

Efficacy of adjunct subgingival minocycline delivery for treatment of peri-implantitis in moderate cigarette smokers

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Abstract. – **OBJECTIVE:** Localized subgingival minocycline hydrochloride (MH) delivery as an adjuvant to with non-surgical mechanical debridement (NSMD) is useful for the treatment of periodontitis; however, there are no trials that have assessed the efficacy of subgingival MH delivery with NSMD for the treatment of peri-implantitis in cigarette-smokers and non-smokers. This randomized controlled trial assessed the efficacy of subgingival MH delivery with NSMD for the treatment of peri-implantitis in cigarette-smokers.

PATIENTS AND METHODS: Self-reported current cigarette-smokers and non-smokers with peri-implantitis were encompassed. These individuals were subdivided into 2-subgroups. Patients in test- and control groups received NSMD with and without a single delivery of subgingival MH. Modified-gingival-index (mGI), modified-plaque-index (mPI), probing-depth (PD) and crestal-bone-loss (CBL) were measured at baseline and at 6-months' follow-up. Demographic-data was also collected. Level of significance was set at $p < 0.01$.

RESULTS: Twenty-four cigarette-smokers and 24 non-smokers with peri-implantitis were included. There was a significant reduction in mPI ($p < 0.01$), mGI ($p < 0.01$), PD ($p < 0.01$) at 6-months among patients with and without type-2 DM in test- and control-groups. There was no significant difference in peri-implant mPI, PD and mGI, patients with and without type-2 diabetes in test- and control-groups at 6-months of follow-up. There was no significant difference in CBL in all patients at 6-months of follow-up.

CONCLUSIONS: A single application of subgingival MH delivery is as effective as NSMD

alone for the treatment of peri-implantitis in cigarette-smokers and non-smokers.

Key Words:

Bone loss, Minocycline hydrochloride, Smoking, Probing depth, Peri-implantitis.

Abbreviations

AGE, advanced glycation endproducts; CBL, crestal bone loss; FMUS, full mouth ultrasonic scaling; IL, interleukin; MH, minocycline hydrochloride; NSMD, non-surgical mechanical debridement; NSPT, non-surgical periodontal therapy; OS, oxidative stress; mGI, modified gingival index; mPI, modified plaque index; PD, probing depth; PISF, peri-implant sulcular fluid.

Introduction

Traditionally, non-surgical mechanical debridement (NSMD) of peri-implant surfaces and sulci is performed for the management of peri-implant diseases. Numerous therapies including probiotic and antibiotic therapy, photobiomodulation, and photodynamic therapy have been proposed as adjuncts to NSMD to facilitate postoperative healing of peri-implant tissues^{1,2}; however, the most reliable or effective adjunct therapy in this regard remains unknown. Systemic antibiotics are often prescribed for the management for periodontal and peri-implant diseases as they exert an antimicrobial effect and facilitate healing^{3,4}. Nevertheless, the risk of superinfections with op-

opportunistic bacteria following administration of systemic-antibiotics for treatment of peri-implant diseases cannot be overlooked⁵. There is mounting scientific evidence which has shown that local antibiotic delivery provides an antimicrobial platform by providing a synergistic effect of “contact-killing”^{6,7}. Minocycline hydrochloride (MH) is a semisynthetic derivative of tetracycline that is commonly used for the treatment of oral and systemic bacterial infections including respiratory infections, and urinary tract infections, and periodontitis and peri-implantitis, respectively⁸⁻¹¹. In a recent experimental study on male beagle dogs, Qian et al⁸ induced peri-implant osseous defects around bone-level implants placed in the region of missing mandibular second and third premolars. Implants in test-group were treated with subgingival MH applications on implant abutments; whereas those in control-group received no treatment. The histologic results showed a larger quantity of neutrophils and osteocytes around peri-implant defects in test- compared with the control-group⁸. The authors concluded that local MH delivery prevents the progression of peri-implantitis⁸.

Cigarette-smoking is a well-known systemic risk-factor of peri-implant and periodontal diseases¹²⁻¹⁴. The habit is associated with an increased formation and accumulation of advanced glycation endproducts (AGEs) in the peri-implant sulcular fluid (PISF)¹⁵. The AGEs augment inflammation by increasing the production of destructive cytokines in PISF, thus worsening the overall soft tissue and osseous inflammatory response¹⁵⁻¹⁷. Moreover, a positive correlation exists between expression peri-implant probing depth (PD) and expression of AGEs in the PISF^{16,18}. Furthermore, the outcomes of oral interventions are also compromised in smokers than non-smokers¹⁹. There are no clinical studies that have compared the efficacy of subgingival MH administration after nonsurgical MD for managing peri-implantitis in non-smokers and cigarette-smokers. It is hypothesized that NSMD with or without subgingival MH administration reduces peri-implant inflammatory parameters (PD, modified plaque index [mPI], and modified gingival index [mGI]) and minimizes the risk of further crestal bone loss (CBL) in current cigarette-smokers as well as non-smokers.

The aim of the present randomized controlled trial (RCT) was to assess efficacy of subgingival MH delivery as an adjunct to NSMD for treatment of peri-implantitis in non-smokers and current cigarette-smokers.

Patients and Methods

Ethical Guidelines

The study was carried out in accordance with guidelines recognized by the Declaration of Helsinki as revised in 2013 for experimentation involving human patients. All volunteering individuals were requested to sign a consent form. All participants could withdraw their participation at any phase of the study without consequences. Ethical approval was obtained from Ethics Research Committee of Centre for Specialist Dental Practice and Clinical Research, Riyadh, Saudi Arabia.

Inclusion and Exclusion Criteria

Self-reported current cigarette-smokers and non-smokers were included. Current cigarette-smokers were defined as individuals who had a smoking history of at least 5-pack years²⁰. Non-smokers were defined as individuals who had not used any type of tobacco product to date²¹. Diagnosis of peri-implantitis was based on the following parameters: (1) bleeding on gentle probing or/and suppuration, (2) PD \geq 4 mm, (3) recession of peri-implant mucosal margin (implant thread exposure) and (4) radiographic CBL \geq 2 mm²². Self-reported current smokeless tobacco product users, dual-smokers, users of electronic nicotine delivery systems, habitual alcohol consumers and patients with systemic diseases such as diabetes mellitus, heart anomalies, renal and hepatic diseases, and patients with viral infections such as HIV were excluded. Patients with or with a history of periodontitis and nursing/pregnant females were excluded. Furthermore, patients that had undergone non-surgical periodontal therapy (NSPT) or had consumed steroids, antibiotics, or/and non-steroidal anti-inflammatory drugs, within 90 days were also excluded.

Study Location and Design and Participants

The present parallel arm RCT was performed at a tertiary healthcare center situated in Riyadh, Saudi Arabia between February and October 2021. All patients were residents of Riyadh, Riyadh province, Saudi Arabia.

Randomization, Grouping, Allocation Concealment and Blinding

Current cigarette-smokers and non-smokers with peri-implantitis were randomly divided into test- and control groups. Randomization was done using an online service by www.sealedenvelope.com.

com. In test-group, patients got NSMD and full mouth ultrasonic scaling (FMUS) around natural teeth with adjunct subgingival MH application. In the control-group, patients received NSMD and FMUS around natural teeth only. The principal investigator concealed the allocation of the participants and none of the investigators involved with clinical and radiographic evaluations were aware of the groups to which, the patients were allocated.

Questionnaire

Demographic data was collected using a questionnaire. Information regarding self-reported drug allergies (especially tetracycline allergy), smoking pack-years and family history of smoking was also collected. Medical records of the participants were also evaluated to verify the systemic health status of participants.

Non-Surgical Mechanical Debridement and Periodontal Therapy

In all patients, peri-implant NSMD was performed at baseline and at 6-months' follow-up using plastic curettes (Hu-Friedy®, Chicago, IL, USA); and full mouth NSPT was performed using sterile stainless steel hand instruments (Hu-Friedy®, Chicago, IL, USA) and an ultrasonic scaler (Dental Equipment Woodpecker Uds-J Ultrasonic Scaler EMS Compatible Original, Guangzhou, China). The NSMD and NSPT were performed by a trained investigator.

Subgingival Minocycline Hydrochloride Delivery

In the study cohort, individuals in test-group underwent subgingival MH administration in the deepest peri-implant buccal sulci immediately after NSMD. The peri-implant region was isolated; and a specifically designed disposable plastic syringe was gently inserted in the deepest peri-implant sulcus and continued to be moved down until resistance was felt. The MH microspheres (ARES-TIN®, Bausch Health Companies Inc. ARE.0190., USA) were then gently released into the sulcus and the tip was slowly withdrawn. Each unit-dose cartridge delivered MH equivalent to 1 mg of minocycline free base. Patients in test-group were instructed to refrain from eating and drinking for at least 60 minutes after the procedure.

Peri-Implant Clinical and Radiographic Parameters

Baseline and 6-months' follow-up clinical and radiographic investigations were performed by

one trained and calibrated examiner who was blinded to study participants. Peri-implant mPI²³, mGI^{23,24}, and PD²³ were measured at four sites per implant. Mesial and distal CBL were gauged in millimeters (mm) on digital bitewing radiographs^{25,26}.

Sample-Size Estimation and Statistical Analysis

Sample size estimation (SSE) was done using data from a pilot study. The SSE was based on the assumption that a 3-mm reduction in mean peri-implant PD would occur in test-group with 0.6 mm standard deviation; and a 2-mm reduction in the control-group with 0.5 mm standard deviation. It was estimated that with inclusion of at least 12 patients in test and control-groups, respectively, the study would have a power of 80% statistical power, and an alpha of 1%. Group comparisons were done using the analysis of variance and level of significance was set at $p < 0.01$.

Results

Questionnaire

Twenty-four self-reported current cigarette-smokers (19 males and 5 females) and 24 non-smokers (19 males and 5 females) with peri-implantitis agreed to participate in the present study. These participants were randomly divided into test- and control groups with 12 patients per subgroup. There was no significant difference in mean ages of all patients. Current cigarette-smokers in test- and control groups had a smoking history of 20.3 ± 0.8 and 20 ± 0.5 pack-years, respectively. Family history of tobacco smoking was more often reported by current cigarette-smokers than non-smokers (Table I). There were no known drug allergies reported by all patients. A total of 24 (5 in maxilla and 19 in mandible) and 24 delayed loaded, bone-level, platform-switched and screw-retained implants (6 in the maxilla and 18 in the mandible) were present in the cigarette-smokers and non-smokers, correspondingly. All implants were located in the regions of missing molars. There was no significant difference in the duration of implants in test- and control groups among cigarette-smokers and non-smokers (Table I). None of the participants presented with adverse reactions, such as intra or extraoral swelling, face rash, and/or headache up to 6-months of follow-up.

Table 1. Demographics of the study cohort.

Parameter	Current cigarette-smokers (n=24)		Non-smokers (n=24)	
	Test-group	Control-group	Test-group	Control-group
Participants (n)	12	12	12	12
Gender	9 males 3 females	10 males 2 females	10 males 2 females	9 males 3 females
Mean age	56.1 ± 4.7 years	52.2 ± 2.4 years	52.8 ± 3.1 years	55.1 ± 1.7 years
Duration of smoking habit	20.3 ± 0.8 pack-years	20 ± 0.5 pack-years	NA	NA
Family history of smoking	9 (75%)	10 (83.3%)	3 (25%)	1 (8.3%)
Implants (n) (Maxilla: mandible)	12 (3: 9)	12 (2: 10)	12 (4:8)	12 (2:10)
Duration of implants in function	4.1 ± 0.6 years	3.8 ± 0.4 years	4.7 ± 0.2 years	4.2 ± 0.6 years

Peri-Implant Parameters

At baseline, there was no significant difference in peri-implant mPI, PD and mesial and distal CBL in smokers and non-smokers. At baseline mGI was significantly higher in non-smokers compared with cigarette-smokers in test- ($p<0.01$) and control-groups ($p<0.01$). There was no significant difference in mPI, mGI, and PD and CBL at 6-months follow-up among cigarette-smokers and non-smokers compared with their respective baseline values. At baseline and 6-months' follow-up, mGI was significantly higher in non-smokers in test- ($p<0.01$) and control-groups ($p<0.01$) compared with cigarette-smokers in test- and control-groups (Table II).

Correlation Between Implant Parameters, Cigarette Smoking and Peri-Implant Parameters

There was no statistically significant correlation between peri-implant mPI, mGI, PD, mesial and distal CBL with gender, duration of implants in function, and implant jaw location in test- and control-groups among cigarette-smokers and non-smokers (data not shown).

Discussion

In the present study, authors hypothesized that NSMD with or without subgingival MH administration reduces peri-implant inflammatory parameters (mPI, mGI and PD) and minimizes the risk of further CBL in in cigarette-smokers and non-smokers with peri-implantitis. Our results are unfortunately in disagreement with this hypothesis as the 6-months' follow-up results showed no

statistically significant reduction in peri-implant soft tissue inflammatory parameters in all patients that underwent NSMD either with or without adjunct subgingival MH delivery. It is important to mention that during the patient recruitment phase all patients were educated about the significance of routine oral hygiene maintenance on overall health and were informed about the detrimental effects of smoking on oral and systemic health. It is speculated that cigarette-smokers continued to smoke after NSMD and non-smokers were uncompliant towards strict routine oral hygiene maintenance protocols. In cigarette-smokers, accelerated interactions between AGE and their receptors (RAGE) are primarily held responsible for inducing oxidative stress (OS) in gingival tissues and increasing the production of destructive cytokines such as interleukin 1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α) that enhance osteoclastic activity^{27,28}. There is a possibility that perhaps due to continued smoking habit and poor compliance towards oral hygiene maintenance, AGE-RAGE interactions remained unaffected, which lead to continued augmentation of the inflammatory response. It is noteworthy that in the present study, subgingival MH delivery was done once throughout the study, that is, after NSMD at baseline. To date, there is no consensus regarding the number of times subgingival MH delivery should be done in order to contain a significant reduction in oral soft tissue inflammatory parameters. In a previous clinical study, Lin et al¹⁷ assessed the effect of non-surgical periodontal therapy (NSPT) with or without adjunct subgingival MH in patients with periodontitis. The authors reported no significant difference in clinical periodontal parameters among diabetic patients

Table II. Peri-implant clinical and radiologic parameters at baseline in the study groups.

Peri-implant parameters	Baseline				6-months' follow-up			
	Current cigarette-smokers (n=24)		Non-smokers (n=24)		Current cigarette-smokers (n=24)		Non-smokers (n=24)	
	Test-group	Control-group	Test-group	Control-group	Test-group	Control-group	Test-group	Control-group
mPI	3.03 ± 0.2*	2.7 ± 0.1 [†]	2.7 ± 0.2*	2.6 ± 0.2*	2.6 ± 0.4	2.8 ± 0.2	2.02 ± 0.1	1.8 ± 0.07
mGI	1.06 ± 0.3*	1.1 ± 0.2 [†]	3.5 ± 0.2 [‡]	3.1 ± 0.3 [‡]	0.8 ± 0.2	0.9 ± 0.1	2.8 ± 0.2	2.3 ± 0.1
PD	6.2 ± 0.4 mm*	5.8 ± 0.3 mm [†]	5.6 ± 0.4 mm	6.02 ± 0.3 mm [§]	4.5 ± 0.2 mm	4.2 ± 0.08 mm	3.5 ± 0.1 mm	3.3 ± 0.08 mm
CBL (mesial)	4.8 ± 0.2 mm	5.1 ± 0.3 mm	4.6 ± 0.2 mm	4.8 ± 0.3 mm	4.3 ± 0.02 mm	4.5 ± 0.07 mm	4.2 ± 0.05 mm	4.2 ± 0.07 mm
CBL (Distal)	51.3 ± 0.3 mm	5.08 ± 0.1 mm	4.5 ± 0.4 mm	4.8 ± 0.5 mm	4.4 ± 0.1 mm	4.3 ± 0.1 mm	4.4 ± 0.1 mm	4.2 ± 0.04 mm

CBL: Crestal bone loss; mm: millimeters. *Compared with non-smokers in test and control groups at 6-months' follow-up ($p < 0.01$). [†]Compared with non-smokers in test and control groups at 6-months' follow-up ($p < 0.01$). [‡] Compared with cigarette-smokers in test-group at baseline ($p < 0.01$).

that underwent NSPT with or without adjunct subgingival MH administration; and suggested that this could have occurred due to a small sample-size¹⁷. Although results of the present investigation were power-adjusted, no significant difference in peri-implant parameters were evident at 6-months' follow-up. It is noteworthy that in the present RCT, subgingival MH administration was done once throughout the study period. We, therefore, perceive that a single delivery of MH was insufficient to help reduce the ongoing inflammatory response in the study population.

The only clinical peri-implant inflammatory parameter that showed a difference in cigarette-smokers and non-smokers at baseline and at 6-months of follow-up was mGI. As shown in Table II, the score of mGI was significantly high in non-smokers than cigarette smokers at baseline and 6-months follow-up. The most justifiable reasoning that can be posed for this is that nicotine exerts a vasoconstrictive effect on gingival blood vessels^{21,29}; and hence masks the clinical markers of periodontal and peri-implant soft tissue inflammation (gingival index and mGI, respectively). Therefore, tobacco-smokers may remain unaware of the ongoing inflammation for prolonged durations and by the time they start experiencing pain around dental and peri-implant tissues, the augmenting inflammation may have compromised the surrounding osseous tissues. Patient health awareness and anti-tobacco programs can help educate the masses about the deleterious effects of poor oral health maintenance and tobacco-product habits.

In the present RCT, efficacy of subgingival MH administration as an adjunct to NSMD was assessed on clinical and radiographic grounds primarily due to limitations in funding sources. It is known that presence of pathogenic bacteria such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Prevotella intermedia* in the subgingival oral biofilm contribute towards the etiology of peri-implant diseases^{30,31}. Moreover, destructive inflammatory cytokines such as IL-1 β and TNF- α are also associated with CBL and progression of peri-implantitis in susceptible patient populations^{13,32}. In an *in-vitro* experiment, Qian et al⁶ showed that MH when loaded on titanium by graphene-oxide shows antibacterial activity against gram-positive and gram-negative bacteria. From a microbiological and immunoinflammatory perspective, it is hypothesized that in contrast to NSMD alone, subgingival MH application as an adjuvant antimicrobial therapy is more effective in reducing subgingival colonization of

pathogenic bacteria; and is also helpful in minimizing the volume of PISF and expression of destructive inflammatory cytokines in this biologic fluid. Nevertheless, based upon the current results it is contemplated that even if microbiological and/or immunological investigations were performed at baseline and follow-up, no significant difference in their respective parameters would have been noticed most possibly due to poor compliance of the patients. However, this explanation is merely a speculation as assessment of oral hygiene maintenance and tobacco control measures at follow-up was beyond the scope of the present study. There is a lack of consensus regarding as to whether surgical MD is superior to NSMD for the treatment of peri-implantitis³³. It remains to be determined whether surgical MD with adjunct local MH administration provides superior outcomes in terms of treatment of peri-implantitis compared with surgical MD alone. Further RCTs are needed to test these hypotheses.

Conclusions

A single subgingival delivery of MH is as effective as NSMD alone for the treatment of peri-implantitis in cigarette-smokers and non-smokers.

Conflicts of Interest

The authors declare that they have no conflict of interest related to the present study.

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Authors' Contributions

T.A., and F.V. were involved in study conception/design and manuscript writing; A.A.A. and K.A.A. were involved in data acquisition and manuscript writing; F.J. and M.A. wrote the manuscript and revised it prior to submission; F.V. performed the statistical analysis. All authors were involved in writing/critical review of draft versions of this manuscript, and all approved it prior to submission.

Data Availability Statement

Data is available on reasonable request.

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