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Abstract

Background: The specific advantage of administering systemic antibiotics during initial, non-surgical therapy, or in the context of periodontal surgery is unclear. This study assessed the differential outcomes of periodontal therapy supplemented with amoxicillin-metronidazole during either the non-surgical or the surgical treatment phase.

Methods: Single center, randomized placebo controlled crossover clinical trial with a one-year follow-up. Eighty participants with Aggregatibacter actinomycetemcomitans-associated moderate to advanced periodontitis were randomized into two treatment groups. A: Antibiotics (3/d 500 mg metronidazole plus 375 mg amoxicillin for 7 days) during the first, non-surgical phase of periodontal therapy (T1), and placebo during the second, surgical phase (T2). B: Placebo during T1, and antibiotics during T2. Number of sites with PD >4 mm and BOP per patient was the primary outcome. Results: 11212 sites were clinically monitored on 1870 teeth. T1 with antibiotics decreased the number of sites with PD >4 mm and BOP per patient significantly more than without (A: from 34.5 to 5.7, 84%; B: from 28.7 [...]

Reference


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Differential Benefits of Amoxicillin–Metronidazole in Different Phases of Periodontal Therapy in a Randomized Controlled Crossover Clinical Trial

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Background: The specific advantage of administering systemic antibiotics during initial, non-surgical therapy or in the context of periodontal surgery is unclear. This study assesses the differential outcomes of periodontal therapy supplemented with amoxicillin–metronidazole during either the non-surgical or the surgical treatment phase.

Methods: This is a single-center, randomized placebo-controlled crossover clinical trial with a 1-year follow-up. Eighty participants with Aggregatibacter actinomycetemcomitans–associated moderate to advanced periodontitis were randomized into two treatment groups: group A, antibiotics (500 mg metronidazole plus 375 mg amoxicillin three times per day for 7 days) during the first, non-surgical phase of periodontal therapy (T1) and placebo during the second, surgical phase (T2); and group B, placebo during T1 and antibiotics during T2. The number of sites with probing depth (PD) >4 mm and bleeding on probing (BOP) per patient was the primary outcome.

Results: A total of 11,212 sites were clinically monitored on 1,870 teeth. T1 with antibiotics decreased the number of sites with PD >4 mm and BOP per patient significantly more than without (group A: from 34.5 to 5.7, 84%; group B: from 28.7 to 8.7, 70%; P < 0.01). Twenty patients treated with antibiotics, but only eight treated with placebo, achieved a 10-fold reduction of diseased sites (P = 0.007). Consequently, fewer patients of group A needed additional therapy, the mean number of surgical interventions was lower, and treatment time in T2 was shorter. Six months after T2, the mean number of residual pockets (group A: 2.8 ± 5.2; group B: 2.2 ± 5.0) was not significantly different and was sustained over 12 months in both groups.

Conclusion: Giving the antibiotics during T1 or T2 yielded similar long-term outcomes, but antibiotics in T1 resolved the disease quicker and thus reduced the need for additional surgical intervention. J Periodontol 2015;86:367-375.

KEY WORDS
Amoxicillin; case management; metronidazole; periodontitis; randomized controlled trial.

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ontemporary periodontal treatment aims at the removal of subgingival bacterial deposits (plaque and calculus) through a mechanical cleaning method called scaling and root planing (SRP). To facilitate SRP and to allow direct visual control in deep pockets, the gums can be lifted back surgically for better access. In clinical practice, periodontal therapy is usually performed in two stages. An attempt to remove a maximum of bacterial deposits is made first without elevating a flap. After 3 to 6 months, the case is reevaluated, and, if deemed necessary, additional root surface instrumentation follows, this time in the context of a local surgical intervention.

The benefit of systemically administered adjunctive antibiotics, notably the combination of amoxicillin plus metronidazole, is well documented. However, their specific indication and the optimal time point for administration are controversial. An early study, indicating that systemic metronidazole as an adjunct to non-surgical debridement could reduce the need for subsequent surgical therapy, and a later publication from the same authors claiming sustained benefits over 5 years, were met with disapproval by distinguished members of the professional community. Postponing antibiotic therapy to the second, surgical treatment phase may be advocated for two reasons. First, because it is known that SRP alone is able to resolve a considerable amount of periodontal pathology on its own, especially in shallow and moderately deep lesions, this strategy may help to constrain the prescription of antibiotics to situations in which non-surgical mechanical therapy alone is evidently insufficient. Second, given the limited effects of antibiotics on intact biofilm and the challenge to remove such bacterial deposits from deep lesions, surgical access may provide a better opportunity for thorough debridement and thus improve the conditions for the antimicrobial agent to work. As much as this reasoning seems to make sense, data from specifically designed controlled trials are unavailable to support the recommendation. Contrary to this view, the vast majority of trials have tested antibiotics as adjuncts to SRP. A systematic review in 2008 that tried to assess the relative benefit of prescribing antibiotics either during the non-surgical phase or the surgical phase of therapy remained inconclusive.

However, two studies, not included in this review, showed better clinical outcomes if patients with generalized aggressive periodontitis (AgP) were given amoxicillin and metronidazole immediately after initial SRP than at a later stage of therapy. The combination of amoxicillin plus metronidazole has been recommended in the past specifically for the treatment of Aggregatibacter actinomycetemcomitans-positive patients. For the present trial, this recommendation is followed. The exclusive advantage of these antibiotics in such patients was questioned later, but specific evidence was not available when this study was designed. A systematic review determined that, on average, 62% of patients diagnosed with AgP and 28% of patients diagnosed with chronic periodontitis (CP) are A. actinomycetemcomitans-positive.

The main purpose of this study is to evaluate the influence of timing of adjunctive systemic antibiotics on the outcomes of periodontal therapy in A. actinomycetemcomitans-positive patients in a controlled randomized clinical trial (RCT).

MATERIALS AND METHODS
This was a single-center, double-masked, placebo-controlled RCT. Using a crossover design for antibiotic administration, 80 participants were distributed randomly into two groups: 1) group A received the antibiotics during the first stage of periodontal therapy (T1); and 2) group B received the antibiotics during the subsequent surgical phase of periodontal therapy (T2). The Ethical Committee of the University Hospitals of Geneva, Geneva, Switzerland, approved the protocol. The study was authorized by the Swiss Agency for Therapeutic Products (Swissmedic), Bern, Switzerland and is registered at ClinicalTrials.gov as NCT02197260. Research was conducted according to the principles outlined in the Declaration of Helsinki on human medical experimentation. Written informed consent was obtained from all participants.

Patients
By screening 319 individuals seeking treatment at the University of Geneva School of Dental Medicine between April 2009 and August 2012, 80 systemically healthy patients (41 males and 39 females, aged 26.1 to 68.8; mean age: 47.3 years) with untreated moderate to advanced periodontitis were included on the basis of the following criteria: 1) aged 25 to 70 years; 2) the presence of ≥12 scorable teeth (not including third molars, teeth with orthodontic appliances, bridges, crowns, or implants); 3) diagnosis of periodontitis with the presence of at least four teeth with a probing depth (PD) >4 mm; 4) clinical attachment loss ≥2 mm; 5) radiographic evidence of bone loss; and 6) detection of A. actinomycetemcomitans in a pooled sample from the deepest pocket of each quadrant (as determined with oligonucleotide probe technology). Exclusion criteria were as follows: 1) systemic illnesses (i.e., diabetes mellitus, cancer, human immunodeficiency virus, bone metabolic diseases, or disorders that compromise wound healing, radiation, or immunosuppressive therapy); 2) pregnancy or lactation; 3) systemic antibiotics taken within the previous 2 months; 4) use of non-steroid anti-inflammatory drugs; 5) confirmed or suspected intolerance to 5-nitromidazole derivatives or amoxicillin; and 6) subgingival SRP or surgical periodontal therapy in the
past year. Smoking history was recorded, but smoking was not an exclusion criterion. Using the 1999 international classification scheme, 65 cases might be diagnosed clinically as CP and 15 as AgP.

**Test Products and Randomization**
The test medication consisted of 500 mg metronidazole and 375 mg amoxicillin to be taken three times per day for 7 days. The control medication was a similar-looking placebo. The capsules containing the test or control medication were packaged in identical neutral boxes. The pharmacy of the Geneva University Hospital prepared the products and randomly allocated the participants to one of two treatment groups using a simple computer-generated randomization list with a random block size of 20. The therapist (NC) gave the package to the participant on the day specified by the study protocol. The treatment group was concealed to the therapist, the patient, and the clinical examiner (AA). The therapist was not involved in any clinical measurements and was unaware of the recorded data, except for the periodontal pocket chart that he needed to provide the treatment.

**Clinical Protocol**
The clinical examiner recorded the medical history and obtained informed consent. He removed all supragingival hard and soft bacterial deposits. He gave instructions in proper oral hygiene to enable the patients to keep ≥80% of tooth surfaces plaque free. The patients were recalled, and, if necessary, additional instructions were provided. Once the appropriate level of plaque control was reached, they were scheduled to receive subgingival treatment by the therapist (T1) within 1 month. Immediately before the therapist started, the examiner recorded the following clinical parameters on six sites of all teeth except third molars: 1) gingival index (GI); 2) PD; 3) recession (REC) (positive if the gingival margin was located apical to the cemento-enamel junction [CEJ] and negative if it was located coronal to the CEJ); 4) bleeding on probing (BOP); and 5) supppuration. In addition, the presence or absence of plaque (plaque score [PS]) was recorded on six sites of all teeth by running a probe across the site. The therapist then cleaned all tooth surfaces and treated the periodontally diseased teeth with thorough SRP to the depth of the pocket under local anesthesia. He first used ultrasonic instruments and then curets§ and finally irrigated the pockets with a 0.1% aqueous solution of chlorhexidine. SRP was completed within 48 hours and usually required two sessions. After completion, the therapist gave the medication to the participants with the instructions to start with the drug regimen on the evening of the same day, to continue three times daily for 7 days, to rinse the mouth twice daily during the next 10 days with 0.2% chlorhexidine, and to come back after 1 week, returning any medication that may have remained. Using a structured questionnaire, the examiner recorded any concomitant medication and all adverse events 1 week and 1 month after SRP. Three months after SRP, the examiner recorded the same clinical parameters as at baseline.

In T2, a surgical access was provided for open-flap debridement of all teeth with residual PD ≥6 mm and all furcation-involved teeth with residual pockets ≥5 mm. A full-thickness flap was elevated, granulation tissue was removed, and the root surfaces were treated with ultrasonic and hand instruments and low-abrasive diamond burs. Non-surgical retreatment by SRP was given to any other sites with residual PD of 4 to 5 mm. Treatments were performed under local anesthesia and were accomplished in one or two sessions within 1 week. Participants were instructed to rinse the mouth twice daily during the next 10 days with 0.2% chlorhexidine. At the end of treatment, each patient received the medication and was advised to start with the drug regimen on the evening of the same day. One week after treatment, the operator removed the sutures and gave specific individualized instructions for oral hygiene after surgery. The examiner collected any remaining medication and recorded any concomitant treatment and all adverse events. The examiner saw the patients again 1, 3, 6, and 12 months after T2. At 6 and 12 months after T2, the examiner recorded the same clinical parameters as at baseline.

**Statistical Analyses**
Sites with PD >5 mm that show BOP are commonly viewed as diseased, and persistence of these signs represents an incomplete treatment outcome with an increased risk for tooth loss. Thus, in the present study, the number of sites per patient with PD >4 mm and that had BOP was the primary outcome. Secondary outcomes included longitudinal changes of PD, BOP, REC, and clinical attachment level (CAL) (calculated as PD + REC) at sites with baseline PD >4 mm. Patient averages were computed for all measures recorded at multiple sites. Adverse events were summarized by treatment group and treatment phase for all evaluable patients.

The sample size was determined on the basis of a previous study comparing SRP with or without adjunctive amoxicillin and metronidazole, with a mean difference in the number of residual pockets with PD >4 mm and BOP, 3 months after therapy, of 3.1. The difference in the number of residual pockets may decrease after crossover because everyone will have been treated with the antibiotics. Thus, 37 patients per treatment arm would provide 80% power to detect a true difference of 2.0 in the number of residual pockets after therapy, assuming that the common standard deviation is 3.0 and α is 0.05. Consequently, 40 participants per arm were included to compensate for 10% possible dropout.

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All analyses were done according to intention to treat by including in the analysis all patients randomized into their allocated group. The effect of treatment group on patient-level categorical variables was estimated using Fisher exact test. Linear regression (t test) was used for the patient-level continuous variables. With respect to site-level outcome, multilevel regressions considered sites as nested within teeth, themselves nested within patients. To compare the effect of treatment group over time, the treatment and the time variables, as well as their interaction, were included in the model. The effect of treatment group on the reduction of the number of sites with PD >4 mm and BOP at 6 months after T2, was further analyzed by linear regression, using sex, age, and smoking as moderating factors. For all continuous outcomes, normality and homoscedasticity was checked using residual plots. A statistical computing program was used for all analyses. $P$ values <0.05 were accepted for statistical significance.

RESULTS
The clinical procedures and evaluations were performed from April 2009 to March 2014. Figure 1 shows the flow diagram for the different phases of the study. Seventy-one of the 80 initially recruited participants completed all visits of the study. One was lost before receiving the first intervention, two were lost after T1, two did not participate in T2, two were lost before 6 months, and two more were lost before 12 months. In addition, one participant was unavailable for the evaluation 6 months after T2. All patients completed the course of systemic medication as allocated. Table 1 displays the baseline characteristics of the participants. A total of 11,212 sites (six per tooth on a total of 1,870 teeth; eight sites were inaccessible) were clinically monitored. Pockets >4 mm had a mean PD of 6.46 mm.

Table 2 shows the clinical results at the 3-month follow-up after T1 by treatment group. The non-surgical treatments provided in T1 with adjunctive antibiotics according to protocol A reduced the number of sites with PD >4 mm and BOP per patient by 83.5% (from 34.5 to 5.7) and with adjunctive placebo (protocol B) by 69.7% (from 28.7 to 8.7), with the difference in reduction being significant ($P<0.01$). Twenty patients (52.6%) treated with antibiotics, but only eight (20.5%) treated with placebo, achieved a 10-fold reduction of diseased sites, with the differences being significant ($P=0.007$).

Consequently, fewer patients of group A than group B received additional therapy in T2 (Table 3). Only three patients of group B had no sites with PD >4 mm and BOP and therefore required no additional mechanical therapy (they still received the allocated medication according to protocol). The treatment time in T2 was >30 minutes shorter for patients of group A compared with group B, although this difference was not significant because of the large variability in treatment times between patients. The mean number of surgical interventions per patient, performed according to preset rules (open-flap debridement in case of the presence of residual PD ≥6 mm or furcation involvement with residual PD ≥5 mm), was lower in patients of group A than group B.

**Figure 1.** Diagram of the different phases of the study.
DISCUSSION

In the vast majority of trials evaluating systemic antibiotics for the treatment of periodontal disease,
the drugs were administered as adjunct to SRP, and the participants were monitored without additional intervention over several months. This does not correspond to common practice, because clinical signs of disease occasionally persist after non-surgical debridement, and additional therapy may thus be indicated. The influence of the timing of antibiotic therapy in a sequential protocol that corresponds better to current practice was evaluated. In the present study, giving amoxicillin plus metronidazole in T1 or T2 had no influence on the long-term outcome: 6 or 12 months after therapy, the mean number of sites with PD >4 mm and BOP per patient was significantly lower than at baseline in both groups, with no significant difference between the two. However, fewer patients treated with adjunctive antibiotics in T1 received additional therapy, the treatment time in T2 was shorter,
and the mean number of surgical interventions was lower. The present findings are in line with recent trials also suggesting that SRP with amoxicillin plus metronidazole can reduce the need for surgical interventions.\textsuperscript{22,23}

Given the debate about the discriminatory significance of the 1999 classification system,\textsuperscript{24} recruitment of participants followed practical rules to identify patients with periodontal disease irrespective of the presumed disease class. So far, the specific moderating effect of disease class on the benefit of amoxicillin and metronidazole has not been determined in an accurately conducted trial. Because amoxicillin plus metronidazole was advocated in the past, especially for the treatment of \textit{A. actinomycetemcomitans}-associated periodontitis,\textsuperscript{13} a positive test for this microorganism was required for inclusion. Recent research refutes claims about an exclusive advantage of these antibiotics in \textit{A. actinomycetemcomitans}–positive patients,\textsuperscript{14,25,26} but this was not yet recognized when the study started. The benefit of the first part of the clinical protocol of the present study—full-mouth SRP completed within 48 hours in T1—has been evaluated in a previous independent trial.\textsuperscript{21,27} Allowing 48 hours to deliver full-mouth SRP gives the clinical staff some leeway for scheduling and permits avoiding anesthesia at both sides of the dentition on the same day. A systematic review concluded that the specific modus of delivering SRP, for example quadrant-wise SRP compared with full-mouth SRP within 24 hours, had little effect on the outcome.\textsuperscript{28}

The selection of efficacy endpoints for clinical trials on periodontal therapy is a subject of debate.\textsuperscript{29} Mean CAL changes have been used as endpoint measures; however, in clinical practice, the most consequential outcome is the disappearance of deep pockets with signs of inflammation. Sites with PD >4 mm and BOP are considered commonly to be in need of additional care and thus were the focus of this investigation. Assuming that pockets >4 mm with BOP need additional therapy, treatment needs can be estimated by the number of residual pockets. However, multiple residual pockets can sometimes be treated in a single intervention, so the number of surgeries also depends on the location and distribution of the lesions. The data collected in this trial allow not only an estimation of treatment needs but also permit a comparison of the interventions actually performed.

A complicated RCT compared treatment outcomes of SRP, with or without adjunctive amoxicillin plus metronidazole and/or local tetracycline therapy and/or followed by periodontal surgery.\textsuperscript{30} Eight groups of \(n=30\) patients were assigned to eight imaginable permutations of these elements and were followed over 24 months. PD reduction was seen to a greater extent in patients receiving periodontal surgery. Patients treated with adjunctive antibiotics continued to gain CAL and showed continuous decrease of PD up to 6 months after therapy. The plateau reached at that point in time was kept throughout the remainder of the observation period. Systemic amoxicillin and metronidazole enhanced mean CAL gains by 0.5 mm. PD was reduced to a similar degree by antibiotics or surgery (0.5 or 0.4 mm, respectively). In the present study, similar outcomes 6 and 12 months after therapy according to either protocol A or B indicate that the clinical improvements obtained from non-surgical treatment were as stable as results obtained by surgical intervention. Studies monitoring patients over longer periods after various treatments have repeatedly identified three crucial factors for long-term stability: 1) the level of self-performed oral hygiene; 2) the inclusion in a maintenance program; and 3) not smoking.\textsuperscript{31-35}

The results from the present study suggest that smokers may have a specific advantage from being treated with the combination of amoxicillin and metronidazole in the non-surgical phase. This is in line with a study showing good results of therapy especially with SRP plus amoxicillin and metronidazole in smokers.\textsuperscript{36} In contrast, an earlier trial reported poorer treatment response to SRP in smokers than non-smokers, regardless of the application of either systemic or locally applied adjunctive metronidazole alone,\textsuperscript{37} and a recent study suggested that smokers do not respond as well as non-smokers.\textsuperscript{38}

The incidence and nature of adverse events observed in this study correspond to observations made in previous studies.\textsuperscript{2,3} Adverse events were generally minor, sporadic, and without a particular association with one group. The specific design of the trial (all participants were treated with antibiotics in either T1 or T2) precludes an evaluation of all aspects of adverse events.

CONCLUSIONS

In patients with moderate to advanced periodontitis, systemic amoxicillin plus metronidazole significantly enhanced the effects of full-mouth SRP. Consequently, fewer patients of this group received additional therapy in T2. Differences in the final results between groups were not significant.

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