ORIGINAL ARTICLE

The effect of locally delivered doxycycline as an adjunctive therapy to scaling and root planing in smokers

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Abstract

Background: Locally delivered doxycycline is found to be effective in managing periodontitis as an adjunct to scaling and root planing.
Aim: To evaluate the effect of locally delivered doxycycline (10%) with scaling and root planing in the periodontal treatment of smokers and to compare it with scaling and root planing alone.
Methods: Twelve smokers with chronic periodontitis and a pocket depth ($\geqslant 5$ mm) on posterior teeth that bleed on probing were selected. Patients were randomly assigned to scaling and root planing (SRP) or scaling and root planing followed by local application of doxycycline (SRP-D). Plaque, bleeding on probing, gingival recession, clinical attachment level (CAL), and probing depth (PD) were recorded at the baseline, 6 and 12 weeks.
Results: Both groups showed a significant reduction in Plaque, Bleeding on Probing and pocket depth at 6th and 12th week from the baseline. A statistically significant gain of attachment was observed in both groups after treatment. Even though the doxycycline group showed slightly higher attachment gain it was not statistically significant compared to the control group.

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Conclusion: The observations of the study reveal that the additional benefit of topical application of doxycycline as an adjunct to scaling and root planing in smokers is not convincing. However, further clinical studies may be necessary to substantiate the present observations.

1. Introduction

Periodontitis is a chronic inflammatory condition characterized by acute episodes of periodontal destruction occurring in response to an elevated bacterial load in a susceptible host (Offenbacher, 1996; Page, 1995). The successful long-term management of periodontitis may require an integrated treatment approach that addresses both the periodontopathic bacteria and the ensuing destructive host responses. Previous studies have demonstrated that topically administrated doxycycline improves some clinical parameters in patients with adult periodontitis (Caton et al., 2000; Ciancio and Ashley, 1998; Crout et al., 1996).

Subgingival scaling and root planing (SRP) is an effective means of slowing or arresting periodontal disease progression (Badersten et al., 1984a; Pihlstrom et al., 1983). The beneficial effects of SRP, which include gains in clinical attachment and reductions in probing depth (PD) and clinical inflammation, arise from a reduction in the microbial burden in the periodontal pocket or a shift toward less pathogenic microflora. However, the efficacy of SRP may be compromised at tooth sites with deep pockets and at sites with furcation involvements. Furthermore, the long-term success of SRP may be affected by remaining bacterial virulence factors and ineffective personal plaque control (Caton et al., 2000).

Smoking is known as a major risk factor for increasing the prevalence and severity of periodontal destruction (Papapanou, 1996). It accelerates the progression of periodontitis and jeopardizes the healing process following non-surgical periodontal therapy (Grossi et al., 1996; Johnson and Hill, 2004; Preber and Bergstrom, 1986). The non-surgical periodontal therapy eliminates or suppresses the putative periodontal microorganisms in the subgingival area. It is effective in reducing the probing depth and improving the clinical attachment gain in the majority of periodontitis cases (Badersten et al., 1984b), however, other cases like smokers respond less favorably to non-surgical periodontal therapy (Grossi et al., 1997).

The adjunctive antibiotics are used in Periodontics either as locally delivered or as systemically delivered agents. The advantages of locally delivered antibiotics include attaining higher concentration in the diseased sites which assures the control of infection, need for one time application only and the absence of systemic adverse effects. In addition, locally delivered antibiotics do not require patient compliance (Deo et al., 2010; Emingil et al., 2008; Golub et al., 2008; Gupta et al., 2008; Paquette, 2005; Slots and Rams, 1990; Tuter et al., 2010).

The locally delivered antibiotic agents are available for periodontal use in different preparations like doxycycline gel (Garrett et al., 1999). Atridox, a 10% formulation of doxycycline in a bioabsorbable, "flowable" poly-DL-lactide and N-methyl-2-pyrrolidone mixture delivery system that allows for controlled release over 7 days. It is safe and can reach and maintain a high concentration in pockets when compared

to other locally delivered antibiotics (Stoller et al., 1998). It sustains in the pockets for 7–10 days with minimum alteration in its concentration (Kim et al., 2004). Doxycycline has other activities beside its antibacterial property, e.g. anti-inflammatory property (Golub et al., 1985).

Only few reports are available on the effect of locally delivered doxycycline (Atridox®) as an adjunctive therapy to scaling and root planing in smokers (Deo et al., 2010; Machion et al., 2006; Ryder, 2007; Shaddox et al., 2007; Tomasi and Wennstrom, 2004; Tuter et al., 2010). Therefore, the present study was done to evaluate the effect of locally delivered doxycycline (10%) with scaling and root planing in the periodontal treatment of smokers and to compare it with scaling and root planing alone.

2. Subjects and materials

2.1. Study population

The data analyzed in the present report was generated from patients attending the Periodontic Clinic in the College of Dentistry, King Saud University, Saudi Arabia. Sixteen male participants with moderately advanced chronic periodontitis were enrolled in this clinical study. The clinical trial was carried out as a randomized, split-mouth design. It compared the clinical parameters response to two different treatment protocols (scaling and root planing with locally delivered doxycycline; Atridox® (Atridox, Tolmar, Inc. CO 80526, USA) and scaling and root planing alone) at different time points; baseline, after 6-weeks and after 12-weeks. The oral cavity of each patient was divided into two halves; right and left. Each half received scaling and root planing with or without locally delivered doxycycline application.

The patients enrolled in the study fulfilled the following inclusion criteria: (1) age between 28 and 60 years; (2) must be a cigarette smoker for more than 5 years; (3) presence of moderate to severe chronic periodontitis; (4) the presence of 16 teeth with a minimum of four periodontal pockets of probing depth of $\geqslant 5$ mm and bleeding upon probing in each half mouth of the posterior teeth and (5) the willingness to participate and to follow up until the end of the study. The exclusion criteria included: (1) periodontal treatment performed in the 6 months prior to baseline examination; (2) use of mouth washes in the last one month from baseline examination; (3) presence of signs of aggressive periodontitis; (4) patients with diabetes mellitus, cardiovascular diseases and those taking medicines; (5) patients with history of allergy to doxycycline or (6) history of use of systemic antibiotics before 6 weeks of the baseline examination or during the study.

All patients were given a verbal explanation of the clinical trial and an informed written consent was obtained from each participant. Each patient was educated about the cause of periodontal diseases and proper oral hygiene was instructed.

Instructions included: brushing teeth with modified Stillman technique, using a toothbrush and using waxed dental floss or inter-proximal brush when interdental spaces were present. Instructions were personalized according to the patient's need, with the objective of obtaining the best plaque control.

2.2. Clinical examination

The principal investigator was calibrated to ensure the level of reproducibility. Duplicate measurements of the probing pocket depth, gingival recession, taken 1 h apart, were performed in 5 patients in a pre-study training period (Machion et al., 2004). A total of 780 probed sites were assessed for calibration. Pearson's correlation test and Student paired t-test were applied to verify reproduction of measurements. The examiner was considered calibrated, once the positive statistically significant correlation was obtained and no statistically significant differences between duplicate measurements were found. Within 1 week, all selected patients were appointed for the baseline clinical examination. The clinical examination was repeated after 6 and 12 weeks after treatment using the Florida probe system (Florida probe corporation, Gainesville, FL, USA).

Occlusal stents were constructed for upper and lower arches in each patient mouth. Fixed guiding steering grooves (buccal, lingual and/or palatal) and interproximal notches were made on the stent for each tooth included adjacent to the measured sites. The stents were used at the baseline, after 6 and 12 weeks examinations.

The clinical parameters examined in the present study included: plaque index (PI) according to Silness and Loe (1964), Bleeding on probing (BOP) (Ainamo and Bay, 1975): (six sites MB, B, DB, ML, L and DL) were examined on each tooth. Pocket probing depth (PPD), gingival recession (GR) and clinical attachment level (CAL) were also measured at six sites around each tooth (Armitage, 1999).

2.3. Scaling and root planing

For each patient 1–2 days following the baseline data collection, a full mouth scaling and root planing were carried using an ultrasonic device and hand instruments until the root surface felt smooth with the tip of a metallic probe. It was followed by professional prophylaxis to remove the stains for each patient immediately after scaling and root planing. The professional prophylaxis and oral hygiene instructions were continued for each patient every 2 weeks during the 12 weeks clinical trial.

Randomization was applied to avoid the bias of scaling and root planing by the clinician. A prepared sealed envelope was produced for each patient according to his series number. The envelope was opened at the day of treatment after the completion of scaling and root planing; then either the right or left half was chosen for doxycycline (Atridox®: Atrix Laboratories Ltd., London, UK) application.

2.4. Doxycycline (Atridox®) application

For each patient one or two packages of Atridox® were used according to the manufacturers' instructions. The product was applied using the cannula in either right or left side of the mouth (molars and premolars only were used) as indicated by randomization procedure. The side of drug application was labeled as Group A (SRP + D) and the contra lateral side as Group B (SRP). Periodontal dressing (Coe-Pak™, GCAmerica, Inc., Chicago, IL) was used to keep the locally delivered doxycycline (Atridox®) inside the pockets and to make the patient more comfortable (Garrett, 1999; Stoller et al., 1998).

All patients attended the first week follow-up visit. First, the periodontal dressing and the residual doxycycline product were removed (Radvar et al., 1996). Then, the evaluation involved a brief history by enquiring about complaints and visual examination of any soft tissue changes after periodontal dressing removal. All patients were asked to resume brushing since then.

2.5. Statistical analysis

The data was analyzed using SPSS software (www.spss.com, version 10). Patient mean values of plaque index, bleeding on probing, probing depth, gingival recession and clinical attachment level were calculated for both groups as a basis for statistical analysis. Repeated Measures Design of Borferoni test was used to detect intra-group differences among all periods. Student's independent t-test was used to detect inter-group differences in clinical parameters for each time interval (baseline, after 6 and 12 weeks). In all inferences, P-value of < 0.05 was accepted as statistical significance.

3. Results

Twelve smokers (10 cigarettes per day) with a mean age of 39.43 ± 8.15-years were treated according to study protocol. Four patients out of the 16 recruited for the study, failed to continue the follow-ups and were excluded from the study.

3.1. Plaque index and bleeding on probing

The results of the mean plaque index and bleeding on probing of the two groups at the baseline, 6th and 12th week are presented in Table 1 and Fig. 1. The mean plaque index and bleeding on probing of Group A were significantly higher than the mean plaque index and bleeding on probing of Group B at the baseline examination ($P < 0.05$). The mean reduction in
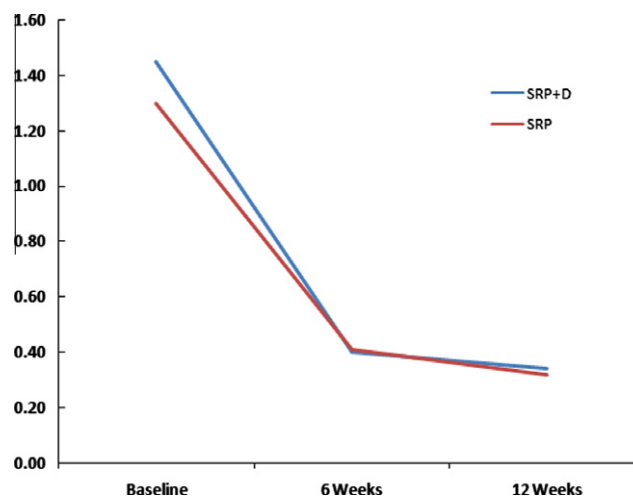

Figure 1 Mean plaque index at baseline, 6th and 12th week (SRP, scaling and root planing; D, doxycycline).

Table 1 Plaque index and bleeding on probing of the two groups (BOP, bleeding on probing; PD, probing depth; GR, gingival recession; CAL, clinical attachment loss).

	Groups	Baseline Mean ± SD	6 Weeks Mean ± SD	12 Weeks Mean ± SD
Plaque index	A	1.45 ± 0.76[a]	0.40 ± 0.63[b]	0.34 ± 0.54[b]
	B	1.30 ± 0.80[a]	0.41 ± 0.56[b]	0.32 ± 0.56[b]
BOP	A	0.43 ± 0.49[a]	0.16 ± 0.36[b]	0.18 ± 0.38[b]
	B	0.30 ± 0.48	0.14 ± 0.35[b]	0.17 ± 0.38[b]
PD (5–6 mm)	A	5.35 ± 0.35	3.22 ± 1.28[a]	3.28 ± 1.14[a]
	B	5.36 ± 0.35	3.47 ± 1.22[a]	3.17 ± 1.15[a]
PD (⩾7 mm)	A	8.00 ± 0.96	4.97 ± 1.68[a]	4.66 ± 1.75[a]
	B	7.72 ± 0.64	4.44 ± 2.26[a]	4.40 ± 2.01[a]
GR	A	0.39 ± 0.97	0.66 ± 1.17[a]	0.89 ± 1.34[a]
	B	0.38 ± 0.96	0.66 ± 1.23[a]	0.93 ± 1.42[a]
CAL	A	3.80 ± 1.75	3.24 ± 1.71[b]	3.28 ± 1.79[b]
	B	3.78 ± 1.65	3.19 ± 1.62[b]	3.25 ± 1.64[b]

[a] ($P < 0.05$) Statistically significant difference at baseline.
[b] ($P < 0.05$) Statistically significant change from the baseline visit (intra-group).

plaque and bleeding on probing in both groups at 6th and 12th week was significant from the baseline. No significant differences were observed between the groups at 6 and 12 weeks visits.

3.2. Probing measurements

Table 1 presents the summary results for gingival recession (GR), probing depth (PD) and clinical attachment loss (CAL). At baseline, mean GR was 0.39 mm for Group A and 0.38 mm for Group B. A statistically significant increase was observed after treatment at 6 and 12 weeks in both groups. The mean pocket probing depth of moderate pockets (sites of 5–6 mm) and deep pockets (⩾7 mm) were similar at the baseline and they showed a significant reduction ($P < 0.05$) after the treatment at the 6th and 12th week visits with no significant differences between the two groups ($P > 0.05$).

At the baseline, similar results of CAL were observed. A statistically significant gain of attachment (Table 2 and Fig 2) was observed after the treatment ($P < 0.05$) with no significant difference between the two groups at the 6th and 12th week visits ($P > 0.05$). Gain in the attachment of Groups A and B was the same at the 6th and 12th week (Group A: 0.53 ± 1.04 mm vs. Group B: 0.58 ± 1.11 mm).

4. Discussion

The study used a split-mouth design that has the advantage of eliminating the inter-individual variables (Imrey, 1986; Radvar et al., 1996). However, it carries a risk of transferring the tested

Table 2 Mean gain of attachment (mm) and SD values of the two groups.

Groups	Baseline to 6-week Mean ± SD	Baseline to 12-week Mean ± SD
A	0.53 ± 1.00	0.53 ± 1.04
B	0.59 ± 0.98	0.58 ± 1.11
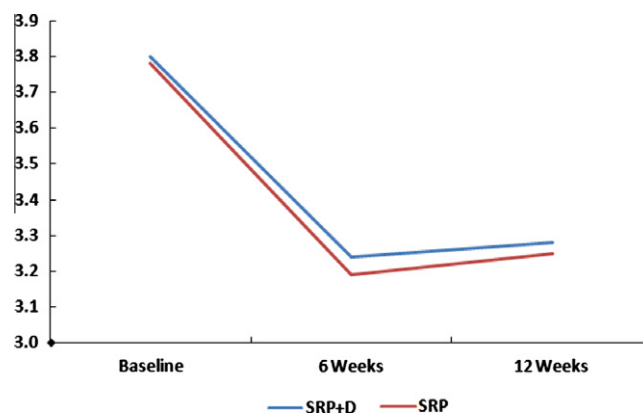
Figure 2 Mean clinical attachment loss (CAL) at baseline, 6th and 12th week (SRP, scaling and root planing; D, doxycycline).

agent from one quadrant to another and may lead to false results (Jorgensen et al., 2004). To minimize this effect a periodontal dressing was applied on the side of doxycycline application.

The mouth design and the allocation of the quadrants to the two groups (Group A: scaling and root planing with locally delivered doxycycline and, Group B: scaling and root planing alone) resulted in similar baseline values of the probing pocket depth, gingival recession and clinical attachment level. Mean pocket probing depth was 3.41 mm in Group A and 3.40 mm in Group B, with no significant difference between the two groups. It was similar in the moderate pockets (5–6 mm) and deep pockets (⩾7 mm). The gingival recession and clinical attachment level also showed similar results in the two groups. However, at the baseline examination, the mean plaque index and mean bleeding on probing were significantly higher in Group A than mean plaque index and mean bleeding on probing in Group B.

It was also proved that the topically administered doxycycline could reach the pockets in higher concentrations and could be maintained for a longer period compared to systemically administered doxycycline (Stoller et al., 1998). Higher

concentrations of the doxycycline in the gingival crevicular fluid (GCF) enhance their action against microbes (Kim et al., 2002, 2004) and may mitigate the effects of smoking effect in the local environment of the pockets (Ryder, 2007).

It is well established in the literature that smokers respond less favorably to periodontal treatment than non-smokers (Ah et al., 1994; Kaldahl et al., 1996). Few studies showed that the use of adjunctive controlled delivery of drugs may improve the clinical response to periodontal treatment in these patients (Machion et al., 2004, 2006; Tomasi and Wennstrom, 2004). Lowenguth and Greenstein (1995) showed a greater reduction in *Porphyromonas gingivalis* after 3 months use of adjunctive tetracycline fibers compared to conventional scaling and root planing (SRP) alone. However, other studies by Salvi et al. (2002) and Jorgensen et al. (2004) found no additional reductions in the subgingival microbiota after treatment with adjunctive local drugs compared to SRP. The observations of the present study are in agreement with the later studies showing no additional benefits of locally applied doxycycline in smokers. Akalin (2004) evaluated the clinical effects of doxycycline as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis. They showed no significant differences between the group of SRP alone and SRP and doxycycline.

A study by Machion et al. (2004) evaluated the effect of scaling and root planing with locally delivered doxycycline (SRP-D) compared to SRP alone in smokers. Their results showed no additional effect of doxycycline on BOP; however better results were observed in probing depth. Moderate pockets (sites of 5–6 mm) responded equally at the 6th week, 12th week and 6th month examinations. In the present study, slightly better PPD reduction of moderate pockets in Group A was observed at the 6th week visit but it was not significant. Regarding the 12th week visit, the findings of the moderate pockets in the present study are in agreement with the observations.

The clinical effects of locally delivered doxycycline to scaling and root planing had been evaluated in several studies (Akalin, 2004; Eickholz et al., 2002; Gupta et al., 2008; Machion et al., 2004; Tomasi and Wennstrom, 2004; Tuter et al., 2010; Wennstrom et al., 2001). These studies had shown varying results, which can be attributed to the treatment regimens followed. Eickholz et al. (2002) compared in a split mouth design the SRP alone, SRP with vehicle application and SRP with doxycycline application on single rooted teeth in 3 and 6 months observation period. They reported better results in mean reduction of BOP, mean probing depth reduction and attachment level gain which favored the group of SRP and doxycycline application.

The reduction of the probing depth of the pockets post-periodontal therapy is mainly due to the gain in the clinical attachment and/or shrinkage in the gingiva. The gingival shrinkage occurs usually as a result of the instrumentation-mainly hand instruments (Ewen et al., 1976) and due to resolution of the gingival inflammation. The mean gingival recession at the baseline examination of this study was similar and increased significantly after treatment with no significant difference between both groups. The reduction of the pocket probing depth in the present study which continued from 6th week to 12th week was due to the attachment gain and the shrinkage of the gingiva. By maintaining a good level of plaque control, the improvements of the clinical

parameters could be sustained. The proposed treatment was well tolerated by the patients. Only one patient developed gingival soreness at the site of doxycycline application that healed within 10 days. In general, the topical application of doxycycline is safe and the observation of the present study is in agreement with previous reports (Deo et al., 2010; Eickholz et al., 2002; Golub et al., 2008; Tuter et al., 2010; Wennstrom et al., 2001). Other patients in both experimental groups complained from dentinal sensitivity after the treatment which disappeared within the period of the study.

It can be concluded that the topical application of doxycycline along with scaling and root planing had no additional benefits over the mechanical therapy alone.

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