



Non-surgical Periodontal Therapy With Adjunctive Topical Metronidazole + Piroxicam Gel Compared With Piroxicam Gel in the Treatment of Chronic Periodontitis

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Abstract

Background: Host modulation therapy represents a treatment concept in which drug therapies are applied as an adjunctive therapy to conventional periodontal treatments to counteract the destructive effects of the host inflammatory response.

Methods: This is a randomized split-mouth clinical trial in which a total of 40 outpatients diagnosed with mild-moderate chronic periodontitis with at least two pairs of contralateral anatomically matching proximal tooth surfaces showing probing depth of ≥ 5 mm were enrolled. Full-mouth scaling and root planing (SRP) was performed for all patients and pockets larger than 5 mm were selected for application of the studied gels. The selected sites were randomly divided into group A (piroxicam + metronidazole) and group B (piroxicam). Recall appointments were scheduled every two weeks within 3 months. The periodontal parameters, assessed in the molar teeth, also recorded that changes in clinical parameters during the study.

Results: A total of 34 patients, with mean age of 45.2 ± 8.6 (range 32-60) years, none of whom developed unpleasant side effect, were enrolled. Plaque index was significantly higher in group A; further it was a statistically significant difference in Bleeding on probing levels in group A at the baseline to last interval recall while current study. The results exhibited significant reductions in pocket depth within 3 months when compared to the baseline values, while the combination adjunctive therapy was more effective to reduce pocket depth. Furthermore, both groups showed a statistically significant mean reduction in clinical attachment level (CAL), but in the test group A had a higher CAL gain than in the control group B ($P=0.039$).

Conclusions: The use of a combination of drugs can help reduce the clinical signs of periodontal disease, therefore, by changing the patient's health habits along with periodontal treatment, the mechanical treatment that a microbial plaque can be obtained, and then the use of piroxicam + metronidazole gel as a complementary therapy, the recovery process can be accelerated.

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Background

Periodontal disease consists of several factors that include bacterial biofilm and an inflammatory response that produces cytokines and metastases of matrix metalloproteinases (1). Moreover, in the preceding decade, periodontal disease has been identified as not only a local infectious disease but also as a chronic, inflammatory disease for the host (2). Although the microbial flora of a periodontally diseased site displays increased quantities of anaerobic motile rods and spirochetes, the flora in a healthy site are predominantly coccoid cells and non-motile rods (3). Periodontal disease can be treated by both surgical and non-surgical treatments. Non-surgical mechanical treatment, which includes mechanical plaque control, scaling and root planing (SRP), is

Highlights

- ▶ A significant decrease was observed in plaque index after the use of piroxicam + metronidazole with SRP.
- ▶ A significant decrease was observed in BOP after the use of piroxicam + Metronidazole with SRP.
- ▶ A significant decrease was observed in pocket depth and CAL after the use of piroxicam + metronidazole with SRP.
- ▶ The locally applied piroxicam + metronidazole gel may slightly beneficial for periodontal healing following non-surgical treatments.

the first recommended step and an essential phase of periodontal therapy (4). Conventional mechanical debridement cannot remove all the bacterial causes of periodontal diseases from the subgingival environment, particularly those inhabiting inaccessible regions such

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as furcations, grooves, concavities and deep pockets (5). As a result, pathogens are re-established after non-surgical periodontal treatment. The optimal procedure of plaque correlated periodontal disease includes decrease in pathogens by numerous methods including SRP and mechanical and chemical debridement (6-9). Another approach is the use of topical and systemic antimicrobial agents. Antibiotics can inhibit or eliminate pathogens that are found in deep periodontal pockets and furcation areas that are difficult to access by mechanical debridement (10,11). Prolonged use of systemic antibiotics increases the risk of nausea, diarrhea, antibiotic resistance, and pseudomembranous colitis (12). Antibiotics have been proven to be effective in the treatment of chronic periodontal disease after surgical and surgical treatments (13,14). Although systemic antibiotic therapy is beneficial, a high degree of frequent intake, which reduces the ability of the immune system to cause additional infections, is needed to achieve the desired concentration in the gingival fluid. However, the increased drug resistance phenomenon and increased allergic reactions limit the systemic use of these drugs (15). Advances in local drug delivery (LDD) systems can be 100 times higher than those in the gingival area, and therefore using topical drugs can respond more effectively in areas that have not responded to treatment and in the maintenance phase. Also patients are systemically compromised who cannot undergo periodontal surgery, Recurrent periodontitis sites that do not favorably respond to scaling and root planing, or resistant to periodontal treatment are beneficial (15-18). Metronidazole is a specific antimicrobial agent for anaerobic pathogens, which is used for the treatment of periodontal disease. At low concentrations, bactericidal agents are effective on agents such as bacteria (19-21). In 2 studies by Klinge et al and Pedrazzoli et al, in which metronidazole 25% topical gel was used for chronic periodontitis, therapeutic effects were more effective than mechanical therapy alone (22,23). Stelzel and Flores-de-Jacoby L also observed similar effects in their studies (24,25). Research has shown that prostaglandin production inhibitors, including non-steroidal anti-inflammatory drugs (NSAIDs), can influence this phase of bone loss in periodontal disease (26). Various studies support this concept, showing that non-steroidal pain medications can reduce gingivitis and alveolar bone resorption. There is also evidence that systemic administration of antibiotics and non-steroidal analgesics is effective in modifying the progression of certain types of periodontitis (27). In this research, the therapeutic effects of metronidazole gel + piroxicam gel in patients referred to the Department of Periodontics with chronic periodontitis were comparatively investigated with the effects of piroxicam gel alone. The results of this study may help reduce or stop the progression of periodontal disease in order to prevent chronic intestinal disorders, and if the results are positive, this combination can be

used as a supplementary and complementary treatment.

Objectives

The hypothesis tested in this study was that the combination of host modulation plus antimicrobial agents and nonsteroidal anti-inflammatory treatment, in addition to traditional SRP, would provide significantly improved clinical treatment for periodontal disease compared to SRP alone. The primary potential objective of this study was an improvement of PD. Secondary objectives are changes in clinical attachment level (CAL), bleeding on probing (BOP), and plaque index (PI).

Methods

Patients

This study is a single-center, examiner masked, randomized clinical trial conducted within 3 months with a two-arm, within-subject parallel including split-mouth design. This study was undertaken to evaluate the clinical usefulness of a combination plus locally administered Metronidazole (7.5%) gel+ piroxicam gel (5%) in combination with SRP versus SRP + piroxicam gel (5%) on clinical measures of periodontal disease on patients attending the Department of Periodontics at the Faculty of Dentistry, Islamic Azad University. Forty patients of both genders, aged 32-62 years, were selected. The individuals who were diagnosed with mild-moderate chronic periodontitis according to the 1999 Classification of Periodontal Disease and Conditions with a probing depth ≥ 5 mm were elected (Academy of Periodontology in 1999) (28).

Inclusion Criteria

The inclusion criteria were diagnosis of early-moderate chronic periodontitis [Having at least 2 residual places with a probing pocket depth (PPD > 5 mm)] in 2 opposite quadrants, and CAL $\geq 1-3$ mm), with at least 20 remaining teeth and three teeth in each quadrant; the following clinical outcome variables were recorded at baseline within seven days for three weeks at the selected teeth, at six sites per tooth, by means of a periodontal probe (William's® probe, Hu-Friedy, USA) by 2 calibrated blinded examiners; pocket depth was considered to be the distance from the gingival margin to the base of the pocket; CAL was considered to be the distance from the cemento-enamel junction to the base of the pocket. PI was measured using a Silness & Loe index (29,30). BOP was measured through the visual inspection 30s after probing according to Carter & Barnes (Score 0: No bleeding after probing; Score 1: A single discrete bleeding point appears after probing) (31).

Exclusion Criteria

Patients with known allergy to the constituents of the formulation, systemic illness; pregnant and lactating women; patients undergoing orthodontic treatment,

multiple bridges and patients with a history of taking anti-inflammatory, antibiotic, or immunosuppressive drugs in the last 3 months, a partial denture or multiple caries and those habitually smoking and with a history of periodontal surgery were excluded.

Clinical Parameters

The following periodontal clinical parameters were investigated at baseline; all participants received full-mouth SRP and polishing at baseline in the current study; oral hygiene instructions were given that included brushing twice a day with a soft brush (soft toothbrushes protect gums and gingival margin against damage). After 2 weeks, they were randomly (Balanced Block Randomization with a block size of 4 and an allocation ratio of 1:1, block randomization was chosen to prevent excessive variability in the number of a reasonably steady flow of patients to each treatment group) divided into 2 equal groups; group A: metronidazole (7.5%, Pars Pharmaceutical Co, Iran) + piroxicam gel (5%, Razak Pharmaceutical Co, Iran) for all patients, group B: Piroxicam gel (5%) was routinely used. To this end, 5 mL of gel was applied to both groups every 15 days for 3 months; furthermore, the appropriate concentrations of these gels are commercially available in Iran and can easily be applied on the gingiva. The periodontal pocket was determined at six sites per tooth. For this purpose, disto-facial, mid-facial, and mesio-facial and disto-lingual, mid-lingual, and mesio-lingual) of each mandibular right and left quadrant were selected; moreover, in both groups, the gels were applied into all periodontal pockets with PD of >5 mm using an insulin syringe with the blunt needle inserted into the base of the periodontal pocket and 0.5 mL of gel was applied on each side of the mandible; then, all pre- and post-treatment, periodontal clinical parameters were recorded by an examiner who was blinded to the type of treatment while another clinician administered the respective treatment of the 2 groups. The patients were recalled at 15-day intervals to examine periodontal clinical parameters.

Sample Size

According to the previous studies and the constraints faced, based on the study of Funosas et al (32), the measure of the difference in the pocket depth was 1.8 mm, and the mean standard deviation was 2.2 and with regard to $\alpha=0.05$ and $\beta=0.2$ using the comparison option, the minimum size of sample size in the Minitab software was calculated at 34 individuals.

Data Analysis

The values of the different parameters collected are expressed as means \pm SD. At several follow-up sessions in both groups, repeated measures two-way ANOVA was used for the comparison of quantitative indices, and $P < 0.05$ was considered significance level. The data was analyzed using the SPSS version 21.

Results

A total of 40 patients who met the inclusion criteria and agreed to participate in the study were enrolled in the study from among 46 individuals; 6 patients (3 from the test group and 2 from the control group) were excluded in the follow-ups, and finally 34 individuals (19 women and 15 men) completed their respective treatments (Figure 1); combination (metronidazole + piroxicam gel) therapy led to significantly greater clinical benefits than piroxicam gel alone for all clinical indices in 3 months. Changes in the periodontal clinical parameters occurred within the 3 months, and there were clinically significant differences between the 2 groups; inter-group comparisons of the clinical periodontal parameters PI and BOP showed significant differences one month after treatment. Moreover, in both groups, PI reduced gradually and significantly while in group A, it was significantly higher in comparison with that in group B ($P=0.009$, Table 1). In addition, we observed that changes in BOP decreased, with greater reduction in group A ($P=0.003$) (Table 2). The other findings of this study were changes in pocket depth in both groups, but the decrease was significant in group A ($P=0.041$, Table 3). In addition, changes in CAL were greater in group A than in group B, with the difference in group A 16% and in group B 14%, and these changes were statistically significant ($P=0.039$, Table 4).

Discussion

Periodontitis is an inflammatory disease caused by microorganisms. The progression of the disease, however, is determined by host factors. One of the mediators that affect this improvement is the prostaglandins which are produced from arachidonic acid under the influence of cyclooxygenase enzymes. NSAIDs have revealed therapeutic benefits in decreasing the progression of the periodontal disease by efficiently inhibiting prostaglandin synthesis (33). The topical application of NSAIDs is a directed site-specific therapy and is beneficial to prevent systemic complications and simultaneously absorb high concentrations of the drug at the diseased site. Most studies have investigated the use of antimicrobial agents. This principle is now applicable to NSAIDs (34). Some NSAIDs used as non-selective cyclooxygenase-1 inhibitors in periodontal research include aspirin, flurbiprofen, ibuprofen, naproxen, and piroxicam (35). This study showed that there was a significant difference between metronidazole + piroxicam gel and piroxicam gel alone, since all indices have improved clinical periodontal parameters in both groups. SRP that is the best treatment for periodontal diseases and is also influenced by the patients' motives for caring and cleaning their teeth and mouth regularly reduced the PI in both groups. In addition, in the current study aimed to reduce the depth of the pocket, BOP increased the CAL in the metronidazole + piroxicam group in comparison with the piroxicam group, which is in agreement with the studies

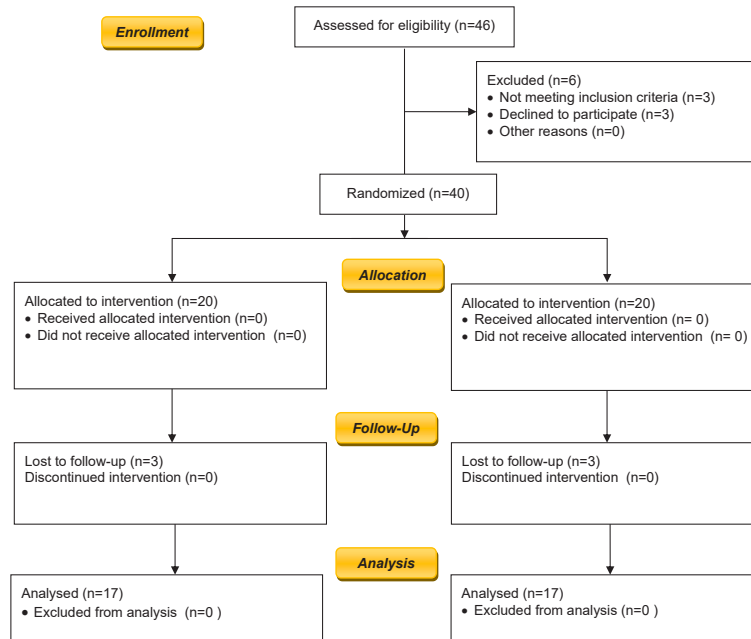


Figure 1. Flow Diagram of the Study.

of Pedrazzoli et al (22), Ainamo et al (36), and Palmer et al (37) showing a reduction of probing depth pocket and decrease of BOP in metronidazole group. Moreover the studies of Salvi & Lang (35), Magnusson (38), Awartani & Zulqarnain (39), and Riep et al (40) are not consistent with the results of the present study, as the replicated local employment of metronidazole gel as an adjunct to SRP and the mechanical treatment alone demonstrated similar clinical effects without statistically significant difference. However, Noyan et al noted that local metronidazole with

SRP appeared to be more useful in providing both clinical and microbial improvements (41). Furthermore, Griffiths et al compared the clinical effects of subgingival scaling plus the subgingival application of 25% metronidazole gel, Elyzol (SRP+gel), in patients with chronic adult periodontitis. They concluded that adjunctive therapy of SRP gel was better than the conventional SRP alone, and these changes were maintained for 9 months (42). Pavia et al conducted a meta-analysis to evaluate the effectiveness of local delivery of metronidazole alone or as

Table 1. Distribution of Mean Plaque Index in Groups A and B at Appointments in Comparison to Baseline Values

Group	Time			
	Baseline	1 Month	2 Months	3 Months
A: Piroxicam + Metronidazole	0.92±0.050	0.60± 0.02	0.48±0.01	0.33±0.01
B: Piroxicam	0.91±.050	0.69± 0.03	0.53±0.02	0.39±0.02
P value	0.6872	0.0151	0.0287	0.0092

Table 2. Distribution of Mean Bleeding on Probing in Groups A and B at Appointments in Comparison to Baseline Values

Group	Time			
	Baseline	1 Month	2 Months	3 Months
A: Piroxicam + Metronidazole	1.2±0.13	0.72±0.04	0.57±0.03	0.32±0.02
B: Piroxicam	1.4±0.35	0.88±0.06	0.68±0.04	0.44±0.03
P value	0.5940	0.0299	0.0313	0.0033

Table 3. Distribution of Probing Pocket Depth in Groups A and B at Appointments in Comparison to Baseline Values

Group	Time			
	Baseline	1 Month	2 Months	3 Months
A: Piroxicam + Metronidazole	4.46±0.44	4.38±0.51	3.41±0.12	3.32±0.05
B: Piroxicam	4.56±0.50	4.43±.55	3.96±0.23	3.87±0.26
P value	0.8811	0.9471	0.0378	0.0417

Table 4. Distribution of Mean Clinical Attachment Level for Groups A & B and Appointments in Comparison to Baseline Values

Group	Time			
	Baseline	1 Month	2 Months	3 Months
A: Piroxicam + Metronidazole	3.76±.39	3.51±0.36	3.02±0.04	2.73± 0.01
B: Piroxicam	3.80±.41	3.62±0.44	3.21±0.080	2.92±0.09
P value	0.9579	0.8472	0.0374	0.0397

an adjunct to mechanical therapy in patients with chronic periodontitis (43). Pandit et al comparatively evaluated the efficacy of subgingivally delivered minocycline microspheres and 25% metronidazole gel when used as an adjunct to SRP in the treatment of chronic periodontitis. That study determined that treatment with minocycline microspheres and metronidazole gel improved PPD and CAL in patients with periodontitis compared to SRP alone (44). Bergamaschi et al compared the effect of metronidazole (local and systemic) as adjunctive therapy to full mouth periodontal debridement in smokers with chronic periodontitis, and concluded that adjunctive use of metronidazole (gel or tablet) to periodontal debridement led to similar clinical and microbiological improvement compared to treatment with placebo + periodontal debridement in smokers with chronic periodontitis up to 6 months after treatment (45). Singh et al conducted a study to comparatively evaluate the efficacy of local delivery of Aloe vera and metronidazole, as an adjunctive therapy to SRP in chronic periodontitis patients. The results showed that the 2 groups were comparable and the local application of Aloe vera could be an effective and affordable herbal substitute for metronidazole (46).

Topical anti-infective agents along with SRP obviously lead to beneficial outcomes for PD and CAL compared to SRP alone. The application of local anti-infective adjunctive therapy remains to depend on individual clinical experience, the phase of operation, and the patient's situation and preferences (47-50). Priyanka et al used satranidazole gel (3%) as an adjunctive therapy to non-surgical periodontal therapy in patients with periodontitis and observed better results compared to those of initial periodontal treatment alone (51). In general, topical application of NSAIDs is possible because these drugs are lipophilic and are absorbed into gingival tissues. NSAIDs that are topically used include ketorolac tromethamine mouthwash and ketoprofen toothpaste (27). Waite et al and Feldman et al performed 2 retrospective studies aimed to evaluate the prevalence of periodontal disease in patients using NSAIDs compared to controls. The results of these 2 studies showed that participants using NSAIDs presented smaller gingival inflammation, PD, CAL and radiographic alveolar bone loss (52,53). Johnson et al investigated the effects of naproxen, another non-steroidal anti-inflammatory drug, on gingival inflammation. The results of their study showed that the drug had no significant effect on plaque, gingival and bleeding index scores. The significant effect of naproxen was only observed in the resolution of gingivitis after the plaque was removed (54). Taiyeb Ali and Waite observed that at the 2-week evaluation following the ibuprofen regimen, a significantly greater decrease in gingival bleeding, color, and pocket depth was detected in the test group compared to the control group (55). Aboul-Dahab showed a significant reduction in pocket depth & gingival index in the experimental group

compared to the control group. Radiographs revealed more bone fill in the experimental group compared to the control group (56). Moreover, Sekino et al evaluated the gingival margin inflammation in combination with SRP procedures and the experimental gingivitis model. The results demonstrated that ibuprofen provided additional benefits to the professional control of biofilm and experimentally, dental plaque-induced gingivitis (57). Pinho et al presented that the percentage of remaining deep pockets after 14 days in the SRP + Loxoprofen group was significantly lower than in the SRP + placebo group (58). Funosas et al showed statistically significant reductions in probing depth, plaque, gingival indices and BOP when the ASA gel 1% and ketoprofen gel 2% were used; however, there was no gain in CAL in both groups (32). Hasan and Najam revealed that when 1% ASA gel was placed in periodontal pockets, it reduced pocket depth, PI, gingival index and bop (59). Aras et al reported the effects of naproxen sodium on periodontal indices and that all of the clinical parameters, except for the GBI index, were significantly lower in the control group (60). Farahmand et al reported SRP with subgingival ibuprofen gel resulted in a significant reduction of PI, BOP, PPD, and CAL within 3 months as compared to baseline and placebo group (61). Therefore, the direction of host modulation agents as an adjunctive therapy to the non-surgical, mechanical therapy may be effective on the early stages of the treatment of periodontal diseases in advanced stages. In addition, the findings in various studies, the choice of patients or dose-response studies, and research design, duration of study may influence the outcome of the study. Finally, traditional periodontal treatment is the most effective procedure for chronic periodontitis, and the use of a combination of drugs can be beneficial to reduce the clinical signs of periodontal disease. Also, as mechanical cleaning alone cannot completely eliminate all periodontal pathogens, can be concerned on the dental bacterial plaque, as a results need to contain various antimicrobial agents in order to reduce, control and ability to remove microbial plaque; Therefore It's recommended that the piroxicam + metronidazole gel can be used as a complementary therapy to accelerate the healing process.

Conclusion

The locally applied piroxicam + metronidazole gel may slightly beneficial for periodontal healing following non-surgical treatment and can offer a new direction in the handling of periodontal treatment. Further, it could be used as a complementary therapy to treat the inflammatory process and clinical symptoms of the disease more quickly.

Authors' Contribution

AMF: study conduct, supervisor, article edition. FS, MG: study implementation, data analysis. AMF, BJE: manuscript preparation.

AG, AS: article edition.

Ethical Statement

The research protocol was reviewed and approved by The Ethics Committee (code of ethics: 2125) of the Faculty of Dentistry, and also registered in the Iranian Registry of Clinical Trials (code: IRCT2014050817587N3). The study procedure conforms to the principles outlined in the Declaration of Helsinki on human medical experimentation. Verbal and written informed consent was obtained from all participants.

Conflict of Interest Disclosures

Authors declare no conflicts of interest regarding the submission of this article or financial relationships (personal financial interest) with other organizations or with the people working with this study.

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