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Clinical Evaluation of Topical Application of Doxycycline 3% + Ketoprofen 2.5% Gel in Chronic Periodontitis Patients

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ABSTRACT

Objectives: 1. To evaluate the clinical effects of localized doxycycline 3% + ketoprofen 2.5% (Dox+Keto) gel as an adjunct to scaling and root planing (SRP) in the treatment of periodontitis.

2. To encourage the use of subgingival (Dox+Keto) gel as an adjunct to conventional periodontal therapy.

Materials and Methods: A total of twenty patients were enrolled. A split-mouth design was carried out; the patients were categorized into two discussion groups: group A: SRP plus (Dox+Keto); group B: SRP plus keto respectively. Clinical parameters such as a plaque index (PI), bleeding index (BI), probing pocket depth (PPD), clinical attachment level (CAL) were assessed at baseline, 1 month and 3 months. The results were subjected to statistical analysis, which was expressed as mean \pm SD and proportions as percentages. Intragroup comparisons were made by paired t-test and one-way analysis of variance (ANOVA) for inter-group comparisons.

Results: The intragroup analysis showed a significant reduction ($P < 0.05$) of clinical periodontal parameters in all two treatment groups. Moreover, the inter-group analysis manifested, that intra-pocket (Dox+Keto) gel application in combination with SRP showed a significant reduction while no statistically significant difference was observed in the second group (SRP with intra-pocket Keto gel alone).

Conclusion: In this study, SRP with (Dox+Keto) gel exhibited clinical results with statistically significant differences. As it appears, (Dox+Keto) gel in this study may have a potential additive effect.

INTRODUCTION

The chronic periodontal disease is the most prevalent form of periodontitis^[1] and engages in a slow to moderate degree of disease development, but intervals of more rapid destruction may be observed. Several agents have been identified which decrease gingival pathogenic biofilm by scaling and root planing in combination with precise oral hygiene is regarded the gold standard in non-surgical periodontal therapy^[2,3]. However, a complete removal of subgingival deposits and a secure and controllable control of the subgingival vital flora has been demonstrated to be improbable and a difficult aim to achieve^[4]. Host response modulation is a relatively recent term in dental science^[5]. The reason behind this procedure is to assist the host in the fight against infectious agents by supplementing the natural innate defense mechanisms or by changing its response to modifying the course of inflammatory process; however, host response modulation probably has fewer side-effects, is not invasive, and does not need involved application methods^[6]. A variety of pharmacological agents has been studied for a possible role as host modulators in the management of periodontal disease. These include nonsteroidal anti-inflammatory drugs, bisphosphonates and the tetracycline family^[7]. Controlled local delivery of the local antimicrobial agents was subsequently developed and are successful in maintaining the higher concentration of the drug in the periodontal pocket for longer periods than systemically delivered methods^[8]. Golub et al. recommended that a systemic regimen of sub-antimicrobial dose doxycycline reduced matrix metalloproteinase

(MMP) activity, periodontal destruction, and alveolar bone resorption in patients with chronic periodontal disease^[9]. Doxycycline has other activities besides its antibacterial property, e.g. anti-inflammatory property^[10]. In one study the stand-alone use of doxycycline was as effective as scaling and root planing in decrease probing pocket depths and in increasing clinical attachment level gain^[11]. It is safe and can reach and maintain a great concentration in periodontal pockets when compared to additional locally delivered antibiotics^[8]. It maintains in the pockets for 7–10 days with minimal changes in its concentration^[12]. The present concept of periodontal pathogenesis declares that microorganisms and their products are able of inducing inflammatory mediators and the resulting inflammation presents as the sign of the periodontal disease. PGs formed by the arachidonic acid cyclooxygenase pathway are one of the central mediators of the disease, although two isoforms of the enzyme cyclooxygenase exist: cox-1 is constitutively expressed and the resulting PGs are responsible for physiological functions and cox-2 is inducible and is said to be created during inflammation^[13]. In former studies, use of NSAIDs to control redness and as an adjunct to mechanical periodontal treatment^[13,14] has proven beneficial in comparison with controls. Ketoprofen, a propionic acid derivative, has been found to be efficient against a number of inflammatory conditions and is currently under as a possible adjunct to traditional periodontal therapy. Besides, its ability to block the cyclooxygenase pathway, in vitro reports has also demonstrated an anti-lipoxygenase activity and here after the added ability of the drug to inhibit leukotriene formation^[13] To the best of our information, there is no published literature on in situ gel using 0.3% doxycycline 3% with ketoprofen 2.5% for direct placing in the periodontal pocket for treatment of chronic periodontitis in patients. Keeping the above facts in mind, the aim of this double-blind, placebo-controlled, randomized clinical trial was to determine the efficacy of subgingivally delivered doxycycline 3% + ketoprofen 2.5% gel as an adjunct to mechanical debridement during periodontal therapy.

MATERIALS AND METHODS

This was a randomized, controlled, double-blinded clinical trial with a split-mouth design at a single-centre clinical study, a total of 20 patients (9 males and 11 females, Age range: 30-50 years) with chronic periodontitis were selected from the outpatient division of the Department of Periodontics, Islamic Azad University Dental School of Tehran, Iran; this study was designed for comparison of two treatment modalities: Intrapocket (Dox+Keto) gel with SRP, and (SRP) plus (Keto) gel in patients diagnosed with chronic periodontitis. The survey plan was reviewed and sanctioned, approved by the ethics commission of the Institutional Ethical Committee (ethical committee- Code of Ethics 2125) and Review Board of the Deputy of Research, School of Dentistry. The study met the criteria of the Helsinki Declaration of 1975, revised in 2008. All subjects received the oral and written explanation of the purpose of the survey and signed an informed consent after having detailed information about the purpose, the benefits, and the potential dangers associated with the trial. The study was registered at the Clinical Trials. Government and the Iranian registry of clinical trials (IRCT) ID number: NCT02538224, registered code: IRCT2014050717587N2.

The trial's inclusion and exclusion criteria are listed as follows:

Healthy patients meeting all of the following criteria were included in the study:

- Aged between 30 and 50 years
- At least 20 natural teeth present
- Diagnosed with chronic periodontitis as defined by 2007, 2012 criteria^[15,16]
- Probing depth (PD) of more than 4 mm and clinical attachment loss (CAL) of 1 - 2mm in all - quadrants of the mouth
- Willingness to comply with the study protocol.

Exclusion criteria

These criteria led to exclusion of patients from study:

- Existing systemic disease that may affect the severity or progression of periodontal disease
- Medication consumption that may influence the periodontium (e.g. non-steroidal anti-inflammatory drugs or antibiotics) within the 6 months preceding the beginning of the study
- Concurrent or planned orthodontic treatments
- Planned extensive dental restorations
- Patients with multiple caries
- Patients during pregnancy or lactation, using mouth rinses during the entire period of the study
- Showing hypersensitivity to doxycycline or ketoprofen
- Patients with previous smoking habits.

Clinical parameters

The following clinical parameters were recorded:

- Plaque scores using Plaque Index (PI; Silness and Loe, 1964), [17]
- Probing depth: Measured by (William's® probe, Hu-Friedy, USA)
- Bleeding Index (Carter HG, Barnes GP, 1974); was recorded through visual inspection 30 seconds after probing, (Score 0: No bleeding after probing. Score 1: A single discrete bleeding point appears after probing) [18].
- Clinical attachment level: Determined by measuring the distance between the base of the pocket and the cement enamel junction.

Medical history was recorded for the selected patients, also all the clinical periodontal parameters were noted at the baseline which was followed by SRP. In each patient, on the completion of SRP, selected sites with probing depths more than 4 mm were randomly designated to either the A or B group, while at least four sites had to be present in the contralateral quadrants in the lower jaw (left and right sections) in both group; On the other hand, the objects were treatment with two different methods in the same Patient. After performing full-mouth SRP accompanied by polishing the patients were given thorough oral hygiene instructions. The instructions were as it follows: twice-daily tooth brushing using the Bass brushing technique with a soft toothbrush and once-daily interdental cleaning using dental floss. The clinical periodontal parameters were recorded in both the groups for every 15 days to 3 months post-therapy. The trial gel for local application contained ketoprofen 2.5% gel (Sanofi Pharmaceutical plant construction in France) + 3% doxycycline (Kharazmi Pharmaceutical manufacture in Iran) in the group (A), another group (B)

The selected sites were grouped as:

- Group A: Those receiving SRP with (Dox+Keto) gel
- Group B: Those receiving SRP with (Keto) gel

Furthermore, in the both groups, the gels were applied into all periodontal pockets with PD of >4 mm using an insulin syringe after 2 weeks. The blunt needle was inserted into the base of the periodontal pocket and 0/5 ml quantity of gel was applied on each side of the mandible. Allocation cover was fixed by using container and labeling that did not reveal the essence of the trial drug packages that was blind to the therapist and the clinical examination. They were asked to report to the department if any of the symptoms developed. All the subjects were recalled after 15 days and evaluation for any clinical sign of inflammatory response. In addition, all pre- and post-treatment clinical parameters were recorded by another examiner who was blinded to the kind of treatment received by the individuals; in the other word, neither patients nor investigators involved in rendering treatment or collecting data was aware of the treatment allocation. The collected data was put to statistical analysis in order to draw conclusions.

Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). Intragroup comparisons between different time periods in various clinical parameters were analyzed by paired t-test; also one-way analysis of variance (ANOVA) was performed for inter-group comparisons.

RESULTS

Twenty-four patients met the study criteria and agreed to participate in the study; four patients (two from the test group and two from the control group) were lost to follow-up, leaving 20 subjects (11 women and 9 men), the Mean age of (34.4 ± 3.5) (Figure 1). The results of the present study showed significant effects for A and B groups. Nevertheless, there was significant variation between the treatment regimens. Changes in the clinical parameters occurred within the first 3 months, and there were clinically significant differences between groups.

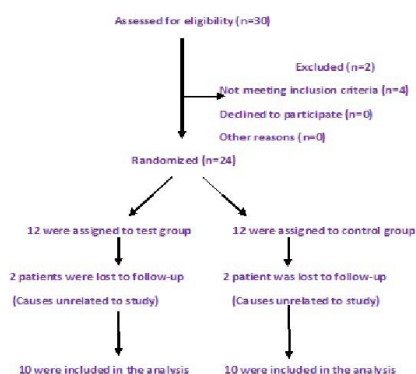


Figure 1. Flowchart diagram.

PD

There was a significant change of PD over time ($P < 0.05$) as revealed by the ANOVA test (**Table 1**). At baseline, the mean PD was 4.85 mm in both investigational groups. In the (Dox+Keto) group the mean PPD at one month was 3.71 ± 0.13 , and in the control group was 3.85 ± 0.16 at four weeks which was statistically significant ($p = 0.0456$). At 3 months, the mean PD of the (Dox+Keto) group was reduced by 1.14 to 1.51 mm, whereas the (Keto) group reduction was 1.0 to 1.35 mm. In adding, one-way ANOVA described that the mean PD in group A was 4.85 ± 0.37 mm at baseline and 3.35 ± 0.11 mm at 3 months, with a reduction of 0.29 mm, also in the group B also showed a statistically significant reduction in PD from baseline to 3 months with a mean of 3.50 ± 0.12 mm ($p = 0.0093$) (**Table 1**).

Table 1. Pocket depth (mean \pm SD) for groups A: ketoprofen + doxycycline (left side) and B: ketoprofen (right side) at different time intervals.

Three Months	One Month	Baseline	Time Group
3.35 ± 0.11	3.71 ± 0.13	4.86 ± 0.35	Left side
3.50 ± 0.12	3.85 ± 0.16	4.85 ± 0.37	Right side
0.0093	0.0456	0.9512	P-Value
S	S	NS	

CAL

There was a significant change of CAL over time ($P < 0.05$) for both treatment techniques (**Table 2**). At baseline, the mean CAL was 4.69 mm in both experimental groups, and at 3 months, the level was 1.22 mm in the (Dox+Keto) group (attachment level gain of 1.5 mm) and 1.07 mm in the (Keto) group (attachment level gain of 1.0 mm). There was a significant difference between the groups, also the within-group changes were statistically significant ($P < 0.05$). The mean CAL gain was greater in the doxycycline 3% + ketoprofen 2.5% Group (A) than in the ketoprofen 2.5% Group (B) at 30 days, ($P < 0.0001$) and 3 months. The gain in CAL was 3.46 ± 0.15 mm for Group (A), and for the Group (B) it was 3.63 ± 0.24 mm; the difference was statistically significant ($P = 0.0096$).

Table 2. CAL (mean \pm SD) for groups 1: ketoprofen + doxycycline (left side) and 2: ketoprofen (right side) at different time intervals.

Three Months	One Month	Baseline	Time Group
3.46 ± 0.12	3.90 ± 0.13	4.68 ± 0.23	Left side
3.63 ± 0.14	4.40 ± 0.17	4.70 ± 0.26	Right side
0.0096	$P < 0.0001$	0.8575	P. Value
S	S	NS	

BOP

BOP was one of the outcomes of the study and was recorded for all the experimental sites at baseline (**Table 3**). The mean BOP of Group A (Dox+Keto) at one month was 0.45 ± 0.06 , in Group B (Keto) at 30 days was 0.50 ± 0.09 but this difference is considered to be not statistically significant ($P = 0.1610$), although at 3 months, Compared to baseline, the reduction in BOP was statistically significant A: (0.24 ± 0.11); B: (0.35 ± 0.12), ($P = 0.0474$), then the difference between (Dox+Keto) and (Keto) groups was significant ($P < 0.05$), moreover the BOP was reduced to 3.2% in the (Dox+Keto) group and 2.9% in the control group but without any significant between-group difference.

Table 3. Bleeding on probing (mean \pm SD) for Groups 1: ketoprofen + doxycycline (left side) and 2: ketoprofen (right side) at different time intervals.

Three months	One month	Baseline	Time Group
0.24 ± 0.11	0.45 ± 0.06	0.99 ± 0.3	Left side
0.35 ± 0.12	0.50 ± 0.09	0.99 ± 0.3	Right side
0.0474	0.1610	1.0000	P-value
S	NS	NS	

PI

All the patients showed statistically and clinically significant improvements in gingival and plaque indices at both follow-up visits when compared with the baseline levels. On intergroup comparison of PI, statistically, the significant outcome was found between groups A (Dox+Keto) and B (Keto) at difference 0-3 months, whereas group A (Dox+Keto) showed statistically significant result only between 0-3 months (**Table 4**). Mean plaque score for Group A (Dox+Keto) at baseline was 0.97 ± 0.04 , at 4 weeks was 0.52 ± 0.10 , at eight weeks, mean, was 0.32 ± 0.10 , besides Mean plaque index score for Group B (Keto) at baseline, was 0.97 ± 0.04 , at 4 weeks was 0.64 ± 0.11 ($P = 0.0200$), at eight weeks 0.43 ± 0.12 ($P = 0.0390$), respectively ($P < 0.05$). The unpaired t-test

Table 4. Plaque index (mean ± SD) for Groups 1: ketoprofen + doxycycline (left side) and 2: ketoprofen (right side) at different time intervals.

Three months	One month	Baseline	Time Group
0.32 ± 0.10	0.52 ± 0.10	0.97 ± 0.04	Left side
0.43 ± 0.12	0.64 ± 0.11	0.97 ± 0.04	Right side
0.0390	0.0200	1.0000	P-value
S	S	NS	

revealed the plaque index score with mean values at baseline between Group A (Dox+Keto) and Group B (Keto) were statistically non-significant and at 4 and 8 weeks were also statistically significant; further clinical studies demonstrated the present observations were significantly greater than the mean PI of Group A at 3 months (**Table 4**).

DISCUSSION

Numerous host modulatory agents have been investigated in clinical trials. Non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobial of doxycycline and or a combination of drugs have been successfully applied as an adjunct to non-surgical mechanical periodontal treatment [19,20]. Even so, the existing study is the earliest one to apply a split-mouth study design to investigate and compare the influence of two various agents (2.5% ketoprofen gel and 3% doxycycline gel) therapy on different treatment protocols for a follow-up period of 90 days. The interesting results of this study throughout the clinical investigation reduced the incidence of BOP during the last 4 recall visits, also some patients gave the description of less bleeding from the gingiva especially in the (dox+Keto) group; In this study, no treatment-related adverse effects were observed in any patients. Frequent usage of dox+keto or keto gels together with a single appointment of SRP at baseline resulted in a mean PD reduction of more than 1 mm within 8 weeks in patients with chronic periodontitis; furthermore, this is the primary study ever to compare these two factors which have such a various method of procedure. The findings of this study showed significant clinical improvement in pocket depth reduction, in accordance with those of the study Puente et al. [21], Funosas et al. [22] and Pinho et al. [23], Nevertheless, in contrast, this study Vardar et al. [24] showed statistically no significant reductions in PD when used a nimesulide [(COX)-2 inhibitor] and likewise, Jeffcoat et al. [25], Taiyeb.et al. [26], have found no differences in PD reduction between research groups after the study period. Moreover, Srinivas et al. [27] demonstrated that PD, CAL no statistically significant inter-group variation; besides, when to use local delivery of tetracycline; in which was the same to the findings of Drisko; Friesen and Heijl [28-30]; they also proposed that these results may be due to split-mouth design of their study. In (keto+Dox) group the reduction in mean probing pocket depth was significant and a similar result was recorded by Heijl et al. [29], Friesen et al. [30] and Wennstrom et al. [31] and Eickholz et al. [32] Garrett et al. [33], then, in agreement with this study, Polson et al. [34] described doxycycline in a delivery system to be an effective means of reducing the periodontal clinical signs of adult periodontitis and In contrast, Akalin et al. Declared the local doxycycline alone treatment seemed more effective than systemic doxycycline alone treatment for pocket depth reduction, but they reported no significant difference when performed the treatment along with the SRP [35]. The secondary outcome measure was the gain in clinical attachment, and Statistically significant differences were found in attachment level change in Dox+Keto group; likewise, Jeffcoat et al. Reported significant differences between experimental and control groups with regard to PPD, CAL and loss of alveolar bone [25]; although in the recent study by Srinivas et al. [27] mentioned that there was a highly significant overall gain in CAL and reduction of PPD, but inter-group alterations were not observed to be statistically significant. In adding, Meharwade et al. indicated that topical therapy with doxycycline to decrease the PPD and the clinical attachment level (CAL) significantly [36]; This was similar to the findings of Garrett et al. [33] Polson et al. [34] Wennstrom et al. [31]; While the reduction of the PPD in this study which continued from the baseline to the last appointment might be caused by the attachment gain and or the shrinkage (recession) of the gingiva; A reduction in mean bleeding percentage in both groups was highly significant at both time intervals and this outcome are in accordance by, Machion et al. which explained that the diminished doxycycline on BOP only differed between groups 45 days after treatment [33]; and this advantage of bleeding reduction was also observed by Wennstrom et al. which used local doxycycline along with mechanical debridement [37]. The latter conclusion was consistent with the findings of Heijl [30] and Friesen [29]. While Haesman et al. declared that the decline of gingival crevicular fluid amounts of PGE2 coincidences with clinically reduced gingival bleeding scores [38], other investigators namely Vogel et al tested the effects of systemic sulindac on experimental gingivitis and concluded that there was no significant effect on the gingival crevicular flow and bleeding index [39]. In another study, local application of 2% w/w nanoemulgel of Ketoprofen had a more significant reduction in inflammatory cell infiltration, alveolar bones resorption, and cementum [40]. Moreover, in a study it was illustrated that the ketorolac gel appears to be effective against gingival inflammation in the periodontal pocket depth through its increased anti-inflammatory activity [41] the another outcome of present study was reduction of plaque accumulation in both group; However, there was a statistically significant reduction in the plaque score in SRP+(keto+Dox) group; in conjunction with this finding, Srinivas et al. demonstrated values significantly reduced plaque index when used ketoprofen gel as an adjunct to SRP in the treatment of periodontal diseases [27]. However, The clinical efficacy of locally delivered doxycycline to SRP has been determined in various research Drisko et al. [28] Mombelli et al. [42], Polson et al. [34] and Chadha et al. [43] showed that the improvements in doxycycline gel and implant groups in clinical periodontal parameters, Garrett et al. [33], Wennstrom et al. [31], Eickholz et al. [32] in different studies They deduced that subgingival doxycycline is a beneficial adjunct to traditional and mechanical therapy in the non-surgical management of chronic periodontitis. In opposite,

Johanson et al. indicated that the drug had no significant effect on plaque, gingival and bleeding index scores^[44]. However, compound treatment of SRP and (Dox+keto) gel obviously illustrated the perfection at all the levels suggesting that the drug can play a significantly advantages role as a complement therapeutic factor in a prevention of the periodontal diseases. The observations of this research illuminated that the extra benefit of topical application of doxycycline 3%+ ketoprofen 2.5% as an adjunct to scaling and root planing in patients is convincing. However, further clinical studies may be necessary to confirm the present observations. Moreover, local drug delivery combined with SRP appears to provide additional benefits in PD reduction compared with SRP alone and improves periodontal health. Therefore, results of the present study evidently the perspective of using the gel as a local drug in subgingival places. The limitation of this study was the small group size and the short duration for preparing the effectiveness of the experimental combine drug. Hence, additional longitudinal investigations are advised with the greater population for the evaluation of the ability of this agents in the treatment of chronic periodontitis. The accompanying immunological and microbial analysis could also improve in the better description of judgments.

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