

Therapy with adjunctive doxycycline local delivery in patients with type 1 diabetes mellitus and periodontitis

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Abstract

Objectives: The purpose of this study was to evaluate the effect of subgingival administration of doxycycline as an adjunct to periodontal therapy in type 1 diabetes mellitus (DM) patients.

Material and methods: Twenty-two paired periodontal defects ≥ 5.0 mm were treated in 11 patients (35–55 years old). After initial therapy the sites were randomly assigned into test (scaling and root planing+subgingival administration of 10% doxycycline hyclate gel) or control (scaling and root planing+subgingival placebo gel) groups. The clinical parameters of clinical attachment level (CAL), probing depth (PD) and gingival margin level (GML) for recession determination were assessed at baseline, after 6 weeks, and 6, 9 and 12 months, using a computerized probe. Data were statistically evaluated using Duncan and *F* tests.

Results: Between study group comparisons indicated PD reduction and CAL gain were greater in the test group than in the control group at 6 weeks and 6, 9 and 12 months but only statistically significant at 12 months ($p < 0.05$). Within study group comparisons indicated statistically significant differences were found for CAL and PD values favouring the adjunctive doxycycline group from baseline to 6 weeks and 6, 9 and 12 months ($p < 0.05$).

Conclusions: These findings suggest that subgingivally delivered doxycycline hyclate produces additional favorable clinical results to periodontal therapy in type 1 DM patients.

Key words: doxycycline local delivery; periodontal therapy; scaling and root planing

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Periodontitis is an infectious disease characterized by loss of periodontal tissue support. In the treatment of periodontally involved teeth, current concepts are based on mechanical scaling and root planing in order to remove bacterial deposits, calculus and cementum contaminated by bacteria and endotoxins (Polson et al. 1984). Specific systemic diseases including uncontrolled diabetes may increase an individual's susceptibility to progressive periodontitis (Genco 2000).

Diabetes mellitus (DM) encompasses a heterogeneous group of disorders with

altered or impaired lipid and carbohydrate metabolism (AAP 2000). Periodontal disease is more frequent and severe in uncontrolled diabetic individuals than individuals without diabetes or individuals with well controlled diabetes in the same population (Novaes et al. 1997, Soskolne 1998, Bacic et al. 1988, Soskolne & Klinger 2001, Tsai et al. 2002). Hyperglycemia progressively glycosylates body proteins, forming advanced glycation end products (AGE). This in turn, may stimulate phagocytes to release inflammatory cytokines such as TNF- and IL-6 that play a central role

in diabetic complications and impair the normal formation of extracellular matrix components (Brownlee 1994). These alterations have an adverse effect on periodontal tissues, especially collagen stability and vascular integrity, increasing susceptibility to tissue destruction (Salmela et al. 1989, Schmidt et al. 1996). Furthermore, it was observed that crevicular fluid collagenolytic activity triggered by collagenase from neutrophils was increased in diabetic patients (Sorsa et al. 1992). This collagenase further compromises the integrity of the periodontal tissues

increasing an individuals susceptibility to progressive periodontitis (Sorsa et al. 1989, Sorsa et al. 1992).

Tetracycline antibiotics, including doxycycline, have been introduced as adjuncts in the treatment of periodontal disease. The rationale for the introduction of tetracycline as adjuncts to periodontal therapy was that their broad-spectrum bacteriostatic activity could shift the potentially harmful Gram-negative subgingival flora towards a Gram-positive microbial flora which is more compatible with periodontal health (Williams et al. 1979). Tetracycline exhibits additional non-antimicrobial pharmacological properties including antiproteolytic activity, inhibition of collagenase activity and bone resorption, anti-inflammatory properties to suppress PMN activity, and scavenging action on reactive oxygen metabolites (Martin et al. 1974, Gabler & Creamer 1991). With respect to collagenase inhibition by the tetracycline family of antibiotics, doxycycline has been found to be the most potent form. Doxycycline has been incorporated into a local delivery system for placement into a periodontal pocket which takes advantage of its antimicrobial activity and also likely its anticollagenase activity.

Local delivery of antibacterial agents into periodontal pockets has been extensively developed and investigated since the late 1970s (Goodson et al. 1979, Lindhe et al. 1979, Friedman & Golomb 1982, Goodson et al. 1983, Minable et al. 1989, Ainamo et al. 1992, Van Steenberghe et al. 1993, Newman et al. 1994, Ciancio & Ashley 1998, Al-Mubarak et al. 2002). Many local delivery systems have been designed to maintain high levels of antimicrobial agents for a prolonged period of time in the crevicular fluid with minimal systemic uptake (Thomas et al. 1998, Wennstrom et al. 2001). One of these local delivery systems is 10% doxycycline hyclate gel.

The use of a local delivery system as an adjunct to periodontal therapy in individuals who have a systemic disease, such as diabetes, and, who would be more susceptible to progressive periodontitis, has not been addressed significantly in clinical investigations. The introduction of local delivery antibiotic therapy to improve the healing response and clinical results after conservative periodontal therapy would be of great value in the treatment of diabetic patients with periodontitis. Therefore, the purpose of this study was to evaluate the clinical effect of a local delivery system with

10% doxycycline hyclate gel as an adjunct to periodontal therapy and specifically root planing in type 1 DM patients.

Materials and Methods

Study population

Patients with type 1 DM were referred for treatment of advanced periodontal disease. Exclusion criteria included subjects with other systemic complications, a history of systemic antimicrobial therapy over the past 6 months or hypersensitivity to tetracycline or any related antibiotic. Eleven subjects, nine females and two males, aged 35–55 years, completed this study. Patients were enrolled for initial therapy which included oral hygiene instruction, supra-gingival ultrasonic instrumentation and appointments for full-mouth scaling and root planing under anesthesia prior to the experimental phase. Each patient contributed two sites which were used for measurements. Sites included were required to have (1) probing depth (PD) ≥ 5.0 mm and (2) bleeding and/or suppuration on probing. Patients fulfilling the inclusion criteria were informed about the study and they signed the informed consent.

Study design

This study had a split mouth design and was conducted to test the null hypothesis of no difference between study groups. Two sites per patient or a total of 22 periodontal defects from the eleven patients in the maxillary incisor or canine areas were randomly assigned to be treated with thorough scaling and root planing under local anesthesia. At the completion of the scaling and root planing, an experimental doxycycline hyclate gel (methocel (Farmacia Escola Comunitaria (FAQFAR), University of Itajaí, Brazil) with 10% doxycycline hyclate (MASE Produtos Químicos e Farmaceuticos Ltda., Cambuci, São Paulo, Brazil) test group) or a placebo gel (methocel, control group) was administered with a syringe subgingivally. The test and control implanted gel material were provided in two different syringes. As a double blind study design, the operator and the patients were blind whether a syringe contained the test or control gel. The gel material was inserted into the periodontal pocket until the gel was extruded from the pocket. Both the test and control sites

were treated at the same appointment and immediately following the root planing procedures. Patients were instructed to modify their mechanical plaque control at the experimental sites by gentle brushing and no flossing for 4 weeks. Patients were seen after 6 weeks, then at 3, 6, 9 and 12 months for periodontal maintenance until the end of the study. Each visit, except at month 3, included the assessment of gingival margin level (GML), PD and clinical attachment level (CAL).

Clinical measurements

Clinical parameters were assessed at baseline and after 6 weeks, 6, 9 and 12 months including (1) GML for determination of recession = the distance from cemento enamel junction (CEJ) to the gingival margin, (2) PD = the distance from gingival margin to the base of the pocket and (3) CAL = the distance from CEJ to the base of the pocket. All measurements were recorded with an electronic probe (Florida Probe, Florida Probe Co., Gainesville, FL, USA).

Statistical analysis

For statistical analysis split plot designs were used. Plots were based on treatment (test or control), and subplots were formed by clinical evaluation times; that is, baseline, 6 weeks and 6, 9 and 12 months. When the interaction evaluation time \times treatment was significant, a partitioned freedom of degrees for evaluation times in each treatment group was completed and it was related to the effect of treatment at each evaluation time. The comparisons among evaluation times and between treatments were done by Duncan and *F* tests, respectively. All statistical tests were conducted at a significance level of $p \leq 0.05$.

Results

Mean clinical measurements in diabetic patients with periodontitis at sites treated with root planing plus adjunctive doxycycline or root planing alone is shown in Table 1.

Recession

Recession measurements demonstrated no significant differences ($p \geq 0.05$) between study groups at baseline, 6 weeks and 6, 9 and 12 month time

Table 1. Mean (\pm SE) clinical measurements in diabetic patients with periodontitis at sites treated with root planing plus adjunctive doxycycline or root planing alone⁺

	Baseline	6 weeks	6 months	9 months	12 months
Recession					
SRP + Dx (n=11)	0.8 (0.2)	2.0 (0.4)	2.0 (0.4)	2.0 (0.4)	2.0 (0.4)
SRP (n=11)	0.9 (0.3)	1.7 (0.6)	1.8 (0.4)	1.8 (0.4)	1.8 (0.4)
Probing depth					
SRP + Dx (n=11)	6.0 (0.3)	2.5 (0.2)	2.1 (0.2)	2.0 (0.2)	2.0 (0.2)#
SRP (n=11)	5.8 (0.3)	3.3 (0.4)	3.6 (0.4)	3.8 (0.4)	3.9 (0.4)
Attachment level					
SRP + Dx (n=11)	7.2 (0.4)	4.5 (0.5)	4.1 (0.5)	4.0 (0.4)	4.0 (0.4)#
SRP (n=11)	6.6 (0.5)	5.1 (0.5)	5.4 (0.6)	5.6 (0.6)	5.7 (0.5)

⁺SRP+Dx = Scaling and root planing+doxycycline study group.

SRP = Scaling and root planing study group.

Values connected by a solid line indicate intra (within) study group statistically significant difference, $p \leq 0.05$.

#Represents inter (between) group statistically significant difference, $p \leq 0.05$.

points. Comparison of recession measurements between baseline and the follow-up examinations (6 weeks, 6 months, 9 months, 12 months) indicated no significant differences ($p \geq 0.05$) for either the adjunctive doxycycline group or the SRP alone group.

Probing depth

PD measurements demonstrated no significant differences between study groups at baseline. For PD, the adjunctive doxycycline group when compared with the SRP alone group at 6 weeks, and 6, 9 and 12 months demonstrated mean PDs of 2.5 versus 3.3 mm (difference = 0.08 mm), 2.1 versus 3.6 mm (difference = 1.5 mm) and 2.0 mm versus 3.8 mm (difference = 1.8 mm) and 2.0 mm versus 3.9 mm (difference = 1.9 mm), respectively. A statistically significant difference for PD between study groups was only present at 12 months favoring the adjunctive doxycycline group ($p \leq 0.05$). Comparisons of PD measurements between baseline and each of the follow-up examinations (6 weeks, 6 months, 9 months, 12 months) indicated significant differences ($p \leq 0.05$) between each time point for the adjunctive doxycycline group or the SRP alone study groups.

Attachment level

Attachment level measurements demonstrated no significant differences between study groups at baseline. For attachment level, the adjunctive doxycycline group when compared with the SRP alone group at 6 weeks and 6, 9 and 12 months, demonstrated mean attachment level values of 4.5 versus 5.1 mm (difference = 0.6 mm), 4.1 versus 5.4 mm (difference = 1.3 mm), 4.0 versus 5.6 mm (difference = 1.6 mm) and 4.0 versus 5.7 mm (difference = 1.7), respectively. A statistically significant difference for CAL between study groups was only seen at 12 months favoring the adjunctive doxycycline group ($p \leq 0.05$). Comparisons of CAL measurements between baseline and each of the follow-up examinations (6 weeks, 6 months, 9 months, 12 months) indicated significant differences ($p \leq 0.05$) between each time point for the adjunctive doxycycline group or the SRP alone study groups.

Discussion

DM can be divided into two main types: type 1, formerly insulin-dependent DM, caused by destruction of the insulin producing β cells in the pancreas, and type 2, formerly non-insulin dependent

diabetes, that results from impaired insulin function, such as insulin resistance rather than deficiency (AAP 2000). Diabetes is a glycemic metabolic disorder with the accumulation of free fatty acids, glucose and AGE products in the extracellular matrix. In addition, DM is associated with changes in the micro- and macrovascularization resulting in adverse consequences for virtually all body tissues, including the periodontium (Tonetti 1997). The major complications of diabetes are retinopathy, nephropathy, neuropathy, heart disease and stroke with periodontal disease often considered the sixth complication of DM. Control of diabetes is therefore directed at keeping the blood glucose levels within normal limits, and there is clear evidence that complications can be prevented by the meticulous control of diabetes. In the diabetic patient, periodontal treatment without and with adjunctive systemic antibiotic therapy has been shown to not only help improve the periodontal status but also contribute to better glycemic control in the uncontrolled diabetic patient (Grossi et al. 1997, Christgau et al. 1998, Stewart et al. 2001, Taylor 2001).

Tetracycline is a broad spectrum antimicrobial that has been reported to exhibit substantivity in the gingival crevice. In addition, the tetracyclines have been reported to exhibit anti-collagenolytic activity in the gingival crevice or periodontal pocket. The in situ higher concentration of the tetracycline enhances its bacteriostatic action, inhibits the development of resistant strains, as well as interferes with the accumulation of toxic components in the extracellular matrix, such as AGE's.

The study design used for this clinical trial was a split mouth design rather than a parallel design. There have been a number of published reports concerning the evaluation of local delivery agents which have used a split mouth study design (Stabholz et al. 1998, Stabholz et al. 1991, Ciano et al. 1992, Fine et al. 1994, Soskolne et al. 1997, Stabholz et al. 1998, Wong et al. 1999, Heasman et al. 2001, Eickholz et al. 2002). Because of the limited number of type 1 diabetic patients available for this study, we chose to use a split mouth study design. One site in a patient's mouth was treated with adjunctive doxycycline local delivery and a controlled site, which had a similar disease

status, received placebo gel. A concern in the split mouth study design was that the adjunctive doxycycline local delivery agent could affect the clinical results observed at a control site treated with placebo in the same patient. If this occurred, and it may have, then we would expect the adjunctive doxycycline to have a favorable clinical effect on the placebo treated site. We still observed significantly better clinical results at 12 months for the adjunctively treated doxycycline sites over the placebo treated sites. However, future investigations with local delivery antimicrobial agents, where a larger number of type 1 diabetic patients would be available, should consider the more ideal parallel study design.

In our study, the experimental sites were treated with scaling and root planning plus a single subgingival administration of 10% doxycycline hyclate gel or scaling and root planing plus a single application of a placebo gel. To insure optimal oral hygiene over the course of this study, all patients were seen weekly in the first month, and monthly until the end of the study to reinforce a strict oral hygiene regimen. However, it should be noted, the clinical parameters were evaluated only at baseline, after 6 weeks, and at 6, 9 and 12 months. No experimental site was lost in this study, and throughout the investigation, patients demonstrated effective plaque control and patient's diabetic status was well controlled.

PD and CAL changes of 3.0 mm or more at 12 months in the adjunctive doxycycline group represented a dramatic improvement in periodontal health and was of clinical significance. In the present study, at 12 months, the percentage of sites that exhibited PD reduction ≥ 3.0 mm was greater in the group with adjunctive doxycycline (90%) than the group with adjunctive placebo (27%). In the same way, the percentage of sites that exhibited a gain in CAL ≥ 3.0 mm was greater in the adjunctive doxycycline group (64%) than the control group (0%). These results indicate that the adjunctive administration of doxycycline to scaling and root planing in the treatment of periodontal disease had a favorable impact on the clinical outcomes of patients with diabetes. However, we are aware that our results need to be interpreted with caution due to the small sample size; that is, only one site in eleven patients received SRP plus

adjunctive doxycycline ($n = 11$ sites) and SRP alone ($n = 11$ sites). In future studies that involve a greater number of patients and sites, data could be evaluated in terms of how extent and severity of disease may reflect the actual efficacy of the adjunctive doxycycline local delivery agent.

Our results are in agreement with those reported by Van Oosten et al. (1986). These investigators, however, used a single dose of amoxicillin administered systemically. Wolinsky et al. (2001) concluded that the treatment of periodontitis with only locally delivered doxycycline hyclate resulted in clinical improvements comparable with scaling and root planning alone irrespective of the patient's prophylaxis frequency. Wennstrom et al. (2001) and Seymour & Heasman (1995) concluded that one single episode of subgingival instrumentation combined with local application of doxycycline in deep periodontal pockets was justified for a non-surgical treatment approach for chronic periodontitis.

Our results also agree with those reported by other investigators in that SRP is an effective therapy for treating periodontitis (Bjorvatn 1983, Listgarten et al. 1974, Hallmon & Mealey 1992, Garrett et al. 2000, Caton et al. 2000, Caton et al. 2001). The most notable changes in PD and CAL occurred during the first 6 weeks for both study groups. However, in the adjunctive doxycycline group the parameter improvements were sustained beyond 6 weeks and over the entire 12-month study period. In contrast, PD and CAL clinical improvements in the SRP only group demonstrated a trend to return toward baseline levels at 12 months.

We have found that adjunctive doxycycline therapy provided better clinical results in a short period of time which are maintained over a longer period of time (12 months) by excellent supportive maintenance therapy. It would be of interest to investigate if the periodontal treatment protocol followed in this study may be of value in type 2 diabetic patients as was found to be the case in type 1 diabetics. We conclude that adjunctive doxycycline local delivery produces additional favorable results when associated with SRP therapy in type 1 diabetic patients. Furthermore, these additional improvements were maintained up to 12 months for patients following a strict oral hygiene regimen.

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