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Research Article

Effectiveness of Adjunctive Subantimicrobial Dose Doxycycline on Phase I of Periodontal Therapy

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Abstract

Background and aims. Periodontal disease is a complex interaction between bacteria and susceptible host. MMPs has a key role in periodontal disease and increase with disease severity which cause destruction of extra cellular matrix in chronic periodontitis. HMT is a therapeutic hypothesis which its objection is the reduction of tissue destrucion. Doxycyclines can inhibit MMPs activation through the synthesis of intracellular enzymes. The objective of this study was to evaluate the Effectiveness of adjunctive Subantimicrobial Dose Doxycycline on phase I of periodontal therapy.

Materials and methods. Forty patients with chronic periodontitis were included in this randomized double blind placebo control parallel group clinical study. After scaling and root planning patients were randomly assigned to two groups, receiving either SDD or placebo bid for 3 months and were evaluate in 3month and 6 month later.

Results. Clinical parameter improved significantly in both groups (p-value□0.0001). Significant reduction in PD, CAL and BOP was seen in SRP +SDD group compare to control group (p-value□0.0001).

Conclusion. Short administration of SDD gives significant benefit in clinical parameters in chronic periodontitis.

Key words: **SDD, clinical parameters, chronic periodontitis, host modulation therapy.**

Introduction

Periodontal disease is a complex interaction between microbial factors and a susceptible host[1]. In the past it was suspected that periodontal disease occurs due to plaque accumulation which accompany with the reduction of host response.[2,3,4]

While bacterial plaque (biofilm) was able to directly cause destruction of periodontal tissues, the greatest destruction of connective tissue and bone structures are the result of immunoinflammatory response - of susceptible host.[5,6] So the bacteria are necessary to cause periodontitis but not sufficient, susceptible host is essential for the progression of periodontitis.[5,6,7]

Matrix metalloproteinases (MMPs), Host-derived enzymes, cause periodontal destruction by changing osteoclast activity like cytokines and prostanoids.[5]

MMPs (including collagenase, gelatinase and Mtalloelastas) are homologues Metallodependent enzymes which are able to destruction and degradation of extracellular matrix and are effective in tissue remodeling in physiological and pathological conditions. MMPs which increase with the severity of periodontal disease cause degradation of extracellular matrix in chronic periodontitis.[8,9]

Successful periodontal treatment depend on the removal or reduction of pathogenic bacteria and proper host response with the purpose of removal pathogenic bacteria.[6] Studies have shown that scaling and root planning (SRP) can be effective in reducing the progression of periodontal disease.[1] However, after SRP, the result of this procedure may not be acceptable especially in deep pockets and in patients with risk factors.[8] SRP does not completely eliminate bacterial invasion completely and re colonization of bacteria occurs. Recently, treatment methods considering Host Modulation Therapy (HMT). In this therapeutic approaches in interaction between host-bacteria, the host will be considered which make the possibility of modifying or reducing destruction from chronic inflammatory response. In this approach, excessive and pathologic inflammatory response adjusted to provide wound healing and periodontal stability.[10] In HMTs, adjunctive to common periodontal treatment like SRP and periodontal surgery applying such drugs through systemic or topically for instance drugs from Tetracycline family.[11,12,13] Recently, a new perspective has been offered on the effectiveness of Tetracyclines in periodontal treatment. In this thesis suggested that tetracyclines and not other antibiotics can prevented collagenase activity. Tetracyclines inhibit collagenase activity which mechanism is independent to its antimicrobial effect.[14,15]

Tetracyclines block MMP activity by different mechanisms. For example Tetracyclines are capable of preventing osteoclasts and osteoblast-derived MMP activity, thus it prevents the bone resorption. Doxycycline was able to inhibit MMP activity derived from epithelial cells by preventing the synthesis of enzymes which are within the cells. The drug also reduces tissue damage by reducing the pre-inflammatory mediators such as IL1 and TNFα expression and increase collagen production, increased osteoblast activity and ultimately bone formation[5].

The only matrix metalloproteinase inhibitors that has accepted for clinical use in America, Canada and Europe and has used for the treatment of periodontitis is a member of the tetracycline family compounds called Doxycycline and specifically sub antimicrobia dose doxycycline (SDD) with the old name of low dose of doxcycline.[5]

SDD with a dose of 20 mg twice a day with brand name of periostat is effective for at least three months. Until now periostat is the only drug approved by the FDA which can inhibited the activity of MMPs involved in the degradation of collagen in connective tissue as a result of periodontal disease.

Materials and Methods

In this 6-month, double masked, randomized, placebo-controlled, parallel group study 40 patients with chronic periodontitis were selected. Inclusion criteria involve patients with at least 14 natural teeth and at least 8 pockets (PD≥5mm, CAL≥4mm). Lactation and pregnancy, systemic disease or hypersensitivity to any antibiotic from tetracycline family, history of using tetracycline antibiotic or any drug in previous 4 months ago, also history of smoking and alcoholism are exclusion criteria.

In the screening phase, after signing informed consent by the patients, PD, BOP and CAL by means of Williams probe in 4 points of each tooth(mesiobuccal, midbuccal, distobuccal and palatal) evaluated by one examiner. After selection of the patients, they randomly divided into two groups (SDD or placebo).

The next stage, in the treatment phase, non surgical periodontal treatment in other words scaling and root planning, was performed in one or two session. It must not be any tactile or visible deposit after scaling and root planning. Oral hygiene instructions, including methods of brushing and using dental floss (between dental health aids) were given in each session.

In the case group, patients take SDD twice a day for 3 months (in mornings and the other in evenings).

The last phase (evaluation phase) includes patient recalls. In each month patients were visited to take drugs and if there was any deposit re-scaling and strengthening oral hygiene instruction was carried out.

All clinical parameters examined in the third and sixth months (3 months after taking drugs).

After collection the data from all patients who participate completely all recall programs and due to normal distribution of data, we used T.test for the clinical parameters (PD, BOP and CAL) in this study

Results

Forty patients who met the inclusion criteria participated in this study. Of these participants, 26 female (65%) with a mean age of 53 years and 14 male (35%) were with a mean age of 51 years.

Among 40 patients, 34 patients participated the whole study period and 6 patients excluded from the study because of lack of participation in their recalls. The 34 patients were divided randomly into two groups, 17 patients in the case group and 17 patients in the control group. The case group were taking 20 mg Doxycycline capsules twice daily, while the control group taking placebo capsules containing starch. In case group at baseline the mean probing depth was 3.83 mm and in the control group, 4.02 mm which at the first 3 months of study the mean probing depth in the case group reached to 2.04 mm and in the control group reached to 3.05 mm, in the second trimester of the study decreased to 1.94 mm and 2.96 mm, respectively, in the case and control group. Comparison of these values showed significant reduction of probing depth in different time intervals (P-value<0.0001). At baseline of the study in the case group the mean BOP was 74.29 percent and in the control group was 75.82 percent which at first trimester of the study decrease to 51.65% and 61.18% respectively, and at last decrease to 40.06% and 58.82% after 6 months which comparison of these values in the different groups, were statistically significant (P-value<0.0001).

At baseline mean CAL in case group was 3.86 mm and 4.08 mm in the control group which after 3-month of the study, decreased to 2.65 mm in the case group and 3.10 mm in the control group, in the next 3 months decrease to 2.02 mm and 2.98 mm, respectively, in the case and control group which comparison of these values in the different groups, were statistically significant (P-value<0.0001).

Discussion

In this double blind, placebo control study, the effect of SDD as an adjunct to scaling and root planning in patients with chronic periodontitis was investigated.

Studies have shown that the progression of periodontal disease is the result of interaction of bacterial plaque in one hand and immunoinflammatory nature of host response on the other hand.

These two phenomena which can directly result in destruction of periodontal tissues related to each other by pre-inflammatory cytokines and proteolythic enzymes such as matrix metalloproteinases.

In new methods for the treatment of periodontitis, the etiopathologic factors involved in reaction chains provoked by bacteria in the host's immune system are being targethed. These reaction also affected by risk factors which causes release of cytokines and matrix metalloproteinase involved in destruction of host connective tissue. Thus, periodontal therapy involves dental plaque reduction, elimination of risk factors and use of tissue matrix metalloproteinase inhibitors. Gilowski et al in 2012 also studied the effect of SDD as adjunctive therapy in diabetic patients with chronic periodontitis.[16]

In this study, three clinical parameter (PD, CAL and BOP) were studied while in most of the studies like Emingil et al in 2004 and Gurkan et al in 2005 examined the effects of SDD on the inflammatory response by measuring cytokines in gingival sulcus.[12,14] The mean probing depth at baseline was 3.83 mm and 4.02 mm in case and control groups respectively. The difference between these indicator was not statistically significant and the severity of disease were similar between both groups at baseline. During the study probing depth decreased significantly in both groups in the first 3 months (P-value<0.0001). This is not unexpected due to mechanical treatment. In fact, scaling and root planning subside the inflammatory response and stop the progression of periodontal disease. This procedure prevent the proper environment for the colonization of periodontopathogen, also. The overall improvement in clinical parameter of mechanical treatment is likely to occur primarily through the reduction of microbial load. Also, after elimination of the inflammation and change in the ratio of cells to fibers, shrinkage occurs in the periodontal pocket and thus cause resistance to the entrance of periodontal probe. In the second three months of the study (6 months later) in both groups probing depths, again decreased to 1/94 mm in the case and 2.9 mm in the

control group, while the reduction of probing depth was more significant in case group than control group(P-value<0.0001). This results was according to Philip et al in 2004, Gulnur et al in 2004, Caton et al in 2001, which can be attributed to the effect of SDD in the reduction of host response.[8,14,18] Cosidering the inhibitory effect of Tetracyclines on matrix metalloproteinase and specifically better absorption of Doxycycline and its more effectiveness in the reduction of of collagenase activity in GCF, this drug was used. Preshaw et al in 2004 showed that SDD didn't cause antibiotic resistance, nor had antimicrobial effect[8]. In the present study only one patient in the case group complained of gastrointestinal upset.

SDD increases the predictability of clinical response to mechanical treatment and improves the cost/effectiveness of surgical and non surgical treatment compared with conventional treatment. BOP, the next index, was 74.29% and 75.82% in case and control groups respectively. Comparison of BOP at the baseline showed no significant difference between two groups. In the first 3 month of the study it decreases significantly to 51.65% and 61.18% in case and control groups and this reduction was more pronounced in the case group than the controls. The reason of reduction in the first 3 months can be attributed to mechanical treatment and reduction of inflammation in the periodontal tissues. Also, effectiveness of SDD must be considered in reduction of inflammation and cause stable condition in periodontal tissue in the case group. These results were according to the results of previous studies (Ciancio et al in 1998).[19] Reduction of BOP is more related to the improvement of the integrity of collagen structure in periodontal pocket.

CAL is the latest indicator of the study which at baseline, was 3.86 mm in case and 4.08mm in the control group. At baseline, comparisons of CAL showed significant differences between two groups but this didn't cause any problem in the design of the study because CAL shows the history of periodontal disease not the severity of present disease. Also, during the study CAL reduces and was more statistically significance in the first and second 3 month of the study than at the baseline; which shows the effectivenss of SDD.

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