Possible Clinical Attachment Level changes resulting from the use of topically delivered antibiotics as an adjunct to Scaling and Root Planing as compared to Scaling and Root Planing alone.

A Meta Analysis.

Even Mjøen, Endre Romstad, Per Gjermo & Hans R Preus

Dept. of Periodontology, Institute of Clinical Odontology, Dental Faculty, University of Oslo, Norway.

Abstract. (<200 words) *Possible Clinical Attachment Level changes resulting from the use of topically delivered antibiotics as an adjunct to Scaling and Root Planing as compared to Scaling and Root Planing alone. A Meta Analysis. Mjøen E, Romstad E, Gjermo P & Preus HR*

Introduction

Periodontal disease is a family of bacterial infections characterized by the destruction of periodontal support of the teeth involved. The bacterial flora at the diseased sites are complex, counting over 500 different bacterial species in the subgingival dental plaque[1], where only a fraction is known by designated names. However, only a limited number of bacterial species have been recognized as true – or putative periodontal pathogens[2]. The treatment of these infections has for a long time been to perform adequate scaling and root planing in order to reduce the number of bacteria present and change the ecosystem in those sites showing disease progression. Although representing a very non-specific form of treatment, it has proven effective in treating most periodontal diseases so far[3].

However, a small – still significant – group of patients harbour sites or whole dentitions that do not respond to this kind of therapy[4]. This unsuccessful treatment is recognized by the continuous destruction of periodontal support as well as continuous presence of inflammatory symptoms like bleeding on probing[5-6-7]. Several hypotheses have been suggested to explain why a non-specific treatment does not result in remission of disease in these patients and sites. One of the more accepted hypotheses is that specific microorganisms, recalcitrant to the mechanical therapy, occupy the habitat of the pocket and still produce antigenic metabolites or maintain the level of infection needed to continue periodontal destruction[8]. Since this situation may warrant the designation "specific infection", although widely disputed, many researchers have suggested the treatment in such cases to be scaling and root planing *in combination* with an antibiotic. In studies this therapy has proved to be a successful form of treatment[9]. The antibiotic should preferably be chosen based on microbiological diagnoses and the bacterial resistance profile[10].

How to identify these patients early in the diagnostic process is still unclear. Patients who experience continuous destruction despite adequate oral hygiene and previous scaling and root planing as well as patients with predisposing medical conditions may be candidates for such risk groups. Some authors recommend antibiotic therapy as soon as certain, specific, putative pathogenic microorganisms are present by microbiological diagnosis[10].

Systemic antimicrobials as adjuncts to mechanical therapy have had a positive effect on clinical as well as microbiological parameters[11-12-13]. The effect of this approach is unfortunately reduced by the fact that the antibiotic is normally difficult to maintain in therapeutic conditions in the gingival crevicular fluid over the course of the treatment period. Moreover, systemic antibiotic therapy carries with it the risk of the host developing resistance towards the antibiotic as well as ill – or side effects of the prescribed drugs.

As the above discussion shows, there are several negative effects of a systemic antibiotic therapy that might be reduced or even removed by using locally delivered antibiotics instead. Several pharmaceutical companies have therefore developed periodontal, topical formulas of antibiotics which theoretically should maintain the pharmaceutical properties of the drugs, but enhance the clinical effect on periodontal diseases, as well as reduce the side effects.

Focused Question

In patients with chronic periodontal disease, what is the effect of scaling and root planing with adjunct topical antibiotic application as compared to scaling and root planing alone, measured by changes in clinical attachment level before and after treatment?

Materials and methods

Protocol – Inclusion criteria

Only randomized controlled clinical trials (RCT) were allowed. The patients groups described in the RCTs should, as a minimum, be followed for 3 months. The diagnosis for the participants had to be aggressive or chronic destructive periodontal disease, and the critical measure was changes in clinical attachment level (CAL) before and after treatment. Topical antimicrobials allowed into the study where those existing on the European market; Tetracyclines (Minocycline, doxycycline, tetracycline), Metronidazol (Elyzol, 25% dental gel), Penicillins and Macrolides

Search Strategies

Databases visited; MEDLINE/PubMed, Cochrane Controlled Trials register (Central CCTR) and WebSPIRS.

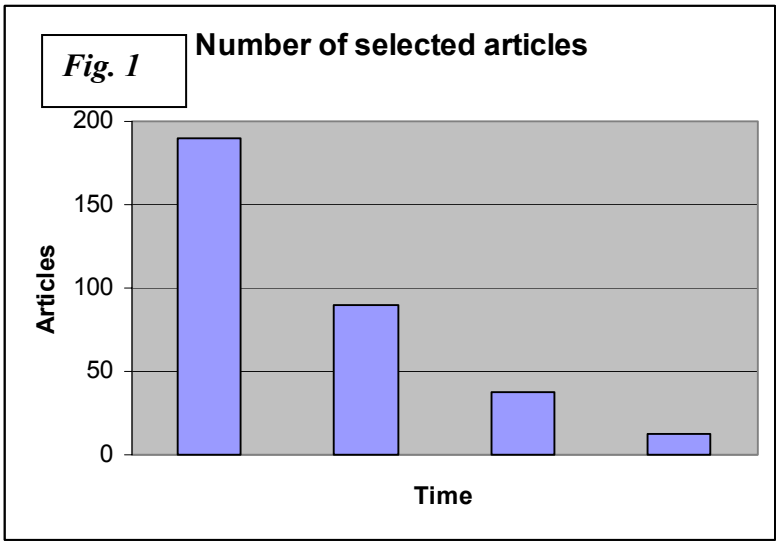
Search terms used were; *periodontitis* and *local antibiotics* and *periodontology* and *topical antibiotics.* Manual search were performed in *Journal of Clinical Periodontology, Journal of Periodontal Research* and *Journal of Periodontology.* Only articles in the English and Scandinavian languages were admitted into the study, and the last performed search was done in January 2003. Additionally, all references in all publications selected were manually searched.

The Selection Process

Primarily all publications which described the use of local antibiotics as a part of the treatment were evaluated. From a selection of 1156 articles, only 190 were selected based on

the criteria in the protocol. The titles of these 190 articles were then evaluated by two of the authors (EM, ER), resulting in the discharge of 100 titles suggesting ill- or no compliance with the protocol at hand, resulting in selection of 90 articles for further and closer studies. Based on the abstracts of these 90 articles, 53 did not comply with our criteria for the present systematic review and was rejected, leaving 37 articles for further evaluation. The firm admission criterion that this review should contain only RCTs resulted in the rejection of another 24 articles leaving 13 articles for final evaluation. During the selection process, all uncertainty regarding exclusion or inclusion of articles were discussed between the authors until agreement was reached. The full text if the 13 articles thereby selected were then examined closely, their main characteristics extracted and evaluated.

Fig. 1



Methodological Quality

Critical criteria for inclusion were randomization as well as blinding. Single blind studies were admitted into the study because there were so few double blind studies found. However, double blind studies were given a more weighted place in the evaluation process

Summary Description of the Individual Studies

Five of the studies were performed in the USA. The other were published by European institutions; (Great Britain=3, Germany=2, Italy=1, The Netherlands=1, Belgium=1). The publications are quite recent, the oldest being from 1994 and the newest from 2002. Industrial support was given to 12 of the studies as extracted from the acknowledgements and 10 of the studies were parts of a multi-centre study.

Different antibiotics were tested in the different publications. Doxycycline alone (Eickholst 2002), Metronidazol alone (Palmer 1998, Stelzel 2000) and comparison of tetracycline and minocyclin (Kinane 1999). Minocycline alone (Archie 1994, Graca 1997, Timmerman 1996, Williams 2001, van Steenberghe 1999) and tetracycline alone (Tonetti 1998, Drisko 1995, Newman 1994, Lynn 2002).

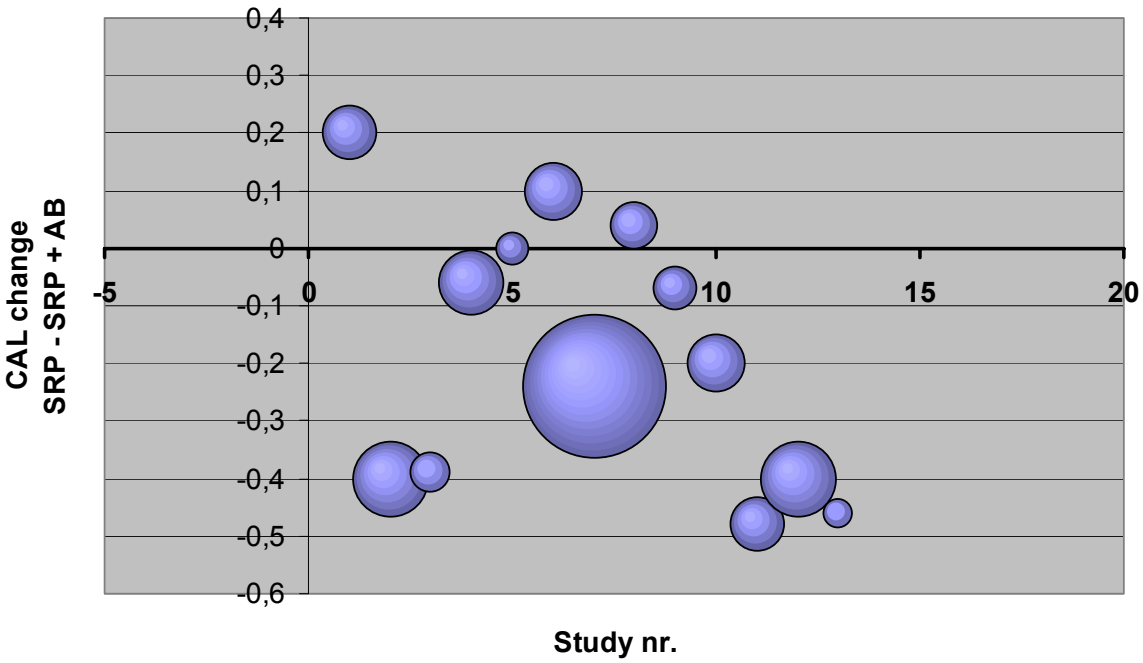
All 13 studies to be finally evaluated were randomized controlled trials. Six of the studies were regarded as double-blind (Archie 1994, Eickholz 2002, Graca 1997, Kinane 1999, Timmermann 1996, van Steenberghe 1999), whereas the remaining studies were classified as single-blinded (Tonetti 1998, Williams 2001, Palmer 1998, Stelzel 2000, Drisko 1995, Newman 1994, Lynn 2002). Time from baseline to end of study was no less than 12 weeks, the longest being 18 months.

There is a great variation in the number of study participants in each of the studies, from 748 (Williams 2001) to 20 (Timmerman 1996). All participants, except for one study (Newman 1994) evaluated the treatment of chronic periodontal disease.

Results

Table 3 shows CAL changes in the different studies. Figure 2 is a graphical display of table 3.

Fig. 2



In 9 of the 13 studies a small CAL gain was observed in the test groups as compared to the controls. In 4 of these studies, the CAL gain was significant, whereas in 5 there was only a trend towards gain. Student's t-test suggested that in the studies of Eickholz (2002), Graca (1997), van Steenberghe (1999) and Newman (1994) showed respectively that the application of topical formulas of doxycycline, minocycline and tetracycline as an adjunct to SRP in each case gave an average of roughly 0.4 mm CAL gain as compared to SRP alone.

Discussion

Only 13 studies on the effect of topical application met the requirements to be part of this review. This is a too small sample to give any conclusive results from the meta-analysis. The study designs were also varying, suggesting that some harmonization should be considered when embarking upon an intervention project as these studies in reality are.

Although we have searched for articles using the largest databases, many journals are not included. For example PubMed contains only aprox. 3000 out of 9000 journals that could contian relevant articles. We can assume that a number of articles on the subject exist in languages not included in our search.

Our approach was to exclude studies with less than 20 participants. This is not according to meta-analysis theory, where one includes all studies – regardless of number of participants – and weights them differently according to number of participants. But according to Petitti[14], one might exclude studies with to small test/control group without affecting the final result.

To simplify the statistics, we stated the hypothesis that all types of local antibiotics used in the periodontal pocket will have the same effect on the periodontitis. This assumption made it possible to compare the quantitative results from all the studies. Against this statement, Kinane 1999 shows that three different antibiotics in combination with SRP give three different changes in CAL. However these differences are not significant better compared to SRP alone.

A large number of studies were rejected due to short post-treatment observation time. The present study decided upon excluding all studies with less than 12 weeks observation time

post-treatment. This is not sufficient anyhow, but the fact that we had to include such short studies reflects that only few studies had a sufficiently long observation time. It takes more than 6 months to establish new or re-establish old periodontal support, and thus no such intervention study should be designed with less than 6 months observation time. It may be discussed if the study with 12 weeks observation time should be excluded altogether, since the other 12 has 6 months or more.

Smoking is a factor in development of periodontal diseases. Only two studies (Tonetti 1998, Palmer 1998) describes the distribution of smokers in both test and control groups. Some studies vaguely describe smoking habits, but does not report clearly enough to implement it as a confounding factor. Smoking was in no regard the reason for exclusion from any of the studies, and therefore one cannot evaluate the impact on smoking on the treatment modalities, nor can it be used as a factor in the analysis. Smokers have elevated risk for developing periodontal disease (Bergstrøm 1989[15], Bergstrøm 2000[16]) and presents themselves with more attachment loss than no-smokers (Haffajee & Socransky 2001[17]). It also seems as if 90% of all refractory periodontitis patients are smokers (Barbour 1997[18]) and studies have shown that there is a dose-response relationship between smoking and loss of periodontal support (Bergstrøm [16]). Thus, intervention studies should in the future consider these factors and weight them accordingly in selection of participants.

Gender seems to play a role in the epidemiology of periodontal diseases. A national study from USA[19] as well as Abdellatif (1987[20]) showed that males display more CAL than women. However, the same study showed that males displayed more plaque and calculus than the average woman. In the present systematic review of 13 studies, 6 reported a selection with more women than men, whereas 4 had more male participants than women. Three studies did

not report the male/female ratio. In this light it is interesting to observe that Graca (1997), who showed a significantly elevation of attachment level after application of Minocycline, had a high female to male ratio (20 females and 6 males). This may not be an explanation to the results, but may be brought to mind when comparing this particular study to other.

With regard to selection of test persons, there was also a difference among the studies as to which periodontitis criteria one used for the selection process. One of the studies selected "refractory" cases, whereas other selected patients with generalized, adult chronic periodontal diseases. There are differences between such diagnosis, both in pathology and successful treatment approaches and thus they are not comparable in systematic reviews.

One can conclude from this systematic review is that it may be a possible benefit from the adjunct use of topical antibiotics with SRP. However, the small number of studies qualifying for this review and the differences in characteristics among these makes it difficult to extract scientific evidence. Thus, in order to have enough harmonized studies in this field, for comparison, future studies should contain more stringent and corresponding characteristics in both selection processes as well as in treatment modalities.

APPENDIX 1.

Systematic review on the effect of local antimicrobials as an adjunct to scaling and root planning in patients with periodontitis

Protocol

Authors E. Mjøen[1]
E. Romstad[2]

Background.

Scaling and root planning (SRP) is the basis of non-surgical therapy in the treatment of periodontitis. However, results from this therapy are often unpredictable and dependable from the severity of the disease and the type of periodontitis.

Objectives.

The aim of this study is to evaluate the effectivness of the adjunctive use of local antibiotics with SRP, versus SRP alone in the treatment of chronic periodontitis.

Search strategy.

Use of databases, namely "MEDLINE/PubMed", "Cochrane Controlled Trials Register" (Central/ CCTR) and WebSPIRS.
The search terms to be used are; *periodontitis* AND *local antibiotics* **and** *periodontology* AND *topical antibiotics.*
In addition the references in the selected articles will be screened.

Selection process.

All papers focussing on systemic antimicrobial therapy, case reports and reviews are discarded.

- Only randomized controlled clinical trials (RCT`s) are to be included
- Patients should be followed for a minimum of three(3) months
- (A minimum of 20 subjects are required for the study to be included)
- All types of registered local antibiotics are considered

The intervention of interest is that of SRP with or without the use of local antibiotics. Studies using chlorhexidine (CLX) in adjunct with either local antibiotics or SRP are excluded. Only studies in english or scandinavian language are considered.

Strategy

From the articles obtained, their titles and abstracts will be screened independently by 2 reviewers (EM and ER). Disagreement regarding inclusion will be resolved by discussion between reviewers. The fulltext of the remaining article`s quality and main study characteristics will be assesed. Finally, data from these selected articles can be extracted and appraised, and verified by Scientific Advisors (Dr. Preus and Dr. Gjermo).

[1] Faculty of dentistry. University of Oslo
[2] Faculty of dentistry. University of Oslo

[1] Moore WEC, Moore LVH. The bacteria of periodontal diseases. Periodontology 2000 1994; 5:66-77.

[2] AAP Consensus Report. Periodontal diseases: pathogenesis and microbial factors. Annals of Periodontology 1996; 1:926-932.

[3] Kaldahl WB., Kalkwarf KL., Patil KD. A review of longditudinal studies that compared periodontal therapies. J Periodontol 1993; 64:243-253.

[4] Walker CB, Gordon JM, Magnusson I., Clark WB. A role for antibiotics in the treatment of refractory periodontitis. J periodontal 1993; 64:772-781

[5] Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing, a predictor for the progression of periodontal disease? J Clin Periodontol 1986; 13:590-596

[6] Griffiths GS, Wilton JMA, Curtis MA, et al. Detection of high-risk groups and individuals for periodontal disease: Clinical assessment of the periodontium. J Clin Periodontol 1988; 15:403-410

[7] Greenstein G, Caton J. Periodontal disease activity: A critical assessment. J Periodontol 1990; 61:543-552

[8] Renvert SN, Wikström MB, Dahlén GG, Slots J, Egelberg J. On the inability of root debridement and periodontal surgery to eliminate Actinobacillus actinomycetemcomitans from periodontal pockets. J Clin Periodontol 1990; 17:351-355.

[9] Van Winkelhoff AJ, Rams TE, Slots J. Systemic antibiotic therapy in periodontics. Periodontology 2000 1996; 10: 45-78

[10] Preus, Laurell. Periohåndboken ISBN-91-630-8907-6. 1999

[11] Kornman KS, Karl EH. The effect of long-term low-dose tetracycline therapy on the subgingival microflora in refractory adult periodontitis. J Periodontol 1982; 53:604-610

[12] Lindhe J, Liljenberg B, Adielsson B. Effect of long-term tetracycline therapy on human periodontal disease. J Clin Periodontol 1983; 10:590-610

[13] Herrera D, Sanz M. Systematic review on the effect of systematic antimicrobials as an adjunct to scaling and root planning in periodontitis patients. J Clin Periodontol 2000; 53: 604-610

[14] Petitti DB. Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine. Kaiser Permanente, Southern CA. 1994.

[15] Bergstrøm. Cigarette smoking as a riskfactor in chronic periodontal disease. Community Dent Oral Epidemiol 1989; 17:245-247

[16] Bergstrøm, Eliassen, Dock. Exposure to tobacco smoking and periodontal health. J Clin Periodontol 2000; 27: 61-68

[17] Haffajee Socransky. Relationship of cigarette smoking to attachment level profiles. J Clin Periodontol 2001; 28: 283-295

[18] Barbour. Tobacco and smoking: Environmental factors that modify the host respons (immune system) and have an impact on periodontal health. Crit Rev Oral Biol Med 1997; 8: 437-460

[19] U.S. Public health service, National Center for health statistics: *Periodontal disease in Adults, USA.* PHS publ No 1000, Series 11, 12, 16. Washington DC, Government printing office, 1965

[20] Abdellatif HM, Burt BA. An epidemiological investigation into the relative importance of age and oral hygiene status as determinants for periodontitis. J Dent Res 1987; 66: 13-18.