Original Article

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The effect of 2% minocycline gel as an adjunct to scaling and root planing at the furcation area in supportive periodontal therapy

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Objective: The aim of this study was to evaluate the clinical outcomes of 2% minocycline gel as an adjunct to scaling and root planing and compare them with scaling and root planing alone at the furcation area in treated periodontal patients during supportive periodontal therapy.

Materials and Methods: Patients entering supportive periodontal therapy who had 2 residual pockets equal to or greater than 5 mm at the contralateral side in the furcation area were recruited in a randomized, controlled, single-blinded study. A full-mouth examination comprising probing depth (PD), relative attachment level (RAL), bleeding on probing (BOP), gingival Index (GI), full mouth plaque index (PI), full mouth bleeding index (BI), and furcation involvement (FI) was performed at baseline, day 30 and day 90. The experiment protocol for the control sites was scaling and root planing (SRP) alone while that of the test sites was SRP and the administration of Periocline® at baseline and day 14.

Results: The full mouth PI and BI, RAL, PD, BOP-positive sites, and GI at the 1-month follow-up were improved in both treatment groups. At the 3-month follow-up, adding minocycline as an adjunctive treatment significantly improved RAL and PD. Furthermore, most teeth showed no progression in the degree of FI. In contrast, the SRP alone group demonstrated a relapse in the degree of furcation involvement more frequently than in the SRP along with minocycline group (18.52% vs 3.70%, respectively). However, the degree of furcation involvement was not significantly different among time points within each group and between groups.

Conclusion: Within the limitations of this study, local application of minocycline HCl 2% gel (Periocline®) as an adjunct to scaling and root planing in the furcation area demonstrated significant improvement in clinical parameters (RAL and PD) and reduced inflammation (BOP-positive sites) than scaling and root planing alone at the 3-month follow-up.

Keywords: furcation defects, maintenance, minocycline, periodontal pocket, periodontitis, randomized controlled trial

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Introduction

Periodontitis is an infectious disease that causes periodontal inflammation. The main cause of periodontitis is a combination of periodontal pathogens [1] that coexist and are intimately connected inside the dental plaque [2]. Thus, the goal of current periodontitis treatment is to reduce the amount of periodontal pathogens in the dental plaque, which includes dental health education as well as scaling and root planing, to reduce inflammation and change the composition of the microorganisms within the subgingival plaque, reducing the microorganisms' ability to cause disease and thus improving clinical changes [3]. To minimize the risk of recurrence and disease

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progression, patients should receive supportive periodontal therapy (SPT) following active treatment [4-5]. However, scaling and root planing (SRP) alone may not be sufficient to manage microbial infections in locations that instruments cannot reach, such as the furcation area [6], which is too narrow for a periodontal instrument to clean [7-8]. Moreover, molar furcation sites also respond less favorably to treatment than molar flat surface sites or non-molar sites [9]. For initial furcation involvement, sufficient plaque control and scaling and root planing can be effective. However, surgical management is required for grade II and III furcations [10]. Therefore, antibiotics are used in conjunction with scaling and root planing by inhibiting microbial growth or killing any remaining periodontal pathogens and preventing disease progression [11-14].

Systemic antibiotics and topical antibiotics are the two types of antibiotics used in dentistry. Systemic antibiotics offer the convenience of easy administration and the ability to target multiple sites with a single dose. However, their prolonged use may lead to antibiotic resistance, opportunistic infections, and adverse effects on non-pathogenic oral microorganisms [12]. Local antibiotics have the advantage of being applied specifically where they are needed, a lower dose, less side effects from drug use, and a higher drug concentration in the periodontal pocket compared with systemic antibiotics [13]. A systematic review [14] revealed that the use of local antibiotics in conjunction with SRP alone resulted in superior clinical treatment outcomes in furcation defects. However, there are disadvantages, such as the need to maintain adequate drug concentrations to inhibit microbial growth or kill periodontal pathogens. The delivery of some active forms of topical antibiotics into the deep region of the periodontal pocket or furcation area remains difficult [15].

Minocycline, a second-generation semi-synthetic, broad-spectrum antibiotic, belongs to the class of tetracyclines. When used orally, it has a better pharmacokinetic impact than tetracycline, with quicker absorption including in the elderly, a longer half-life, high lipophilicity, excellent tissue penetration, and nearly 100% bioavailability [16-17]. Minocycline gel (Periocline®) has a waxy texture and contains 2% minocycline hydrochloride. It is a long-acting local drug delivery system in which the drug carrier regulates the slow release of the topical drug so that it remains in the periodontal pocket for as long as 24 hours after administration and maintains its effective dose without being washed away by the gingival crevicular fluid (GCF). A meta-analysis study [18] found that scaling and root planing combined with the use of minocycline gel, the periodontal pocket depth was reduced and the clinical attachment level was significantly increased compared with scaling and root planing alone. However, several studies assessed the clinical effect of topical antibiotics on poor response sites to scaling and root planing or a recurrence of periodontal disease following scaling and root planing in patients receiving supportive periodontal therapy [19-22]. McColl *et al.* [22] evaluated the effectiveness of two treatment modalities in reducing residual pockets of 5 mm or more in SPT patients in a 1-year follow-up study. They reported that these pockets became shallower, however, no significant difference was found between the two treatments. Thus, there are numerous limitations in the treatment of periodontitis in multi-root teeth [7-8]. Furthermore, compared with scaling and root planing alone, monotherapy using minocycline gel did not produce better clinical effects [22]. Hence, the aim of this study was to evaluate the clinical outcomes of 2% minocycline gel as an adjunct to scaling and root planing and compare them with scaling and root planing alone at the furcation area in treated periodontal patients during supportive periodontal therapy.

Material and Methods

Study design

A prospective, randomized, single-blinded experiment with a split mouth design was conducted from October 2021 to May 2022 at a single site (Periodontics and Oral Medicine Clinic, Faculty of Dentistry, Mahidol University, Thailand). Ethical approval for this study was obtained from the Ethics Committee in Human Research (Faculty of Dentistry/Faculty of Pharmacy, Mahidol University Institutional Review Board; MU-DT/PY-IRB) (COA.No.MU-DT/PY-IRB2021/048.2005).

Sample size

The sample size was calculated based on a power of 95% and an alpha level of 5% using a standard deviation of 1.2 mm and precision of 0.7. Based on a previous study [23], we determined the minimal sample size of 24 sites for each group. The sample size was increased by 20% to account for the potential withdrawal (dropout) of the sample over the course of the study. Consequently, this study needed at least 30 sites in each group.

Subjects

Patients with periodontitis (as defined by the AAP/EFP 2018) [24] who were over 35 years old, had undergone active periodontal therapy for more than a year, had supportive therapy for no longer than six months, still had pocket depths of at least 5 mm area in the furcation area of multiple rooted teeth of at least 2 teeth on the contralateral side, and were available for monitoring for the full duration of the clinical study (3 months), were invited to participate in this study. The study excluded patients who met any of the following conditions: systemic diseases associated with periodontitis (such as diabetes), the requirement for antibiotic treatment, a history of systemic antimicrobial therapy within the previous three months, pregnancy or breastfeeding, or a known allergy to minocycline (tetracycline group). Patients who met the inclusion criteria were provided with information about the study. Furthermore, throughout the study, patients who became pregnant required antibiotic or anti-inflammatory medication, or developed allergies to minocycline were also excluded from further participation.

Treatment regimen

Patients undergoing supportive periodontal therapy were screened and those meeting the inclusion criteria were recruited to participate and signed informed consent forms. Prior to taking an impression to create an occlusal stent, patient information was collected and assigned code names for identification. At baseline (day 0), a full-mouth examination comprising probing depth (PD), relative attachment level (RAL), bleeding on probing (BOP) [25], gingival Index (GI) [26], full mouth plaque index (PI) [27], full mouth bleeding index (BI) [25] and furcation involvement (FI) [28] was performed by an investigator (TS). After collecting subject data, the investigator (TS) advised the patient on oral hygiene care using the modified Bass technique and interdental cleaning aids, such as dental floss or interdental brushes. Next, the subject received scaling and root planing with periodontal instruments and ultrasonic scalers, and full mouth polishing. The treatment modalities at each site were randomly assigned using a computer program by a co-investigator (YK). Minocycline gel (Periocline®; SUNSTAR, JAPAN) was injected into the periodontal pocket at the randomly selected test sites by inserting the tip of the syringe into the deepest site of the periodontal pocket, then injecting minocycline gel until it overflowed the gingival margin and the excess was wiped off. Following the procedure, the patient was told to avoid eating or drinking for

2 hours and refrain from brushing their teeth for 12 hours. Fluoride-containing toothpaste was given to the participants, and mouthwash use was strictly forbidden during the study period. At day 14, a co-investigator (YK) asked the patients about abnormal symptoms and checked for abnormalities in the oral cavity, including irritation at the injection site, gingival edema, dental abscess, and hematoma (ecchymosis). The co-investigator (YK) gave the patient full mouth polishing and in the test sites, minocycline gel was injected into the periodontal pocket. At 1 and 3 months after treatment, the patients underwent a re-examination, and clinical parameters were recorded. The study design comprising screening, examination, and data collection is seen in Figure 1.

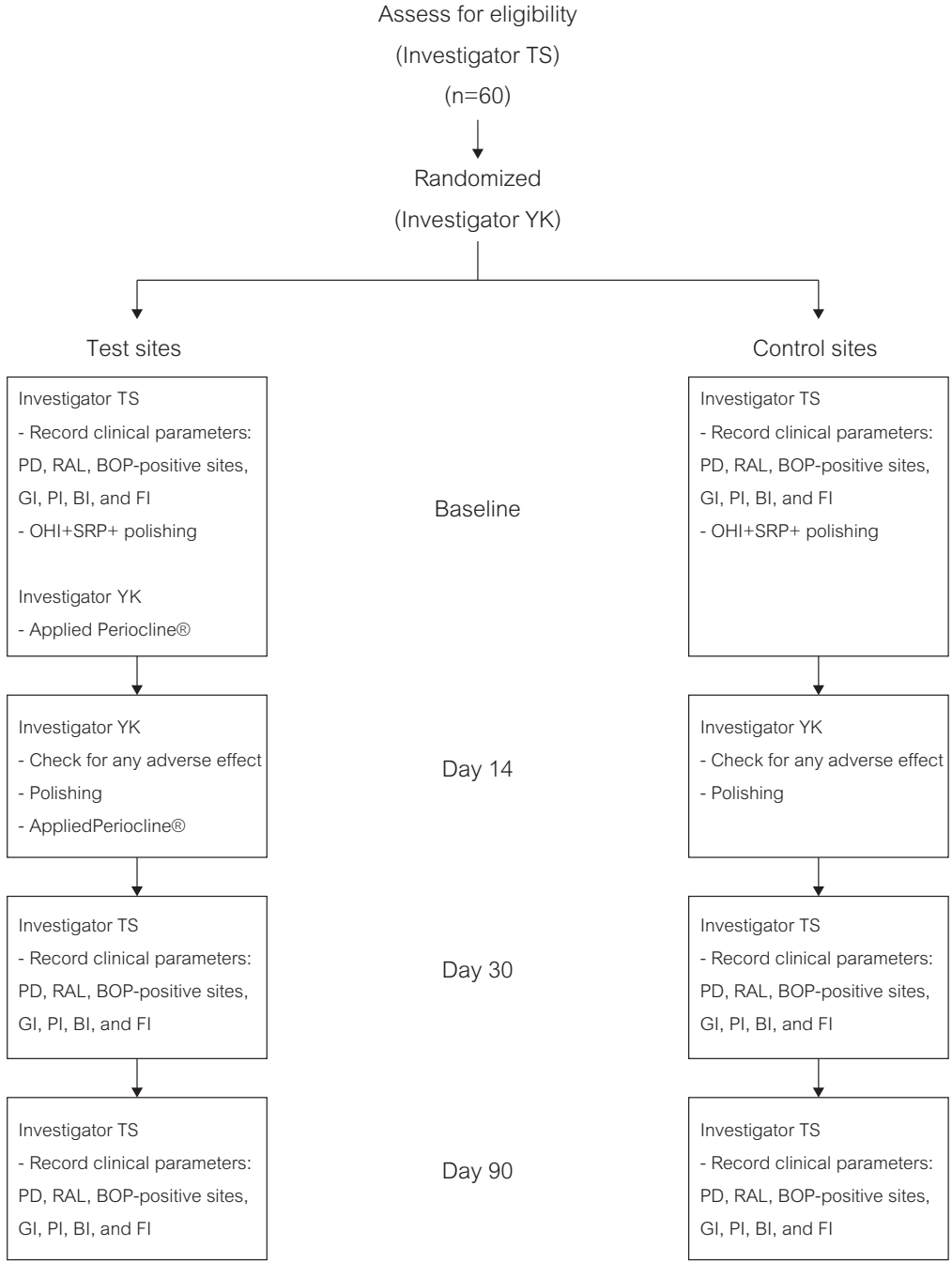

Figure 1 A flowchart illustrating the study's materials and methods

The data was collected by the same examiner (TS). Before the start of the study, the examiner was trained to adequate levels of accuracy and reproducibility for the various clinical parameters. The standard error of the measurement was 0.5. The intra-examiner reproducibility within ± 1 mm was 98% for PD and 97% for RAL assessments.

Statistical analysis

The data were analyzed with SPSS version 28.0 (IBM Corp., Armonk, NY, USA). To determine whether the data distribution was normal or not, the Shapiro-Wilk test was used. For full mouth PI values, the data are shown as mean (SD), and for full mouth BI, RAL, and PD values, they are presented as median (P25, P75). Repeated Measures ANOVA and the Friedman test were used to determine the significance of the change in full mouth PI values over time and the change in full mouth BI, RAL, and PD values over time, respectively. The Wilcoxon Signed Rank test was used for each paired group of RAL, and PD values. The McNemar test was used to assess the significance of the change over time and in each paired group for BOP, GI and FI values. The level of significance was set at $p<0.05$.

Results

Patients

Sixty sites in 23 patients, 44–81 years old, (9 males and 14 females) took part in the study. At the 3-month follow-up, two patients dropped out. Thus, 54 sites in 21 patients were analyzed. All patients were non-smokers.

Full mouth plaque index (PI)

The mean full mouth PI at day 30 showed a significant reduction from 45.25±14.52% to 32.69±12.16% (P<0.05). A slight increase in mean full mouth PI was observed at day 90, however, this was significant compared with the mean PI at day 0 (Figure 2).

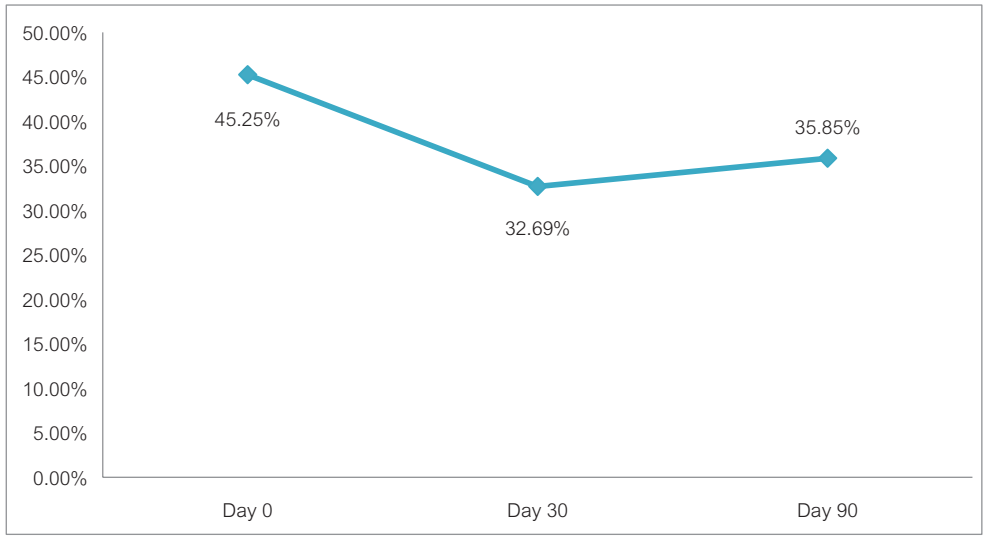

Figure 2 The mean full mouth plaque index (PI) at day 0, 30, and 90 follow-up periods

Full mouth bleeding index (BI)

The median full mouth BI at day 30 showed a significant reduction from 22.32% to 12.97% ($p<0.05$) and continued to decrease through day 90 (Figure 3).

Relative attachment level (RAL)

The median RAL displayed a significant gain at day 30 and day 90 compared with the baseline for the control and test sites ($p<0.05$). At day 90, the test sites showed a significant RAL gain compared with control sites ($p<0.05$) (Table 1).

Probing depth (PD)

At day 0, the PD range was 5–10 mm at control sites and 5–11 mm at the test sites. When the follow-up period ended (day 90), the PD range was 3-8 mm at control sites and 3-6 mm at the test sites. The median PD displayed significantly reduced scores at day 30 and day 90 compared with the baseline for control and test sites ($p<0.001$). At day 90, the test sites showed a significant reduction in PD scores compared with control sites ($p<0.05$) (Table 2).

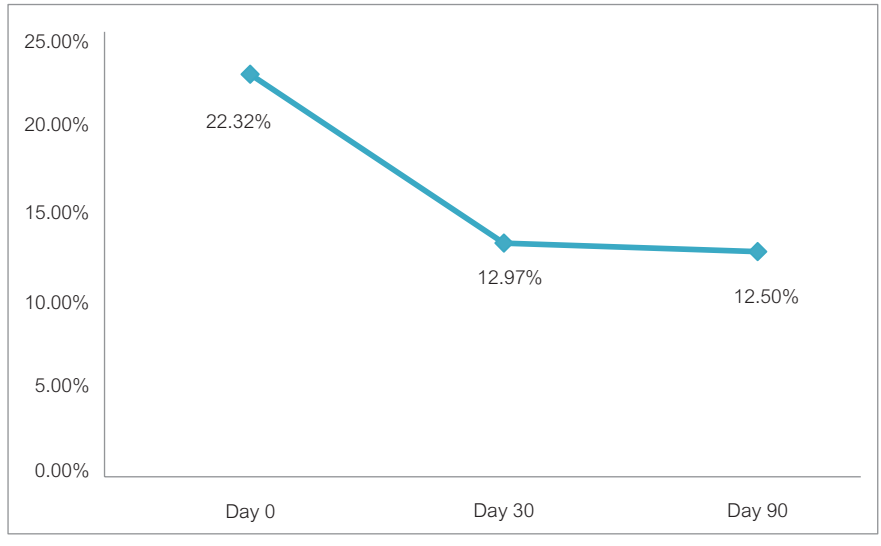

Figure 3 The median full mouth BI at day 0, 30, and 90 follow-up periods

Table 1 Relative attachment level (RAL) at day 0, 30, and 90 follow-up periods at control sites and test sites

	Median (P25, P75)			*p-value*
Day	0	30	90	
Control	12(10.75,13.25)[a]	11(9.00,13.00)[b]	11(9.00,13.00)[b]	<0.001*
Test	13(10.00,13.25)[a]	11(9.00,12.00)[b]	10(9.00,12.00)[b]	0.022*
P-value	0.702	0.272	0.022*	

The different letter indicates a significant difference ($p<0.05$), whereas the same letter indicates no significant difference between each time point in each row.

Table 2 Probing depth (PD) at day 0, 30, and 90 follow-up periods at control sites and test sites

	Median (P25, P75)			*p-value*
Day	0	30	90	
Control	5(5.00,6.25)[a]	5(4.00,5.00)[b]	5(4.00,5.00)[b]	<0.001*
Test	5(5.00,6.00)[a]	4(4.00,5.00)[b]	4(3.00,5.00)[b]	<0.001*
P-value	0.746	0.059	0.006*	

The different letter indicates a significant difference ($p<0.05$), whereas the same letter indicates no significant difference between each time point in each row.

Bleeding on probing (BOP)

In control sites, there was no significant difference between time points in the number of BOP-positive sites. In the test sites, the number of BOP-positive sites at day 30 was significantly reduced from 26 sites (86.67%) to 12 sites (40.00%) (*p<0.001*). A slight increase in the number of BOP-positive sites was observed at day 90 that was significant compared with the number of BOP-positive sites at day 0 (*p<0.05*). At day 30 and day 90, there was no significant difference between the control and test sites (*p<0.05*) (Table 3).

Gingival index (GI)

At day 0, the control sites and test sites had GI scores ranging from 0–3, with GI score of 2 being the most prevalent value (20 sites (66.67%) at the control sites and 23 sites (76.67%) of the test sites. At day 30, none of the sites had a GI score of 3; the number of sites with a GI score of 2 had dropped; the number of sites with a GI score of 1 had increased in both sites; however, the number of sites with a GI score of 0 had increased in the test sites. By day 90 compared with day 0, the test sites with GI scores of 2 had reduced, whereas those with GI scores of 0 and 1 had increased. Furthermore, the number of sites with GI scores of 2 had increased in the control sites, however, there was no significant difference between control and test sites in the number of GI score sites on day 90 (*p<0.05*) (Table 4).

Furcation involvement (FI)

At day 0, the control and test sites exhibited furcation involvement ranging from grade 1–3. Most of the teeth had grade 1 furcation involvement, with 14 sites (46.67%) in the control group and 19 sites (63.33%) in the test group. Moreover, grade 2 furcation involvement was observed

Table 3 Number of bleeding on probing (BOP)-positive sites in control sites and test sites at day 0, 30, and 90 follow-up periods

	n (%)			*p-value*		
Day	0 (n=30)	30 (n=30)	90 (n=27)	0 vs 30	0 vs 90	30 vs 90
Control	23 (76.67)	17 (56.67)	22 (81.48)	0.180	1.000	0.267
Test	26 (86.67)	12 (40)	16 (59.33)	<0.001*	0.016*	0.289
p-value	0.508	0.180	0.109			

Table 4 Number of sites with gingival index (GI) scores (0-3) at control sites and test sites at day 0, 30, and 90 of the follow-up periods.

Day		n (%)			
	GI score	0	1	2	3
0 (n=30)	Control	1 (3.33%)	6 (20.00%)	20 (66.67%)	3 (10.00%)
	Test	1 (3.33%)	3 (10.00%)	23 (76.67%)	3 (10.00%)
	p-value	0.736			
30 (n=30)	Control	-	13 (43.33%)	17 (56.67%)	-
	Test	8 (26.67%)	9 (30.00%)	13 (43.33%)	-
	p-value	N/A			
90 (n=27)	Control	1 (3.70%)	4 (14.81%)	22 (81.48%)	-
	Test	3 (11.11%)	8 (29.63%)	16 (59.26%)	-
	p-value	0.250			

in 11 sites (36.67%) of the control group and 8 sites (26.67%) of the test group, as illustrated in Figure 4. Importantly, no significant differences were found between the groups regarding the degree of furcation involvement ($p>0.05$).

At day 30, most of the sites did not exhibit any progression in the degree of furcation involvement. Furthermore, sites initially categorized as grade 1 or grade 2 furcation involvement demonstrated improvements. Specifically, grade 1 furcation involvement transitioned to no furcation involvement in 4 sites (13.33%) in the control group and 1 site (3.33%) in the test group. Additionally, grade 2 furcation involvement improved to grade 1 furcation involvement in 4 sites (13.33%) in the control and test groups.

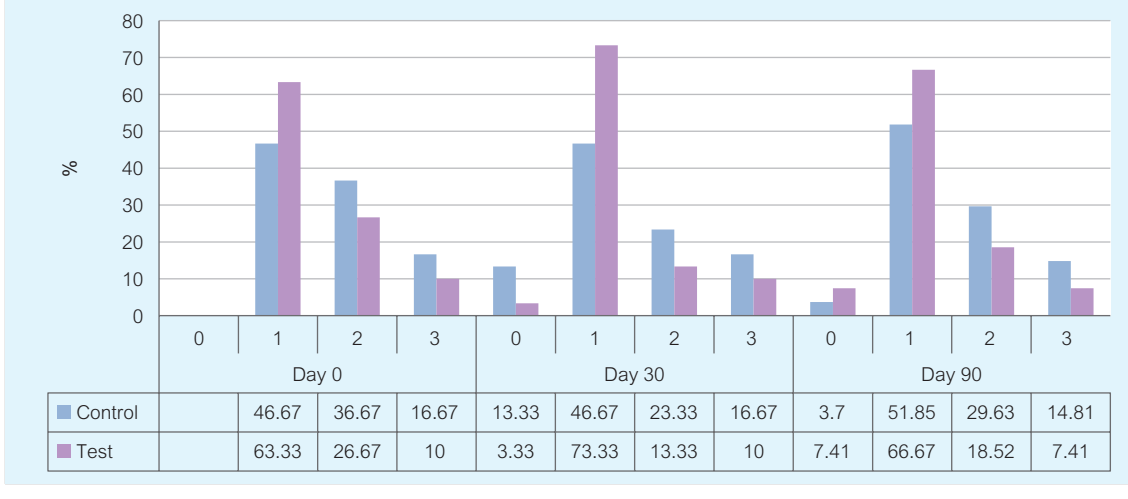

Figure 4 The number of sites that had furcation involvement (0-3) in control sites and test sites at day 0, 30, and 90 follow-up periods.

By day 90, most sites did not exhibit any additional progression in the degree of furcation involvement. However, a relapse in the degree of furcation involvement was observed. Specifically, in the control group, there was a transition from no furcation involvement at day 30 to grade 1 furcation involvement in 4 sites (14.81%). Furthermore, in both the control and test groups, there was a relapse in furcation involvement, with 1 site (3.70%) transitioning from grade 1 furcation involvement at day 30 to grade 2 furcation involvement. However, the difference in the degree of furcation involvement among time points within each group and between groups did not reach statistical significance. (Figure 1, Table 5)

Table 5 Change of degree of furcation involvement (0-3) in control sites and test sites at day 0, 30, and 90 follow-up periods

day	Group	No progression	furcation improvement	furcation worsening
		n (%)		
0 vs 30	control	22 (73.33%)	8 (26.67%)	0 (0.00%)
		grade 1>1 10 (33.33%)	grade 1>0 4 (13.33%)	
		grade 2>2 7 (23.33%)	grade 2>1 4 (13.33%)	
		grade 3>3 5 (16.67%)		
	test	25 (83.33%)	5 (16.67%)	0 (0.00%)
		grade 1>1 18 (60.00%)	grade 1>0 1 (3.33%)	
		grade 2>2 4 (13.33%)	grade 2>1 4 (13.33%)	
		grade 3>3 3 (10.00%)		
0 vs 90	control	24 (88.88%)	3 (11.11%)	0 (0.00%)
		grade 1>1 12 (44.44%)	grade 1>0 1 (3.70%)	
		grade 2>2 8 (29.63%)	grade 2>1 2 (7.41%)	
		grade 3>3 4 (14.81%)		
	test	23 (85.19%)	4 (14.81%)	0 (0.00%)
		grade 1>1 16 (59.26 %)	grade 1>0 2 (7.41%)	
		grade 2>2 5 (18.52 %)	grade 2>1 2 (7.41%)	
		grade 3>3 2 (7.41%)		
30 vs 90	control	21 (77.78%)	1 (3.70%)	5 (18.52%)
		grade 1>1 10 (37.04%)	grade 1>0 1 (3.70%)	grade 0>1 4 (14.81%)
		grade 2>2 7 (25.93%)		grade 1>2 1 (3.70%)
		grade 3>3 4 (14.81%)		
	test	25 (92.59%)	1 (3.70%)	1 (3.70%)
		grade 0>0 1 (3.70%)	grade 1>0 1 (3.70%)	grade 1>2 1 (3.70%)
		grade 1>1 18 (66.67%)		
		grade 2>2 4 (14.81%)		
		grade 3>3 2 (7.41%)		

Discussion

In this study, we evaluated the clinical outcomes of adjunctive local delivery of 2% minocycline HCl gel (Periocline®) at the furcation area in treated periodontal patients during supportive periodontal therapy. We noted that there was an improvement in clinical parameters (Full mouth PI and BI, RAL, PD, BOP-positive sites, GI) at the 1-month follow-up regardless of the therapeutic method used. At the 3-month follow-up, adjunctive minocycline significantly improved RAL and PD. For FI, there were no significant differences among time points within each group or between groups. These results are similar to the short-term, double-blind, parallel studies by Nakagawa *et al.* [19], which showed that patients in the treatment group exhibited better improvements in RAL and PD compared with those in the placebo group. In contrast with Choi *et al.* [20] in SPT patients, their results showed significant improvements in clinical parameters (PPD, CAL, BOP, PPD ≥5 mm sites, and PPD ≥5 mm + BOP-positive sites) at 1 and 3 months from baseline, but at the 3-month follow-up, there was no significant difference between the groups. It is important to note that our study protocols differed from those of Nakagawa *et al.* [19] and Choi *et al.* [20] in terms of study design and patient selection. We utilized a single-blind, split-mouth design and specifically focused on the pockets remaining in the furcation area. In contrast, Nakagawa *et al.* [19] conducted double-blind, parallel studies, and Nakagawa *et al.* [19] and Choi *et al.* [20] evaluated any teeth without a specific focus.

Maintaining good oral hygiene is essential for the efficacy of antibiotic therapy in treating periodontal disease because dental plaque can harbor bacteria carrying antibiotic-resistant genes (ARGs). [29-31]. At the 1-month follow-up, we found that full mouth PI was greatly reduced, as was full mouth BI, corresponding with an improvement in RAL and PD in the test group more than in the control group. However, the 3-month follow-up showed an increase in full mouth PI corresponding with an increased number of BOP-positive sites. We speculate that supragingival plaque caused gingival inflammation, which resulted in an increase in BOP-positive sites. In addition, Loos *et al.* [32] found that patients who better complied with the oral hygiene instructions experienced greater gingival condition improvements and greater reduction in probing pocket depth than those who did not. Another possible explanation for this result is the residual plaque in the posterior area after brushing. Sreenivasan *et al.* [33] found that mid-vestibular and anterior sites demonstrated lower average scores for dental plaque than lingual, posterior, and molar sites. Therefore, emphasizing practicing correct oral hygiene and using efficient cleansing instruments, particularly in the furcation area, is essential.

The aim of SPT is to minimize the recurrence of disease and maintain the most stable condition of the attachment apparatus. According to Lang *et al.* [34], the absence of BOP indicated stability. In the present study, full mouth BI showed a significant reduction at 1-month post-treatment and continued to decrease through the rest of the study. At the 1- and 3-month follow-ups, we discovered that adjunctive minocycline significantly reduced the number of BOP-positive sites. Although there was no significant difference between the control and the test sites in the number of GI score sites on day 90, the number of bleeding sites in the test site trended toward being lower than at baseline. These results demonstrated that minocycline gel as an adjunctive to scaling and root planing can effectively reduce gingival inflammation. Minocycline has been demonstrated to inhibit matrix metalloproteinase and pro-inflammatory cytokines, reduce the inflammatory

response in LPS-challenged monocytes, and prevent bone resorption by directly acting on osteoclast precursors [35-37].

The treatment modality for furcation involvement is determined by the extent of the involvement and the overall condition of the tooth and surrounding tissues [10]. Nonsurgical treatment is typically initiated for all degrees of furcation involvement. However, as the severity of furcation involvement increases, the response to nonsurgical treatment may be less effective. In our study, most of the samples exhibited grade 1 furcation involvement. In the group that received SRP alone, a relapse in the degree of furcation involvement was observed more frequently than in the group that received SRP along with minocycline, however, the difference in the degree of furcation involvement among time points (from day 0 to day 90) within each group and between groups was not significant. These results are similar to parallel studies by Tomasi and Wennstrom [38] that failed to demonstrate an improvement in the degree of molar furcation involvement after using 8.8% doxycycline gel as an adjunct to scaling and root planing. In contrast to parallel studies by Dannewitz *et al.* [39], they used 14% doxycycline gel for treating furcation sites in patients participating in a maintenance program and discovered an improvement in the degree of molar furcation involvement at 3 months, but not at the 6- and 12-month follow-ups. It is worth noting that our study protocols differed from those of Tomasi and Wennstrom [38] and Dannewitz *et al.* [39] in terms of study design. Specifically, we employed a single-blind, split-mouth design, while the studies conducted by Tomasi and Wennstrom [38] and Dannewitz *et al.* [39] followed parallel study designs. The treatment of a multi-rooted tooth with furcation involvement is still a challenge because the unusual anatomic morphology of the furcation makes it difficult or impossible to thoroughly debride with general periodontal instruments [8]. These results suggest that the adjunctive use of minocycline alongside scaling and root planing (SRP) can lead to a reduction in the degree of grade I and grade II furcation involvement in the short term. However, it was observed that the degree of furcation involvement in grade III cases remained unchanged despite the treatment. Nevertheless, further investigation through long-term studies is warranted to provide a deeper understanding of these outcomes. Further laboratory investigations, i.e., microbiological findings or inflammation reactions, might reveal the mechanism of action of Periocline® responsible for the important clinical outcomes.

Conclusion

Within the limitations of this study, including a small number of participants and short-term evaluation, local application of 2% minocycline HCl gel (Periocline®) as an adjunct to scaling and root planing in furcation area demonstrated significant improvement in clinical parameters (RAL and PD) and reduction of inflammation (BOP-positive sites) compared with scaling and root planing alone at the 3-month follow up.

Author contributions

Sathitthammaphon T performed the study, collected data, statistical analysis, and wrote the first draft of the manuscript. Rodanant P provided a conception of study, designed and supervised the study. Kuphasuk Y provided a conception of study, designed and supervised the study, and gave the final approval for the version submitted for publication. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

The authors do not have any financial interests, either directly or indirectly, in the products listed in the study.

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