

Clinical effect of 2% minocycline gel as an adjunct to scaling and root planing on single-rooted teeth in supportive periodontal therapy

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Objective: In supportive periodontitis patients, local minocycline gel is used as an adjunct to scaling and root planing (SRP) in deep probing depth sites. However, there are currently few randomized clinical studies confirming its effectiveness. The objective of this study was to assess whether SRP with minocycline impacted this patient group.

Materials and Methods: Nineteen patients with 2 pockets ≥ 5 mm deep at contralateral sites were recruited and randomized into the test group (SRP+minocycline, 28 sites) and control group (SRP alone, 28 sites). Clinical parameters were collected at baseline, and at 30, and 90 days post-treatment.

Results: All clinical parameters improved from baseline in both groups, with no significant difference observed between the groups at any time point. The relative attachment level (RAL) significantly decreased from baseline to day 30 and day 90 in the test group, but significantly decreased only from baseline to day 30 in the control group. Moreover, the percentage of bleeding on probing sites was significantly improved in both groups from baseline to day 30.

Conclusion: The results from this study demonstrate that there was no significant difference in the clinical parameters on single-rooted teeth with moderate deep pockets in previously treated periodontitis patients over a three-month period between the SRP+minocycline and SRP alone groups.

Keywords: antibiotic, maintenance, minocycline, periodontal pocket, periodontitis

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Introduction

Periodontitis is a disease caused by many factors. The primary causative agent is infection with the many types of bacteria that live in dental plaque. This infection stimulates the body's immune system response and causes gingivitis, periodontal pockets, and attachment loss. The tooth support apparatus can be destroyed, eventually resulting in tooth loss [1]. Periodontitis

treatment focuses on eliminating bacterial plaque through scaling, root planing, and providing dental health education to patients. However, some hard-to-reach areas may not be sufficiently cleaned using instruments. Rabbani *et al.* [2] found that efficient scaling decreased deep periodontal pockets (90% of periodontal pocket depth < 5 mm, 77% 5–6 mm, and 65% > 6 mm.). Regarding tooth type, single-root teeth tend to have less calculus (10%) than multi-rooted teeth (30%) [3].

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Treatment with scaling and root planing (SRP) may be insufficient to control plaque and bacterial infections in periodontal pockets [4]. Some bacterial strains are resistant to SRP. Mombelli *et al.* [5] reported that after treatment by SRP, *Porphyromonas gingivalis* was frequently found in locations with periodontal pockets depths > 4 mm, and especially in deeper periodontal pockets. Furthermore, bacteria can enter the root surface of teeth that have been treated, e.g., *Prevotella intermedia* and *Porphyromonas gingivalis* [6]. Thus, some lesions do not respond to SRP alone.

Local antibiotics has been used an adjunctive periodontal treatment to reduce periodontal infection or modify the human immune-inflammatory response [7]. In Thailand, a local antibiotic is available as a gel containing 2% minocycline. Based on a systematic review and meta-analysis [8], local minocycline gel adjunct to scaling and root planing significantly improved clinical parameters compared with scaling and root planing alone.

Following the active phase of periodontal treatment, supportive periodontal treatment (SPT) is implemented to prevent and reduce the likelihood of disease recurrence [9]. Although mechanical instrumentation is necessary for deep pocket sites in supportive periodontal therapy, clinical studies suggested that the repeated use of SRP during the maintenance phase might not increase the effectiveness of subgingival debridement in periodontal pockets that had already been treated during the initial periodontal therapy [10,11]. Therefore, adjuvant therapies, such as antimicrobial drugs, have been suggested to increase the effectiveness in these sites and reduce the need for periodontal surgery. Because residual inflammatory pockets after routine periodontal maintenance are prone to worsen, minocycline used in conjunction with SRP has

been shown to be clinically successful [12]. However, it is unclear which protocol should be used and whether adjunctive therapies offer better results than repeated instrumentation alone [13]. Furthermore, a 3-month minocycline gel monotherapy study failed to reduce periodontal pocket depth better than SRP after 12 months [14]. Therefore, the present study was a randomized controlled trial with a split-mouth design conducted to determine the efficacy of minocycline gel combined SRP compared with SRP alone in single-root teeth with a periodontal pocket depth ≥ 5 mm.

Objective

The objective of this study was to evaluate the clinical outcome of 2% minocycline gel (Periocline®) as an adjunct to scaling and root planing compared with scaling and root planing alone in treated periodontitis patients with a remaining pocket depth ≥ 5 mm in single-rooted teeth during supportive periodontal therapy.

Materials and Methods

Study population and research design

A prospective, randomized, single-blinded study with a split mouth design was performed at a single center (Periodontics and Oral Medicine Clinic, Faculty of Dentistry, Mahidol University, Thailand) from October 2021 to May 2022. The study was approved by the Ethics Committee of the Faculty of Dentistry and Faculty of Pharmacy Institutional Review Board (MU-DT/PY-IRB) (COA. No.MU-DT/PY-IRB 2021/049.2005). Prior to the trial, all participants provided written informed consent. The clinical parameters were evaluated by a single investigator. The inclusion criteria

comprised being at least 35 years old and American Society of Anesthesiologists; ASA assessment¹⁵ of class ASA I-II diagnosed as a periodontitis patient (AAP 2017), completed active periodontal treatment for more than a year, no more than six months since the last supportive therapy visit, and at least two single-rooted teeth in the split mouth design with a pocket depth of at least 5 mm. The exclusion criteria consisted of a history of systemic disease related to periodontitis (e.g., Diabetes mellitus) and/or required antibiotic treatment while participating in the trial, current smoking, allergy to the tetracycline group (antibiotics including minocycline), antibiotic use within three months prior to enrollment in the trial, pregnancy or lactation. Withdrawal criteria: allergy or had an adverse reaction to minocycline, took antibiotics or anti-inflammatory medicines during the study, pregnant, or decided to stop participating in the study.

Sample size calculation

The sample size was determined based on a power of 95% and alpha level of 5% using a standard deviation of 1.2 mm and precision of 0.8. Each group required a minimum sample size of 18 sites based on Stelzel *et al.* [16]. This was expanded by 20% to account for potential sample loss over the course of the study. Thus, the minimum sample size was 23 sites in each group.

Patient selection, clinical measurement, and treatment

Sampling and sample size allocation: Two therapies were compared in this split mouth study. Test group: Scaling and root planing adjunct with minocycline gel (SRP+ minocycline) and Control group: Scaling and root planing only (SRP). Both treatments were given to all patients. Computer software was used to choose a random course of therapy for each tooth.

Screening: The subjects were recruited from the patients at the Periodontics and oral medicine clinic, Faculty of Dentistry, Mahidol University. An investigator (PI) screened the subjects from the periodontal charts of patients undergoing supportive periodontal therapy. The investigator (PI) examined each patient who met the inclusion criteria before enrolling them in the experiment. The study's objectives were explained to the selected participants, who then provided informed consent. The investigator (PI) allocated the patients' names to codes and gathered patient data before taking an impression to fabricate an occlusal stent and select the sites that met the inclusion criteria.

At day 0, the investigator (PI) recorded the pre-treatment clinical parameters, i.e., Full mouth plaque score (FMPS: O'leary *et al.* (1972)[17]), Modified gingival index (GI: Loe and Silnes (1963) [18]), Full mouth bleeding score (FMBS) and bleeding on probing (BOP) (Ainamo and Bay (1975)[19]), Probing depth (PD) (measured from the gingival margin to the deepest site of the gingival sulcus) and relative attachment level (RAL) (measured from the reference point of the occlusal stent to the deepest site of the periodontal pocket). The investigator (PI) provided the patient with oral hygiene instructions. The participants were given fluoride-containing toothpaste, and using mouthwash was prohibited over the course of the study. The patient received SRP with ultrasonic scalers and periodontal instruments, and full mouth polishing. A co-investigator (YK) used a computer program to randomly assign the treatment regimens at each site that was selected by the investigator (PI). The randomly selected test sites' periodontal pockets were loaded with minocycline gel according to the manufacturer's instructions. **At day 14,** the co-investigator (YK) questioned the patients about atypical symptoms and examined the oral cavity for anomalies,

including hematomas (ecchymosis), abscesses, gingival edema, and discomfort at the injection site. The co-investigator (YK) polished their teeth and applied minocycline gel to the periodontal pockets at the test sites.

At day 30 and day 90, the investigator (PI) recorded the full mouth clinical parameters.

Outcome

The primary outcome measure was relative attachment level gain. The secondary outcomes were reduced probing depth, reduced percentage of plaque score, improved gingival index, and reduced percentage of bleeding on probing sites.

Statistical analysis

SPSS version 28.0 was used to analyze the data (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to identify whether the data's distribution was normal or not. The results are presented as mean (SD) for the FMPS and RAL values and as median (P25, P75) for the FMBS and PD values. The significance of the change in the FMPS and RAL values over time was assessed using repeated measures ANOVA, and the change in the FMBS and PD values over time was assessed

using the Friedman test. For each paired group of RAL, the Paired t-test was performed and for the PD values, the Wilcoxon Signed Rank test was performed. The significance of the change over time and in each paired group for BOP and GI was evaluated using the McNemar test. Significance was defined as $p < 0.05$.

Results

Nineteen subjects were recruited in this split mouth study, resulting in 28 sites in the test group (minocycline gel + SRP) and 28 sites in the control group (SRP only). One patient was lost to follow up at day 90. Thus, 54 sites in 18 patients were analyzed. All patients were non-smokers. Most of the patients were female (63.16%). The average age was 60.68 years old, ranging from 49–79 years old.

Full mouth plaque score (FMPS)

The mean FMPS demonstrated a reduction from $43.19 \pm 20.10\%$ at baseline to $35.85 \pm 14.05\%$ at day 30 ($p > 0.05$) and to 32.32 ± 13.40 at day 90 ($p < 0.05$) (Figure 1).

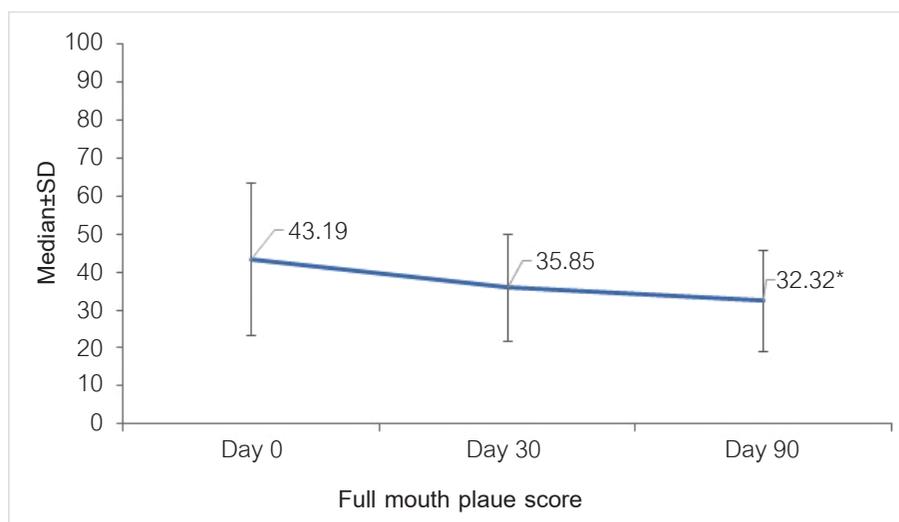


Figure 1 Full mouth plaque scores. * significant differences from baseline ($p < 0.05$)

Full mouth bleeding score (FMBS)

The median FMBS at day 30 and day 90 was significantly reduced from baseline 23.10% to 10.53% ($p < 0.05$) and 13.77% ($p < 0.05$), respectively (Figure 2).

Relative attachment level (RAL)

The mean RAL had a significant gain at day 30 and day 90 compared with baseline in the test group ($p < 0.05$), while the control group had a significant gain at day 30 compared with baseline ($p < 0.05$). However, there was no significant difference in RAL scores between the test group and the control group at any time point (Table 1).

Probing depth

At day 0, the test group and the control group had PD values = 5 mm, which was the most prevalent value (23 sites (82.1%) in the test sites and 24 sites (85.7%) in the control sites). At day 30 and day 90, the number of sites with a PD value = 4 mm was the most prevalent value in the test group (14 sites, 50% and 13 sites, 46.4%, respectively). In contrast, in the control group, PD value = 5 mm was the most prevalent value (16 sites, 57.1% and 15 sites, 53.6%, respectively) (Table 2).

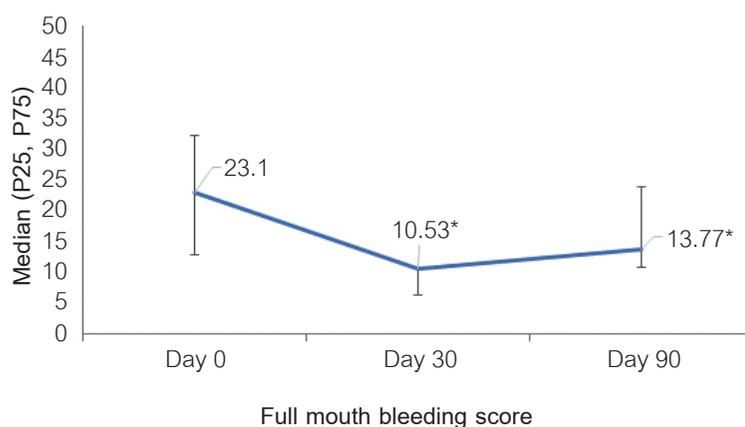


Figure 2 Full mouth bleeding scores. * significant differences from baseline ($*p < 0.05$)

Table 1 Relative attachment level (RAL) at day 0, 30, and 90

	Mean \pm SD			p-value
	Day 0	Day 30	Day 90	
Test	10.30 \pm 2.54	9.89 \pm 2.5 ^{§†}	9.93 \pm 2.57 [†]	< 0.001*
Control	10.00 \pm 2.18	9.78 \pm 2.2 ^{§†}	9.82 \pm 2.24	0.034*
p-value	0.583	0.841	0.839	

[†]significant differences from baseline ($*p < 0.05$)

Table 2 Probing depth (PD) at day 0, 30, and 90

PD	N (%)								
	Day 0			Day 30			Day 90		
	4	5	6	4	5	6	4	5	6
Test	0(0)	23(82.1)	5(17.9)	14(50)	12(42.9)	2(7.1)	13(46.4)	12(42.9)	2(7.1)
Control	0(0)	24(85.7)	4(14.3)	12(42.9)	16(57.1)	0(0)	12(42.9)	15(53.6)	0(0)

The median PD demonstrated a significant reduction in scores at day 30 compared with baseline in the test group ($p < 0.05$), however, the control group demonstrated a significant reduction in scores at day 30 and day 90 ($p < 0.05$) compared with baseline. There was no significant difference in PD between the groups at any time point (Table 3).

Bleeding on probing site (BOP)

There was a significant difference in BOP between day 30 compared with baseline in the test groups and control groups ($p < 0.05$). However, a slight, but not significant, increase in the number

of BOP-positive sites was observed at day 90 in both groups ($p < 0.05$). There was no significant difference in BOP sites between the groups at any time point (Table 4).

Gingival index site (GI)

At day 0, the test and the control groups had GI scores = 2, which was the most prevalent value (14 sites (50.0%) in the test sites and 19 (67.86%) control sites). At day 30 and day 90, GI=1 was the most prevalent value in both groups. There was no significant difference in GI between the groups at any time point ($p < 0.05$) (Table 5).

Table 3 Median of probing depth (PD) at day 0, 30, and 90

Median (P25, P75)				
	Day 0	Day 30	Day 90	p-value
Test	5(5, 5)	4.5(4, 5) [¶]	5(4, 5)	0.003*
Control	5(5, 5)	5(4, 5) [¶]	5(4, 5) [¶]	0.003*
p-value	0.317	1.000	0.796	

[¶]significant differences from baseline ($*p < 0.05$)

Table 4 Bleeding on probing site (BOP) at day 0, 30, and 90

N (%)				
	Day0	Day30	Day90	p-value
Test	14 (50.00)	6 (21.43) [¶]	10 (37.04)	< 0.05*
Control	18 (66.67)	10 (35.71) [¶]	10 (37.04)	< 0.05*
p-value	0.388	0.388	1.000	

[¶]significant differences from baseline ($*p < 0.05$)

Table 5 Gingival index site (GI) at day 0, 30, and 90

N (%)										
		Day 0			Day 30			Day 90		
GI		0	1	2	0	1	2	0	1	2
Test		2(7.14)	12(42.86)	14(50.0)	7(22.22)	15(55.55)	6(22.22)	4(14.82)	13(48.15)	10(37.0)
Control		0(0.0)	9(32.14)	19(67.86)	6(21.43)	12(42.86)	10(35.71)	6(22.22)	11(40.74)	10(37.0)
p-value		N/A			0.584			0.761		

Discussion

The results of this study revealed that the clinical parameters in the test and control groups improved by day 30 (16 days after the last visit that minocycline gel was applied) and slightly dropped by day 90. However, they did not return to baseline, with the exception of FMPS, which demonstrated improvement over time and significant differences from baseline at day 90 ($p < 0.05$). Similar results have been found in other studies using minocycline as an adjunct to SRP in supportive periodontal therapy. Kinane and Radvar [20] observed significant improvements in PD, CAL gain, and BOP reduction in the SRP + minocycline and SRP alone groups after 6 weeks and 3 months compared with baseline. Furthermore, the modified gingival index scores considerably improved in both groups. However, there was no significant difference between the groups. A long-term study [21] found that after 1 year (2 periods of SPT) in ≥ 5 mm posterior interproximal pockets, there were no differences between the groups at any time point (6 months and 12 months), and all clinical parameters (PD, CAL, BOP) significantly improved from baseline in both groups.

Our study demonstrates that although FMPS decreased over time, the improvement in clinical parameters in both groups declined by day 90. This might be because deep pockets demonstrate bacterial recolonization of subgingival plaque after subgingival debridement. The period required for recolonization to rebound to the mean pretreatment counts and proportions of the subgingival microflora varies based on the severity of the disease and the depth of the debridement. Several oral reservoirs, e.g., the epithelium and lamina propria of the pocket wall and epithelium of the buccal mucosa,

dorsum of the tongue, tonsillar crypts, and saliva, can contribute to the repopulation of treated periodontal pockets by microbial pathogens in addition to insufficient removal of calculus and biofilm [22]. In contrast, supragingival plaque control demonstrated a slight effect on subgingival bacteria, indicating that this effect was restricted to 3 mm subgingivally [23].

The effects of SRP and minocycline during initial periodontal therapy have been investigated in numerous trials. Goodson *et al.* [24] reported that at day 30, a 1.2 mm gain of clinical attachment was observed in the SRP adjunct with minocycline group compared with 0.8 mm in the SRP alone group after 1 month. Similarly, Williams *et al.* [25] reported a 1.32 mm reduction in moderate to severe PD in the SRP adjunct with minocycline sites, whereas the SRP alone sites showed a 1.08 mm PD reduction after 9 months. The difference reached statistical significance after the first month and was maintained throughout the trial (9 months). These results revealed that following the initial treatment, the pocket frequently markedly decreases as the inflammation declines. Therefore, in this study, less improvement may have occurred with SRP if some of these factors have already been diminished by the initial therapy [26]. Furthermore, it has been demonstrated that in the first year of treatment for moderate pockets, PD reduces by ~ 1 mm [27-29], indicating that good root planing can reduce pocket depth without the use of other treatments. The PD improvement in both groups may be further evidence of the effectiveness of root planing, particularly in single-rooted teeth [20,21]. The impact of the additional antibiotic application may have been reduced because the mechanical debridement may have been very effective and obscured the effects of the antibiotic [30]. Moreover, gingival plaque control resolves marginal inflammation and consequent pocket

reduction in 4–5 mm pockets [23,31]. In our study, the single-root teeth pockets were typically 5 mm deep at baseline in both groups. The marginal inflammation reduction in these teeth may have resulted in the lack of significant differences in clinical parameters between groups.

Based on the results of this study, we advise further investigation using a larger sample size with deeper pockets that may reveal the relevant use of minocycline and a statistically meaningful improvement in these sites. Additionally, investigating the bacterial population *in vitro* to validate the potential benefits of minocycline gel in combination with SRP on single-rooted teeth is also recommended. Furthermore, investigating higher concentrations of minocycline gel and other local drug delivery methods (such as fibers, or chips) may have a greater effect on the bacterial load and clinical parameters.

There was no information on drug allergies or side effects in this analysis. However, this study has some limitations, including a small participant pool and moderate periodontal pocket depths in the study population.

Conclusion

Based on the finding of this study, it can be concluded that the local adjunctive use of 2% minocycline gel with SRP did not demonstrate a significant difference in clinical parameters compared with SRP alone in periodontitis patients in single rooted-teeth over a three-month interval.

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