

What's new for the clinician?

Summaries of and excerpts from recently published papers

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Compiled and edited by V Yengopal

1. Is progression of periodontitis relevantly influenced by systemic antibiotics? A randomized clinical trial

Harks I, Koch R, Eickholz P, Hoffmann T, Kim T-S, Kocher T, Meyle J, Kaner D, Schlagenhauf U, Doering S, Holtfreter B, Gravemeier M, Harmsen D, Ehmke B. *J Clin Periodontol* 2015; 42: 832–42

Periodontitis is an inflammatory disease caused by a microbial biofilm.¹ Mechanical debridement in patients with moderate to severe periodontitis can be supplemented with systemic antibiotics, such as amoxicillin and metronidazole. The rationale for the adjunctive use of antibiotics is to effect an antimicrobial effect at sites inaccessible to mechanical therapy, and possibly to suppress periodontal pathogens.¹ However, the indiscriminate use of antibiotics could increase bacterial resistance and thus a critical appraisal of routine prescription and its clinical relevance is mandatory for each patient.¹ Harks and colleagues (2015)¹ undertook a large multi-centre trial aimed at determining the efficacy of systemic antibiotics on the progression of periodontal disease. Their hypothesis was that empiric systemic adjunctive antibiotics could reduce the proportion of sites exhibiting further disease progression.

MATERIALS AND METHODS

The study was a prospective, randomized, stratified, double-blind, multi-centre (eight university hospital centres) trial with parallel-group design. Patients with untreated moderate to severe chronic and aggressive periodontitis were included. For inclusion, patients had to have pocket probing depths (PPDs) of ≥ 6 mm at a minimum of four teeth, at least 10 natural teeth, etc. Patients allergic to the tested antibiotics, those with systemic disease, rampant caries, etc. were excluded.

Per patient, 12 visits over 27.5 months were scheduled. Participants were divided into four strata according to the extent of periodontal disease [localized: $<38\%$; generalized: $\geq 38\%$ of teeth with pocket probing depths (PPD) ≥ 6 mm] and smoking habit [non-/light smoker: <7 ppm CO in exhaled air;

ACRONYMS

ITT:	intention to treat
OHIP-G 49:	Oral Health Impact Profile
PPDs:	pocket probing depths
PSAL:	proportion of sites per patient with new clinical attachment loss
RAL:	Relative attachments level

moderate to heavy smoker: ≥ 7 ppm)]. The four strata were defined as follows: stratum 1 (localized periodontal disease, non-/light smoker), stratum 2 (generalized periodontal disease, non-/light smoker), stratum 3 (localized periodontal disease, smoker) and stratum 4 (generalized periodontal disease, smoker).

After screening (visit1), baseline measurements and subsequent randomization were performed (visit 2). After dental biofilms were disrupted during initial treatment (mechanical debridement), blinded amoxicillin/metronidazole or placebo was dispensed (visit 3). Re-evaluation (visit 4) was performed 3.5 months after visit 2. Maintenance therapy (mechanical debridement) was carried out at 3 monthly intervals (visits 5 through 12). Measurements were also conducted 9.5, 15.5, 21.5 and 27.5 months after visit 2 (visits 6, 8, 10 and 12).

From 506 randomized patients, 93 dropped out over the 27.5 months study period. Overall, 406 patients were included in the intention to treat analyses, but, due to incomplete medication intake, only 345 patients were included into the per-protocol analysis.

Within 1.5 months after baseline examination (visit 2), patients received supra- and subgingival debridement in up to two sessions on two consecutive days (visit 3). All mechanical therapy was performed with different hand instruments and/or machine driven scalers. After completion of mechanical therapy, in the antibiotics group, patients received two empiric antibiotics [Amoxicillin-ratiopharm 500mg®; metronidazole 400mg (Flagyl®)] and placebo group patients two placebo drugs, each to be taken three times a day for 7 days.

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The patients kept a medication diary to document drug adherence. Patients were informed about the medications' side effects according to the package inserts of amoxicillin and metronidazole. Re-evaluation (visit 4) was performed 3.5 months after baseline. Thereafter, all patients received maintenance therapy, including full-mouth supra- and subgingival debridement and oral hygiene instruction at 3 months intervals (visits 5 through 12). Sites with PPD ≥ 4 mm also received subgingival re-debridement. All treatments were performed by blinded qualified dentists or dental hygienists.

Full-mouth periodontal measurements were carried out at six sites of each tooth by blinded examiners not involved in periodontal therapy. Relative attachments level (RAL) measurements, corresponding to the distance from occlusal surface to the bottom of the periodontal pocket, were performed in duplicate with an electronic pressure-sensitive probe (Florida Disk Probe) in increments of 0.2 mm. The difference between baseline and follow-up RAL readings described the changes of the clinical attachment level (gain or loss of tooth supporting tissue).

The primary outcome was the proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm between baseline and the 27.5 months visit. The ≥ 1.3 mm threshold was considered clinically relevant, because conversely, 1.3 mm gain in clinical attachment after periodontal therapy is considered a relevant outcome, too.

Attachment loss was used as outcome variable instead of attachment gain, because it is associated with tooth loss, which constitutes a true endpoint. Therefore, the presence of attachment loss is tantamount to disease progression. The following secondary endpoints were assessed exploratorily using a Florida standard probe: PPD, clinical attachment, gingival bleeding on probing and supragingival plaque. All measurements were performed at "baseline" (visit 2), after 3.5 months (re-evaluation, visit 4), and at 9.5, 15.5, 21.5 and 27.5 months "follow-ups" (visits 6, 8, 10 and 12).

The medical history and the body mass index were assessed at visit 1, and non-fasting blood samples were drawn to determine the HbA1c levels (visits 1, 8 and 12). As an indicator of subjective oral health perception, the German version of the Oral Health Impact Profile (OHIP-G 49) was recorded at visits 1, 8 and 12.

All efficacy analyses were based on the intention to treat (ITT) principle, comparing groups according to the randomly assigned treatment and strata. Primary and secondary endpoints were evaluated in the per-protocol collective at each visit. A sensitivity analysis was performed with PSAL ≥ 2 mm.

RESULTS

Of 506 randomized patients, 406 (; placebo: $n = 200$, antibiotics $n = 206$) finished the therapy regime by visit 12 (drop out $n = 100$; 19.8%). All patients who followed the study timeline according to the protocol and took all tablets within 6 through 8 days according to their medication diaries were included in the per-protocol collective (PP, 345 patients, placebo: $n = 175$, antibiotics: $n = 170$). Most patients in the sample had been diagnosed with chronic periodontitis.

In the Intention to treat (ITT)-collective, the median proportion of sites per patient with new clinical attachment loss (PSAL) ≥ 1.3 mm over the 27.5 months period was 7.8% in the placebo versus 5.3% in the antibiotics group. The difference between the patient groups was significant ($p < 0.001$).

At baseline (visit 2), the percentage of PPD ≥ 5 mm was not different in both groups ($p = 0.66$). Beginning with visit 4, although both groups achieved clinically favourable levels, the antibiotics group patients showed statistically noticeable lower presence of PPD ≥ 5 mm compared with placebo patients ($p < 0.001$).

At 27.5 month, % PPD of ≥ 5 mm had decreased to 5.5% in the placebo and to 2.1% in the antibiotics group ($p < 0.001$). The median proportion (ITT-collective) of sites with attachment gain ≥ 1.3 mm over the 27.5 months period was 12.2% for the placebo and 19.4% for the antibiotics group ($p < 0.001$). Clinical attachment level overall improved over the study period: mean attachment gain was 0.4 ± 0.7 mm for the placebo and 0.6 ± 0.7 mm for the antibiotics group ($p < 0.001$). In both groups, this gain was considerably more pronounced at sites with initially advanced probing depths of ≥ 6.5 mm (placebo 2.1 ± 1.7 mm versus antibiotics 2.8 ± 1.5 mm; $p < 0.001$).

In summary, other secondary parameters, for example proportions of PPD and absolute PPD and bleeding on probing improved over the 27.5 months observation period, whereas the plaque index scores improved initially, but returned to baseline levels later.

Overall, 90 serious adverse events, 39 in the placebo and 43 in the antibiotic group were reported over the course of the study. Eight serious adverse events occurred prior to medication intake.

At baseline, the mean OHIP scores were 39.2 ± 27.2 for the placebo and 46.0 ± 33.8 for the antibiotics group. These scores decreased in the course of the study to 32.2 ± 29.4 and 32.9 ± 29.4 for placebo and antibiotics patients with mean changes of -5.5 ± 21.3 and -11.0 ± 26.1 respectively. The effect size (Cohen's d) of the score changes from baseline to 27.5 months between the two groups was $d = 0.23$ (95% CI 0.03; 0.44).

CONCLUSION

The authors found that in the present trial, compared with placebo, the prescription of empiric adjunctive systemic amoxicillin plus metronidazole was highly effective in terms of PPD reduction, but showed little absolute, although statistical significant, reduction in further attachment loss in formerly untreated patients with moderate or severe chronic periodontitis.

IMPLICATIONS FOR PRACTICE

Mechanical debridement was highly effective in the prevention of new attachment loss and improves the majority of other clinical parameters. Results of mechanical therapy were statistically significant improved by the prescription of adjunctive antibiotics, but these improvements depend on the outcome parameter and are of conflicting clinical relevance in real life. Against the background and danger of increasing microbiological resistance, it seems even

more reasonable that for routine treatment of periodontitis clinicians should consider the patient's overall risk for periodontal disease when making a decision for or against antibiotic prescription, and should be careful not to underestimate the effect of proper mechanical debridement and modification of behavioural risk factors.

Reference

1. Harks I, Koch R, Eickholz P, Hoffmann T, Kim T-S, Kocher T, Meyle J, Kaner D, Schlagenhauf U, Doering S, Holtfreter B, Gravemeier M, Harmsen D, Ehmke B. Is progression of periodontitis relevantly influenced by systemic antibiotics? A clinical randomized trial. *J Clin Periodontol* 2015; 42: 832–42

2. Effect of application of a PVP-iodine solution before and during subgingival ultrasonic instrumentation on post-treatment bacteraemia

Sahrman P, Manz A, Attin T, Zbinden R, Schmidlin PR. *J Clin Periodontol* 2015; 42: 632–9.

The presence of germs in the bloodstream is referred to as bacteremia. Bacteremia frequently occurs after treatment procedures such as extractions, scaling, root planing, periodontal probing, periodontal surgery, [suture removal, orthodontic treatment, restorative dentistry, non-surgical root canal treatment, subgingival irrigation, and oral hygiene procedures such as tooth brushing and flossing. Guidelines have been developed for the preventive systemic administration of antibiotics before dental treatment, especially for well-defined high-risk patients such as those with cardiovascular disease, diabetics, those with immunosuppressive conditions with weakened immune states, etc.¹ Despite the fact that some studies showed that the antibiotic approach might be highly potent in terms of bactericidal effects on circulating germs in the bloodstream, this medication does not actually provide a safe elimination of bacteria or any obstacle for the transition of viable bacteria into the bloodstream.¹

PVP-iodine is a cheap broad-spectrum antiseptic agent frequently used in the therapy of periodontitis. Its spectrum of action covers bacteria associated with periodontitis and its use as a rinse during initial periodontal therapy has been proven to provide a significant therapeutic benefit in terms of pocket depth reduction.¹ Sahrman *et al* (2015)¹ reported on a trial that sought to assess the impact of PVP-iodine rinsing before ultrasonic root instrumentation and concomitantly with this instrumentation, on the prevalence and the extent of oral-borne bacteraemia in patients with chronic periodontitis.

MATERIALS AND METHODS

This was a single-centre, randomized, placebo-controlled clinical study with a split-mouth crossover design. The study was composed of 20 male and female patients over 18 years of age with moderate or severe chronic periodontitis with at least two sites with probing depth (PD) $\geq$ 5 mm in each quadrant. Patients with systemic diseases or medications known to interfere with periodontal therapy were not included. Furthermore, patients who underwent antibiotic therapy or anticoagulation therapy during the preceding 6 months, those on thyroid medication or with a known allergy to PVP-iodine were excluded from this study. Females who were pregnant or breastfeeding were also not included in this trial.

A computer-randomized list was generated prior to the start of the study. During the first appointment, an envelope with the group and allocation of the first course of instrumentation, i.e. left or right half of the mouth, and the solution to be applied was defined: PVP-iodine for the test or tap water for the control treatment.

After local anaesthesia was administered to areas with deep periodontal sites of the appropriate half of the oral cavity, the patient rinsed the mouth for exactly 1 min with the corresponding test or control liquid. Meanwhile, a tourniquet was loosely placed around the upper arm, and the bend of the elbow was disinfected twice. Then, all periodontal sites in the area of interest were rinsed for another 60 sec with the same liquid using a 10 ml single-use plastic syringe and a blunt tip with an inner diameter of 0.49 mm. Thereafter, these pockets were instrumented using an ultrasonic-driven device (CavitronPlus® and Slimline inserts) at the highest settings for power and lavage to churn up a maximum of subgingival biofilm for 60 s. During the study process, the ultrasonic device ran with the allocated liquids provided from the external cooling tank (either PVP-iodine – test or water – control). Exactly 3 min after the start of the subgingival instrumentation, a blood sample of 10 ml was taken from the most visible arm vein after tightening the tourniquet.

The second treatment was performed after a wash-out period of at least two weeks. The treatment was performed in line with the first treatment using the residual liquid so that the patient would have received exposure to both the test and the control liquid as is consistent with crossover trials.

Samples were labelled and stored in a dark place at room temperature until they were processed in the laboratory. Due to the coding of the glass tubes, the microbiology staff was blinded regarding the treatment type of the corresponding blood samples. The samples were centrifuged at 3500g for 10 min and placed in growing media for culture at 37°C for 2–3 days. As soon as colonies were visible, they were counted and sub-cultured using standardised procedures.

Clinical data from the periodontal findings sheet were transferred and inserted into an Excel spreadsheet to automatically calculate the total epithelialized and inflamed surfaces from the pocket depth, recession and BOP data, based on reference data for the anatomy of the individual teeth.

RESULTS

Of the 20 patients enrolled in the study, results were presented for 19. Baseline clinical data (PI, BOP, number of sites with deep probing depths, mean probing depth, the mean overall (PESA) and inflamed periodontal surface area (PISA)) did not reveal any statistically significant differences between the groups. For the cultures, bacteria of oral origin included different *Streptococcus spp.*, *Lactobacillus spp.* and facultative anaerobic bacteria such as *Actinomyces spp.* but also strictly anaerobic bacteria such as *Prevotella spp.*, *Clostridium spp.* and *Fusobacterium spp.*

Bacteraemia was found in 11/19 cases in the control group and in 5/19 cases in the test group. After the exclusion of cases with typical skin bacteria species, 10/19 (53%) oral-borne bacteraemia were found in the control group and 2/19 (11%) in the test group [$p = 0.0133$]. When the average number of colony forming units per case of oral-borne bacteraemia was calculated, 12.2 [1; 46] in the control and 3.0 [1; 5] in the test group were found ($p = 0.003$). Comparing the ratio of aerobic and anaerobic bacteria in the two groups, 83.0% turned out to be anaerobic species in the control group, whereas there was no anaerobic colony found within the test group.

Multiple regression revealed no correlation of the parameters BOP, PI, number of sites ≥ 4 mm, PESA or PISA

with the prevalence of bacteraemia (p-values 0.087, 0.245, 0.214, 0.242, 0.417) or with the number of bacteria per case of bacteraemia (p-values 0.868, 0.310, 0.493, 0.802 and 0.672 respectively). However, there was a correlation of BOP and the number of sites > 4 mm ($p=0.004$).

CONCLUSION

The researchers concluded that rinsing with 10% PVP-iodine significantly reduces the risk for post-treatment bacteraemia during non-surgical periodontal therapy.

IMPLICATIONS FOR PRACTICE

Before undergoing dental treatment, patients at a high risk for endocarditis or inflammation of endoprosthesis are encouraged to take prophylactic antibiotics to kill vital bacteria that have entered the bloodstream. However, antibiotics do not hinder the passage of vital bacteria into the host organism. Intensive rinsing with PVP-iodine before and during biofilm disruption might be an alternative approach to lower the risk of bacteraemia

Reference

1. Sahrman P, Manz A, Attin T, Zbinden R, Schmidlin PR. Effect of application of a PVP-iodine solution before and during subgingival ultrasonic instrumentation on post-treatment bacteraemia: a randomized single-centre placebo-controlled clinical trial. J Clin Periodontol 2015; 42: 632–9.

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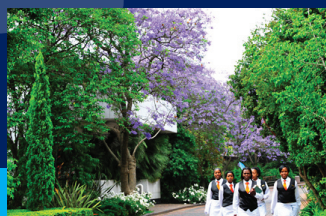
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