higher incidence of disease progression (Claffey & Egelberg 1994). As given by their design, the chlorhexidine chips were positioned in approximal sites only and the extent of penetration of effective levels of chlorhexidine into furcation areas is not known. Tissue levels of chlorhexidine after chip insertion have not been reported, whereas subgingival placement of a tetracycline-loaded fibre produces effective concentrations of tetracycline within periodontal soft tissues (Ciancio et al. 1992). This fact may contribute to the similar clinical outcome of tetracycline fibre therapy and systemic amoxicillin and clavulanic acid in GAP patients (Purucker et al. 2001) and indicates that the effect of the combined mechanical and antimicrobial treatment with the chlorhexidine chip may be particularly limited in sites with furcation involvement.

As a result of these divergent changes within both treatment arms between 3 and 6 months, significantly higher PD reduction and ''gain'' of CAL were noted for amoxicillin/metronidazole patients at the end of the study. This observation proved valid for the full-mouth values as well as for the subgroups of single- and multi-rooted teeth. Consequently, the proportions of deep sites were significantly higher in test patients after 6 months, whereas control patients presented significantly more shallow sites.

It is well established that measures of outcome of periodontal therapy can estimate periodontal stability or future disease progression (Renvert & Persson 2002). Higher proportions of remaining deep sites and persistent suppuration indicate lack of periodontal stability and are clinically relevant for treatment planning. In addition, increases in PD – as noted in the chlorhexidine chip group combined with persisting suppurating sites – are considered to be the strongest predictor for future attachment loss (Badersten et al. 1990, Claffey et al. 1990). As a result of such coherence, the proportion of remaining deep sites is regularly used as an indicator for the need of additional periodontal surgery (Loesche et al. 1991, 1992) and this interrelation strengthens the clinical relevance of the superior clinical efficacy of amoxicillin/metronidazole in the present study.

Smoking had a significant effect on the clinical outcome, irrespective of the adjunctive antimicrobial treatment provided. After 6 months, full-mouth PD reduction was significantly higher in non-smokers than in smokers. Likewise, non-smokers presented less moderate and deep sites after 6 months, whereas smokers exhibited a significantly lower proportion of shallow sites. Such differential response of smokers and non-smokers to non-surgical therapy has repeatedly been reported for periodontitis patients in general (Labriola et al. 2005, Heasman et al. 2006). In addition, our findings confirm results regarding the effect of smoking on the clinical outcome of non-surgical therapy for GAP in particular (Guerrero et al. 2005, Hughes et al. 2006a).

After completion of the hygiene phase, plaque levels were similarly low

in both groups and were maintained at a low level throughout the study, indicating good oral hygiene performance of all patients and successful re-motivation and instruction in supportive periodontal care. Interestingly, there was a further continuous decrease of supragingival plaque measures in the amoxicillin/metronidazole group only. The chlorhexidine chip group did not show further significant changes of plaque levels after baseline and finally, the control group presented significantly less supragingival plaque after 6 months. As most studies do not suggest a persistent effect of systemic antibiotics on formation of supragingival plaque (for review: see Slots & Ting 2002), it may be argued that better oral hygiene by chance could have contributed to the significantly better clinical outcome regarding PD reduction and ''gain'' of clinical attachment in amoxicillin/metronidazole patients. However, significant changes of PDs and CALs are unlikely to occur following improvements of self-performed oral hygiene (Cercek et al. 1983, Westfelt et al. 1998), because improved oral hygiene alone only marginally affects the subgingival microflora (Loos et al. 1988). On the contrary, it has repeatedly been shown that gingival as well as periodontal inflammation increase de novo supragingival plaque formation (Quirynen et al. 1991, Ramberg et al. 1994, 1995, Rowshani et al. 2004), as the amplification of gingival crevicular fluid flow facilitates both nutrient supply and attachment of bacteria to the dental pellicle (Rudiger et al. 2002). In this regard, continuous periodontal improvements in the amoxicillin/metronidazole group may have been reflected by diminished supragingival plaque formation and measures.

The highest evidence for a significant clinical benefit of the chlorhexidine chip as an adjunct to SRP comes from two large-scale multicentre trials investigating chronic periodontitis patients (Soskolne et al. 1997, Jeffcoat et al. 1998). Six months after initial therapy, reductions of mean PD/patient of 0.89–1.16 mm had been found for SRP plus chip placement and of 0.65–0.72 mm for SRP alone, respectively. CAL ''gain'' ranged from 0.47 to 0.74 mm for the chip groups and from 0.31 to 0.7 mm for SRP alone. Finally, significant additional PD reductions of 0.17–0.46 mm and – in one study – an additional CAL ''gain'' of 0.16 mm favouring the chlorhexidine chip groups were reported. Although statistically significant, these additional benefits appear rather small from a clinical point of view and clinical relevance has been a matter of debate (Greenstein 2006). Moreover, it should be considered that even small intergroup differences may reach statistical significance, provided the sample size is high enough (here: $n = 447$ and 118). Furthermore, a comparison of the clinical performance of the SRP-alone groups with the collective data obtained from classical studies (PD reduction on average: 1.29 mm for moderately deep sites; for details see Cobb 1996) indicates that the clinical outcome of the control groups of these two chlorhexidine chip studies was below the expected average. A recent systematic review has related this observation to the comparatively short time applied for SRP (full-mouth treatment time: 1 h) (Cosyn & Wyn 2006).

Chlorhexidine per se is a potent antimicrobial drug and inhibits the growth of periodontal bacteria in vitro at concentrations that may be achieved by controlled delivery via the chlorhexidine chip in vivo (Stanley et al. 1989, Soskolne et al. 1998). To our knowledge, the microbiological effect of the chlorhexidine chip as an antimicrobial adjunct to SRP has been investigated in two controlled clinical trials only (Daneshmand et al. 2002, Grisi et al. 2002). Unfortunately, neither study was able to detect a significant additional antimicrobial effect of the chlorhexidine chip, when compared with meticulous SRP alone. This remains in contrast to the well-documented clinical and microbiological efficacy of adjunctive systemic antibiotics in general and amoxicillin/metronidazole in particular. Our positive clinical findings for the control group are in line with other studies investigating SRP combined with systemic amoxicillin/metronidazole. Especially, the striking effect on reduction of suppuration and proportions of deep sites confirms results of previous studies of therapy for advanced (but not necessarily aggressive) periodontitis (Berglundh et al. 1998, Rooney et al., 2002) and supports the suggestion that GAP patients strongly benefit from adjunctive systemic antibiotics (Herrera et al. 2002). On the other hand, it has recently been reported that SRP alone resulted in a good treatment response in GAP therapy, implicating that adjunctive antimicrobials may be indicated at most in a subgroup of GAP patients only (Hughes et al. 2006b). This challenges our finding that SRP combined with even repeated adjunctive chlorhexidine chip placement did not provide a stable clinical outcome in the same disease category, although substantially more time had been spent for mechanical treatment. Nevertheless, this discrepancy may be due to marked differences regarding disease severity, because the positive findings for SRP alone had been obtained in a cohort of GAP patients presenting a mean full-mouth PD of less than 3 mm, only 13.34% sites with a baseline PD of at least 5 mm and virtually no suppuration, which remains in contrast to the clinical presentation of the subjects investigated in the present study.

Only a few controlled clinical studies focus on the additional effects of adjunctive antimicrobials in the therapy for well-defined GAP in patients with a significant level of disease. In these reports (Purucker et al. 2001, Sigusch et al. 2001, Guerrero et al. 2005, Xajigeorgiou et al. 2006), the combination of SRP and various antibiotic regimens (including amoxicillin and clavulanic acid, tetracycline fibre, clindamycin, doxycycline, metronidazole and amoxicillin/metronidazole) resulted in full-mouth mean values of 1.0–2.3 mm for PD reduction and of 0.5–1.9 mm for ''gain'' of CAL, respectively. The results of the present control group (PD reduction: 1.91 mm; IQ -2.12, -1.24; CAL ''gain'': 0.79 mm; IQ -1.29, -0.67) appear comparable. A direct comparison of these measures of clinical treatment outcome is tempting; however, the reported clinical results are of remarkably high variability. In this regard, it should be considered that the respective study protocols differ largely with regard to the types of periodontal probes used for clinical measurements (pressure-sensitive or not), treatment intensity and sequence, time of clinical measurements (before or after subgingival instrumentation, with or without preceding hygiene phase) or the timing of drug administration. Interestingly, only the amoxicillin/metronidazole group of the present study showed a significant continuous improvement of PD, a finding that has not been reported previously. This may possibly be due to the fact that, in contrast to the other GAP trials referred to above, SPT after 3 months included subgingival instrumentation at individual need.

The variation between studies concerning the onset of adjunctive antimicrobial regimens is noticeable, as medication has been started simultaneously with SRP (Guerrero et al. 2005), 6 weeks after SRP (Xajigeorgiou et al. 2006), at supportive therapy 3 months after first-line SRP (Purucker et al. 2001) or, in the present study, 1 week after first-line SRP had been completed. It is recommended to apply systemic antibiotics immediately after completion of SRP, seeing that subgingival debridement should precede medication (Loesche & Giordano 1994). For our study, we chose to delay the onset of both test and control medication for 1 week, as a dryable, nonbleeding site is preferable for insertion of the chlorhexidine chip, given that a moistened chip may become soft and more difficult to apply (Killoy 1998). Furthermore, the antimicrobial effectiveness of chlorhexidine applied to a ''pocket'' exhibiting profound bleeding after thorough instrumentation may be reduced by partial inactivation of the cationic drug via binding to serum proteins (Roberts & Addy 1981).

After chip placement, 50% of the test patients suffered from local side effects, in contrast to the low occurrence of adverse events reported previously (Jeffcoat et al. 1998). However, we had to apply a considerably higher number of chlorhexidine chips in each test patient by reason of including severe cases of GAP only. Apparently, the high incidence of local side effects in our study was associated with the high number of chips placed.

In conclusion, our results show that SRP plus adjunctive chlorhexidine chips provided clinical improvements, but these were not maintained in full over the entire observation period. SRP plus systemic amoxicillin/metronidazole was more efficacious with regard to reduction of PDs, ''gain'' of clinical attachment and other clinically relevant improvements such as reduction in the proportion of sites considerable for additional periodontal surgery. In line with previous reports, these findings confirm the high value of systemic amoxicillin/metronidazole for adjunctive antimicrobial therapy of severe generalized aggressive periodontitis.

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Address:
Dr. Doğan Kaner
Institute for Periodontology and
Synoptic Dentistry
Campus Virchow-Klinikum
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany
E-mail: dogan.kaner@charite.de

Clinical Relevance

Scientific rationale of the study: Subgingival application of CHX chips enhances the clinical outcome of non-surgical therapy (SRP) for chronic periodontitis. The efficacy of CHX chip placement as an adjunct to SRP in generalized aggressive periodontitis patients has not been evaluated.
Principal findings: SRP plus CHX chip placement resulted in significant clinical improvements, but these were not maintained over the entire observation period. SRP plus systemic amoxicillin/metronidazole provided significantly more PD reduction, ''gain'' of clinical attachment and less remaining deep sites.
Practical implications: As an adjunct to first-line non-surgical therapy for generalized aggressive periodontitis, systemic amoxicillin/metronidazole is more efficacious than CHX chip placement.