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Clinical Efficacy of Local Delivered Minocycline in the Treatment of Chronic Periodontitis Smoker Patients

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Abstract

Aim: The aim of this study was to evaluate the efficacy of a locally delivered 2% minocycline as an adjunct to scaling and root planing plus oral hygiene measures in treating chronic periodontitis smoker patients.

Materials and Methods: This was a randomized controlled trial using a split-mouth study design. Twenty pairs of sites in twenty smoker patients with similar deep probing depths were randomly allocated to test and control groups. The test sites received minocycline after root debridement. The clinical parameters included the plaque index, probing pocket depths, attachment levels, and bleeding upon probing. They were evaluated at the baseline, and after 3 and 6 months.

Results: Both the test and control sites showed statistically significant improvements in the clinical periodontal parameters over the baseline measurements during the study period (P<.05). In follow-up, the intervals sites that received minocycline showed more favorable results manifested by probing depth reduction. This improvement was constant at 3 and 6 months and the difference between the two groups was statistically significant (P<.05).

Conclusion: The study results show that patient motivation to maintain meticulous oral hygiene self-care with adjunctive professional dental care using local delivery 2% minocycline can significantly enhance treatment outcome of deep periodontal pockets in chronic periodontitis smoker patients.

Keywords: Minocycline; Local delivery; Smoking; Chronic periodontitis

Introduction

Local delivery of antimicrobial agents in treating periodontitis patients is becoming more prevalent since it leads to higher concentration of the drug at the intended site of action using a lower dose with an associated reduction in side effects relative to systemic administration [1,2]. However, despite many studies in the periodontal literature on the local delivery concepts, surprisingly there are few studies that demonstrate the clinical efficacy using intra-pocket delivery systems [3-5]. Moreover, several studies have failed to show clinically important effects provided by the intra-pocket drug delivery systems when used as individual mono-therapy. Other studies have demonstrated that these systems have beneficial effects in terms of probing depth reduction; however, the statistical significance reached in these studies was not always clinically significant [6,7]. Smoking is known as a major risk factor for increasing the prevalence and severity of periodontal destruction. In general, studies have shown that smoking increases the risk for developing periodontal disease by two to five folds, and these effects seem to be dose dependent. Also, smoking accelerates the progression of periodontitis and jeopardizes the healing

process following non-surgical periodontal therapy [8-10]. The non-surgical periodontal therapy eliminates or suppresses the putative periodontal microorganisms in the subgingival area with beter treatment outcome in non-smokers than smokers in most of periodontitis patients [10]. The use of local drug delivery system to improve the clinical response in chronic periodontitis smokers patients is an area of controversy, as conflicting results have been reported and many studies called for further clinical trials to objectively evaluate its effectiveness [11-13]. The purpose of this study was to evaluate the clinical efficacy (i.e. success in terms of bleeding upon probing and probing depth reductions as well as improving clinical attachment level) of a 2% minocycline as an adjunct to scaling and root planing plus oral hygiene measures in managing moderate to severe chronic periodontitis in smoker patients.

Materials and Methods

Participants

This study was conducted at the Department of Oral Surgical Sciences, Division of Periodontology, Faculty of dentistry, Beirut Arab University (BAU)-Lebanon after approval of Institutional Review Board (IRB) with trial NO.2014H-004-D-R-0017.Patients were first briefed about the study and written consent was obtained. The study was performed in compliance with the principles of the Declaration of Helsinki and was conducted from November 2013 to June 2014.

Inclusion criteria: Twenty smoker patients suffering from moderate to severe chronic periodontitis, with clear medical history were included in the study. Subject was classified as current smoker if he or she regularly smoked more than 10 cigarettes/day for a minimum of 5 years. Subjects with no history of any periodontal treatment 6 months prior to the study. Moderate chronic periodontitis was defined as an attachment loss of 4mm on at least two teeth and severe chronic periodontitis was defined as attachment loss of >5 mm on at least two teeth

Exclusion criteria for patients included systemic illnesses (i.e., diabetes mellitus, diseases or disorders that compromise wound healing), pregnancy or lactation, systemic antibiotics or NSAIDs taken within the previous 3 months, confirmed or suspected hypersensitivity to minocycline.

Clinical protocol

Initial therapy was performed on all patients and consisted of full mouth scaling and root planing on 2-4 sessions, by hand and ultrasonic instrumentation, with oral hygiene instructions reinforcement and proper brushing technique (modified Bass technique) instructions.

Using a split mouth design, sites were randomly allocated using a coin-flip method into two groups; one is a test group including the sites were thoroughly dried to get rid of blood and debris, then received locally delivered minocycline (Arestin™, OraPharma, Inc., Horsham, PA, USA) Figure 1, in all sites probing depth ≥ 5 mm at this time. The applicator tip was gently advanced to the deepest point of the pocket till resistance is felt and the cartridge content was expelled by gently pressing the plunger till some material overflowed according to manufacture instructions Figure 2. Control sites received only subgingival scaling and root planning. Patients were advised to postpone brushing for 12 hours, not eating hard or sticky foods for 1 week and not using interproximal cleaning aids for 10 days. No antibiotics or anti-inflammatory agents were prescribed after treatment.

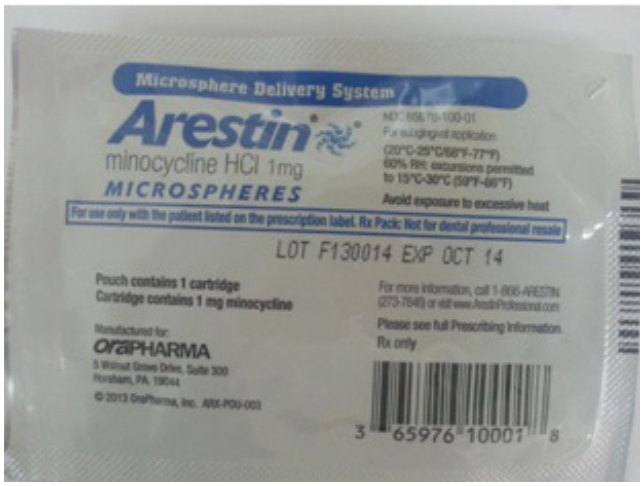

Figure 1: Arestin used in the study

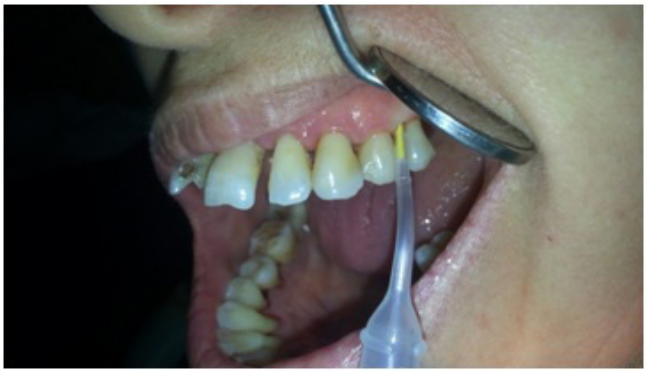

Figure 2: Application of the minocycline at the test site

Clinical measurements

All pre- and post-treatment clinical parameters were recorded by one blinded and calibrated examiner who was masked to the type of treatment received by the subjects while another clinician provided treatment to both groups. Intra-examiner calibration was achieved by examination of 10 patients twice, 24 hours apart before beginning the study. Calibration was accepted if measurements at baseline and 24 hours were similar to 1 mm at the 95% level.

The expert periodontal examiner measured the following clinical parameters at baseline, 3 and 6 months, using a colour-coded periodontal probe (PQWBR - Hu Friedy Mfg. Inc. Chicago, IL, USA): Plaque Index (PI) [14], Probing Pocket Depth (PPD), Clinical Attachment Level (CAL); Bleeding upon Probing (BOP) [15] judged as positive if appearing within 20 seconds after probing.

Statistical analysis

Data were analyzed with the Statistical Package for Social Science (SPSS) program, version 12. A sample size of 20 patients for each site was estimated to detect a clinically relevant difference for a reduction in PD of 0.5 mm with 80% power (SD = 0.62 and α = 0.05). Primary outcome variable was the average change in PD from baseline to 6 months and secondary outcome variables were PI, BOP, and CAL. The results were averaged (mean standard deviation) (SD) for each clinical parameter at baseline and 6 months. The unpaired t-test was used to assess the degree of statistical significance between test and control sites at different time points. The comparison of the changes in clinical parameters from the baseline to 6 months between the sites was analysed using repeated-measurement analysis of variance (rmANOVA) and Bonferroni's post hoc test. Results were considered to be significant when the P value was <0.05.

Results

Twenty patients (15 female and five male) with an age range of 31–49 years and a mean age of 37 years were included in this study. They presented with at least ten sites with more than 4 mm of clinical attachment loss spread over several teeth, as well as radiographic evidence of bone loss of more than one-third of the root length on at least two teeth per quadrant. The patients had two contra-lateral periodontal sites with probing depths ≥5 mm and radiographic evidence of bone loss of at least 3 mm from the alveolar crest to the base of the defect. A total of 40 sites were treated [34 molars (ten in the maxilla and 24 in the mandible), four premolars (two in the maxilla and two in the mandible) and two lower canines]. All patients who were enrolled in the study returned for scheduled maintenance visits every second week during the first 2 months after application and once a month for 4 months. There were no inflammatory reactions observed following the application of minocycline.

Plaque index

The mean plaque index for treatment groups at baseline was 2.46 ± 0.54 in minocycline sites whereas the mean value at 3 and 6 months were 1.06 ± 0.29 and 0.71 ± 0.25 respectively. In control sites, the mean value was 2.58 ± 0.36 whereas at 3 and 6 months were 1.15 ± 0.25 and 0.85 ± 0.15 respectively. There was significant reduction in plaque index scores at both 3 and 6 months interval. However, between the groups, the difference was not statistically significant at any time period (P>0.05) (Table 1).

Bleeding upon probing index

There was a significant reduction in overall mean bleeding scores in both groups from baseline (52.12%) in minocycline sites and (50.35%) in control sites, to three months (35.77%) in minocycline sites and (33.17%) in control sites. This improvement was maintained till the end of study, with (33.45%) in minocycline sites and (32.50%) in control sites. Between the groups, the difference was not statistically significant at any time period (P> 0.05) (Table 1).

Table 2 shows the clinical probing depth parameters of the minocycline sites and control sites at different time intervals. At baseline the probing depths ranged from 5–8 mm for both groups, with a mean and SD of 6.28±0.5 for minocycline sites and 6.53± 0.34 for control sites. There was no statistical difference between the two sites at baseline (P>0.05). At 3 months both sites showed significant improvement in probing depths over baseline. For minocycline sites, probing depths ranged from 4–6 mm, with a mean and SD of 4.8± 0.7 mm. For control sites, the range was 4–7 mm with a mean and SD of 5.9±0.6mm. There was a statistically significant difference between the two sites (P < 0.05). At 6 months the probing depths remain ranging from 4–6 mm, with a mean and SD of 4.4 ±0.4 mm for minocycline sites. For control sites, the range was 4–6 mm, with a mean and SD of 5.58±0.41 mm. There was statis-

Table 1: Plaque index and bleeding upon probing values of minocycline sites versus control sites at time intervals

Clinical parameters		Minocycline sites			Control sites		
		Baseline	At 3 months	At 6 months	Baseline	At 3 months	At 6 months
Plaque index	Mean ± SD	2.46 ± 0.54	1.06 ± 0.29	0.71 ± 0.25	2.58 ± 0.36	1.15 ± 0.25	0.85 ± 0.15
Bleeding upon probing index	Percentage (%)	52.12	35.77	33.45	50.35	33.17	32.5

*Values are expressed as mean ± SD and percentage

Table 2: The probing pocket depth and clinical attachment level of the minocycline sites versus control sites at time intervals

Clinical parameters		Minocycline sites			Control sites		
		Baseline	At 3 months	At 6 months	Baseline	At 3 months	At 6 months
Probing pocket depth	Range	5-8	4-6	4-6	5-8	4-7	4-6
	Mean ±SD	6.28±0.5	4.8±0.7 *	4.4±0.4 *	6.53±0.34	5.9±0.6	5.58±0.41
Clinical Attachment level	Range	5-9	4-8	4-7	5-8	5-8	4-7
	Mean ±SD	6.8 ±0.2	5.75±0.35 *	5.7±0.15 *	6.9±04	6.4±0.3	6.45±0.7

Values are expressed as range and mean ± SD (indicates statistical significance at P < 0.05).

tically significant difference when the two groups were compared (P < 0.05).

With regard to the clinical attachment levels at baseline, both minocycline and control sites ranged from 5–9 mm, with a mean and SD of 6.8 ±0.2 mm for minocycline sites, and 6.9±0.4 mm; in control sites, there was no statistical difference between the two sites at baseline (P>0.05). At 3 months, both sites showed significant improvement of clinical attachment levels over baseline measurement, ranging from 4–8 mm, with mean and SD for minocycline sites of 5.75±0.35 mm. For control sites, the range was 5–8 mm, with a mean and SD of 6.4±0.4 mm. There was a statistically significant difference between the two groups (P<0.05). At 6 months the range of clinical attachment levels was 4–7 mm for both groups, with a mean and SD of 5.7±0.15 mm for minocycline sites and 6.45±0.7 mm for control sites; there was statistically significant difference when both groups were compared (P<0.05).

Discussion

Providing successful periodontal treatment for smokers is often frustrating because they tend to have a less favorable therapeutic response to non-surgical or surgical therapy compared to non-smokers [9-11]. Periodontal tissue breakdown is caused by periodontopathogenic bacteria and their products that play key roles in local amplification of the immune response. Successful treatment modalities in smokers should include quitting smoking and/or eliminate the causative bacteria [12,13]. It worth mentioning that the dental profession has a crucial role to play in smoking cessation counselling, particularly for patients with chronic periodontitis as success rates in quitting smoking following smoking cessation advice given as part of a periodontal treatment compared very favorably to British national quit rates achieved in specialist smoking cessation clinics [16,26].

There is a fair well established biologic rationale for the negative effects of cigarette smoking on periodontal tissues. These include: immunosuppressive effect on the host, adversely affecting host-parasite interactions, impaired peripheral blood polymorphonuclear leukocyte motility, chemotaxis, and phagocytosis, decreased antibody production, alterations in the subgingival vascular oxygen tension, increased adhesion of bacteria to epithelial cells, reduced proliferation, migration, and attachment of fibroblast to the root surface, and impaired collagen synthesis and protein secretion [9-13].

The use of local delivery system in combination with scaling and root planning was supported by evidence from the periodontal literature, indicating that as probing depth increases, scaling and root planing alone become less efficient [17,18]. It was reported that the concentration of minocycline in human crevicular fluid even after 14 days of local administration using (Arestin) exceed the Minimum Inhibitory Concentrations (MICs) for periodontal pathogens [17, 21]. In addition, it was postulated that healing of diseased periodontal pockets is due to possibility of minocycline absorbing onto mineralized dental structures, where it may act as a transient reservoir of the antimicrobial agent during period of substantively [17, 20-22]. Plaque control is usually difficult to be achieved in smokers that lead to poor results after periodontal therapy [11-13]. However, in this study all patients showed statistically and clinically significant improvements in plaque index at follow-up visits, when compared to baseline levels. Also, bleeding indices remained satisfactory during the entire study period, suggesting that patients complied very well with the oral hygiene instructions.

All treatment groups showed significant reduction in probing pocket depth and clinical attachment level gain at 3 and 6 months when compared to baseline. It seems that there is semi consensus that treatment of the infectious component of periodontal diseases achieves its maximum benefits from 3 to 6 months after therapy, and that any clinical and microbial benefits slowly reverse thereafter [19, 23-25].

Conclusion

This clinical trial demonstrates that local delivery of minocycline into deep periodontal pockets of chronic periodontitis patients who were current smokers stimulated a significant improvement in the clinical attachment level and probing depth reduction when compared to scaling and root planing alone. This can offer a new trend in the field of periodontal treatment in this special group of patients who are at greater risk for periodontal destruction. However, future long-term multicentre randomized, controlled clinical trials with a larger patient population and using different vehicles and concentrations should be carried out to confirm the observations of this study.

Disclosure

The authors declare that they have no conflict of interests, and no financial support or relationships that may pose a conflict of interest.

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