# Adjunctive use of local minocycline in comparison to instrumentation alone in patients under supportive periodontal therapy: a randomized controlled clinical trial

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**Abstract**

**Aim:** To examine the clinical effects of subgingival instrumentation with the application of a 2% minocycline hydrochloride controlled-delivery system in residual deep pockets of supportive periodontal therapy (SPT) patients.

**Materials and Methods:** Patients undergoing SPT were recruited in this randomized, double-blinded controlled trial. Clinical data were collected by blinded periodontists at baseline, 3, 6, 9, and 12 months. All patients were treated with mechanical debridement. Intervention group patients received the application of the 2% minocycline gel by a different operator in sites with probing pocket depths (PPD) of 5 mm or deeper, and in teeth adjacent to the intervention sites. Control group patients received a placebo gel. The gels were re-applied on Day 4 and 3, 6 and 9 months.

**Results:** 68 patients were randomized, of which 64 (33 intervention, 31 control) were analyzed. The intervention group demonstrated a greater reduction in mean probing depths, the mean number of sites with residual PPD ≥ 5mm and the mean number of sites with baseline PPD ≥ 5mm and PPD reduction of ≥ 2mm at 9 and 12 months.

**Conclusion:** Adjunctive minocycline gel application at 3-monthly intervals was effective in reducing mean probing depths and stability in residual deep pockets of patients undergoing SPT.

*Keywords: Local minocycline. Residual pockets. Supportive periodontal therapy. Double-blinded randomized controlled clinical trial.*

## Introduction

Regular maintenance of patients with treated periodontal disease is the key consideration in the long-term periodontal prognosis of their dentition. Periodic prophylaxis may prevent loss of clinical attachment over long periods of time even in patients with less than optimal plaque control (Ramfjord, 1987). However, there are limitations in routine subgingival re-instrumentation especially in bleeding pockets, as only 50% of these sites show improvement (Tonetti *et al*., 1998). Furthermore, the persistence of bleeding and residual pockets increase the risk of disease progression and tooth loss (Matuliene *et al*., 2008; Matuliene *et al*., 2010). Thus, there is a need for adjuncts that may improve the outcome especially in patients with recurrent periodontitis during supportive periodontal therapy (SPT). Some studies reported significantly

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better results with subgingival administration of local minocycline in residual pockets post initial periodontal therapy over a short period of time (Lu *et al*., 2005; Miyazawa *et al*., 2020). There are only few studies assessing the efficacy and long-term effect of topical minocycline application in patients with residual pockets while on SPT (McColl *et al*., 2006; Killeen *et al*., 2016; Killeen *et al*., 2018; Chackartchi *et al*., 2019).

The present study examined the significance of the adjunctive effect of the subgingival application of a 2% minocycline hydrochloride controlled-delivery system (MHS) in comparison to subgingival instrumentation with the application of a placebo gel, in patients with residual pockets during SPT. The hypothesis of this trial was that there would be a difference in the mean change in probing pocket depth (PPD) from baseline to 3, 6, 9 and 12 months with the adjunctive administration of a 2% MHS (intervention) together with subgingival instrumentation when compared to subgingival instrumentation with placebo gel (control), in patients with recurrent and/or persistent probing depths, receiving SPT.

## Materials and Methods

The study protocol was submitted for approval to the SingHealth Centralized Institutional Review Board in Singapore (CIRB Ref No. 2015/2815). The study was a randomized double-blinded placebo-controlled clinical trial in parallel groups.

### *Subject population*

The study population included patients who had previously been diagnosed with periodontitis and received at least a full cycle of periodontal therapy consisting of oral hygiene instructions, scaling and root planing in the National Dental Centre Singapore, Singapore. Informed consent was obtained from all patients entered in the study, before the baseline visit.

### *Inclusion criteria*

1) Medically healthy adults (ASA classification I-II) (Anesthesiologists, 2020), at least 21 years of age.
2) Previously diagnosed with moderate to severe periodontitis (Armitage, 1999) and had completed at least 1 cycle of periodontal therapy including oral hygiene instructions and scaling and root planing,.
3) Treated periodontitis patients in maintenance care.
4) Ability to comply with the 12-month study follow-up.
5) No history of surgical periodontal treatment in the area with lesions or previous systemic antibiotic therapy during initial periodontal therapy.
6) At least 4 teeth present with residual PPD of ≥ 5 mm on each (Matuliene *et al*., 2008) and positive bleeding on probing (BOP) (Lang *et al*., 1986).

### *Exclusion criteria*

1) Medically compromised patients (ASA classification III-V) (Anesthesiologists, 2020).
2) Known allergy or other severe adverse reactions to minocycline and related drugs.
3) Patients who reported local and/or systemic antibiotic therapy within 3 months prior to baseline examination of the study, and were placed on antibiotics during active initial periodontal therapy.
4) Patients with a plaque control record of > 30%.

### *Clinical examination*

At baseline (Day 0), full mouth bleeding scores, plaque scores, probing depths and attachment levels were recorded. The full mouth bleeding scores, probing depths and attachment levels were also collected at 3, 6, 9 and 12 months. Probing pocket depth (PPD) and attachment levels (PAL) were measured to the nearest millimetre with a UNC-15 probe (Hu-friedy®) with 1 mm incremental markings.

Bleeding on probing (BOP) was assessed dichotomously with a UNC-15 probe (Hu-friedy®). Full mouth bleeding and plaque scores were calculated. The examiners (WCT, MO, CGK) were specialist periodontists who performed clinical examinations at baseline and at the recalls (3, 6, 9 and 12 months). Inter-examiner calibration was performed. 6 patients with presence of Ramfjord teeth (#16, 11, 24, 36, 31, 44) as being representative of the dentition and teeth contralateral to the Ramfjord teeth (#14, 21, 26, 34, 41, 46) were selected for the calibration exercise. Inter-rater agreement was high (intraclass correlation coefficient = 0.84, p-value < 0.001).

### *Procedure*

At baseline (Day 0), all patients were treated by designated oral health therapists with supragingival debridement as required and subgingival ultrasonic/ hand instrumentation (without using antimicrobial agents such as irrigating solutions) at all sites with PPD of ≥ 5 mm. All the dentition were polished to complete the SPT appointment. After completion of the ultrasonic/ hand instrumentation, the assigned randomization envelope was opened by the research co-ordinator and intervention patients received application of the test agent in all sites with PPD of ≥ 5 mm, and in the adjacent teeth next to the test sites, while the control patients received a placebo gel. Patients (both intervention and control groups) were instructed to avoid food or drinks for the next 2 hours and to avoid any form of interdental cleaning for the first 12 hours following treatment. Routine oral hygiene procedures were resumed after 12 hours. On day 4, another application of gel was administered for each respective group.

Patients were recalled at 3, 6, 9 and 12 months after the baseline visit. At 3, 6, and 9 months, clinical re-examination, as well as mechanical instrumentation and gel application were administered for each respective group.

### *Trial product*

The test product was a highly viscous gel composed of an ointment containing micro-capsule particles for sustained release and the active ingredient: 2% minocycline gel (10mg in each syringe of 0.5g) (Periocline, SUNSTAR, Osaka, Japan). The other ingredients include magnesium chloride, hydroxyl-ethylcellulose, aminoalkylmethacrylaye copolymer, triacetin and concentrated glycerine, giving the preparation a sustained-released property. This gel, meant for local subgingival placement, was applied into the pockets of experimental teeth and the adjacent teeth by gently inserting the tip of a specially designed applicator until the paste flowed over the gingival margin. The placebo gel was manufactured by SUNSTAR (Osaka, Japan) and had the same ingredients as the test gel without the active ingredient of minocycline hydrochloride.

### *Rationale for selection of dose*

Minocycline hydrochloride concentrations in the pockets have been shown to decrease rapidly for the first 7 hours after administration. The subsequent decrease was very slow, with the concentration at 72 hours being 3.4μg/ml. At 100 hours, the concentration of minocycline was still effective against Prophyromonas gingivalis, Prevotella intermedia, and Eikenella corrodens. At 168 hours, the concentration was reduced to 0.1μg/ml (Satomi *et al*. 1987). Thus, in this study, a second application was timed for Day 4 before the concentration was reduced to 0.1μg/ml (Figure 1).

### *Primary objective*

To compare the mean change in PPD (mm) at 3, 6, 9 and 12 months from baseline between intervention and control groups.

### *Secondary objectives*

To compare the following endpoints at 3, 6, 9 and 12 months from baseline between intervention and control groups:

» Change in mean number of sites with PPD ≥ 5 mm.
» Change in mean number of sites with PPD ≥ 5 mm and BOP.
» Change in mean full mouth BOP (%).
» Change in mean probing attachment level (PAL) (mm).

### *Exploratory objectives*

To compare the following endpoints at 3, 6, 9 and 12 months from baseline between intervention and control groups:

» Mean number of sites with baseline PPD ≥ 5 mm and PPD reduction ≥ 2 mm from baseline.
» Mean number of sites with baseline PAL ≥ 5 mm and PAL reduction of ≥ 2 mm from baseline.

### *Randomization and blinding*

Patients were randomized into intervention and control groups in 1:1 allocation based on a randomization list after receiving their consent for the study. The list was generated using a computer program by an independent statistician. It used the stratified block-randomization technique with smoking status as the stratification factor. The examiners were blinded to the randomization and block size. Based on the allocation from the randomization list, an unmarked envelope with the test

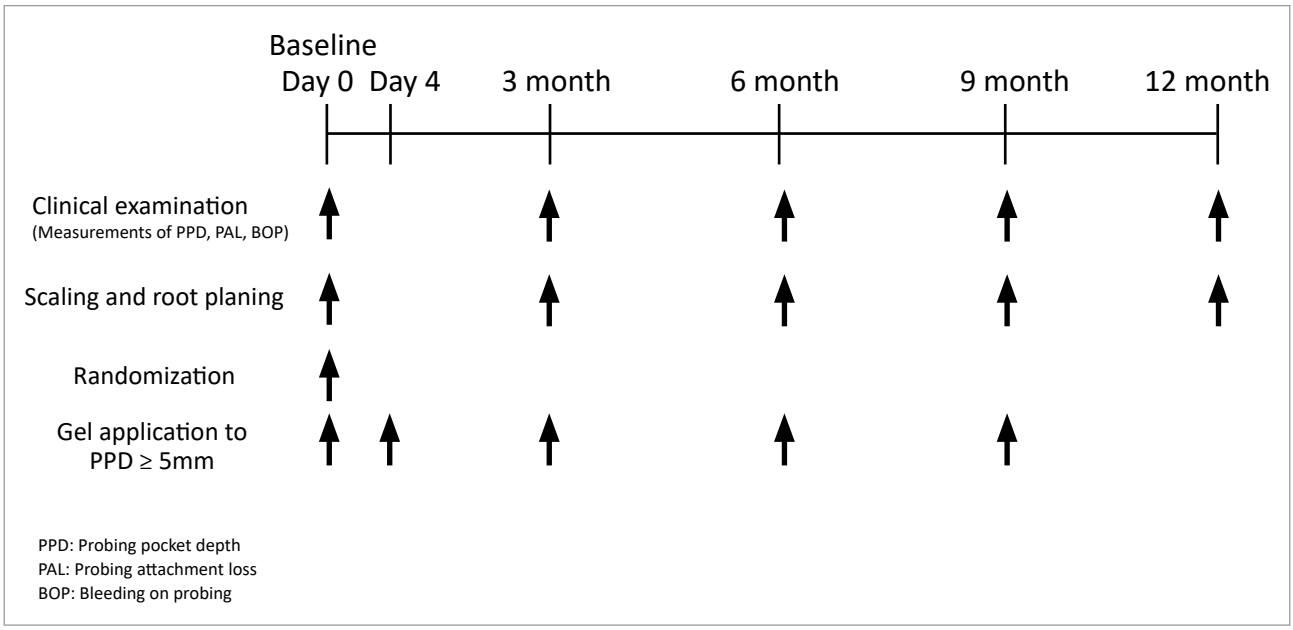


***Figure 1. Sequence of events.***

or control gel was given to the designated oral health therapist. The instrumentation of the tooth sites with PPD of ≥ 5 mm and gel application were administered by the designated oral health therapist, who was not involved as an examiner. Blinding was only broken at the conclusion of data collection for the study.

### *Sample size*

The sample size was estimated to detect a pre-specified difference in mean change in PPD at post-baseline time-points between intervention and control groups. A standardized mean difference (effect size) of 0.5 was considered clinically important. It is considered a moderate effect size. To detect this difference, the required sample size was estimated to be 58 patients (29 per group) to achieve 85% power at 20% one-sided type I error using the two-sample t-test. Allowing a 10% potential drop-out, the study was planned to recruit 66 patients (33 per group). This study design is referred to as Screening Design for phase II clinical trials for identifying potentially effective intervention for further testing in a confirmatory trial. Considering the exploratory nature of the study, no correction was applied for multiple hypothesis testing. Although measurements were obtained for multiple teeth per patient, all the analysis were performed at patient-level summary of the measurements. Hence, clustering effect was not expected.

### *Statistical methods*

Mean changes in PPD at post-baseline time-points were compared between the intervention and control groups using a separate linear regression model for each post-baseline time-point with an intercept and intervention group as independent variables. The models were adjusted for baseline PPD value to account for potential imbalance in baseline values between the two groups as well as to improve precision in estimating the intervention effect. The coefficient of intervention group along with its 95% confidence interval (CI) was presented as the mean difference between the intervention and control groups. The effect size was calculated as the beta coefficient divided by the standard deviation of baseline PPD values. Change in the number of tooth sites with PPD ≥ 5 mm, change in the number of tooth sites with BOP & PPD ≥ 5 mm, change in full mouth BOP and probing attachment level PAL at post-baseline values were compared between intervention and control groups similar to PPD. The mean number of tooth sites with a reduction in probing depth ≥ 2 mm at post-baseline time-points for sites with baseline measurements PPD ≥ 5 mm was compared between the two groups at each time-point using the two-sample t-test. A similar analysis was performed for the mean number of tooth sites with baseline measurements PPD ≥ 5 mm with a reduction in probing attachment ≥ 2 mm at post-baseline time-points. All the analyses were performed on the intention-to-treat population, including all randomized patients who provided at least one post-baseline visit data.

## Results

Sixty-eight patients were recruited and randomized from June 2016 to October 2018, 63 (33 intervention, 30 control) completed the study, which ended in October 2019 (Figure 2). The trial concluded after the sample size was reached. The majority of the patients were Chinese. The intervention group had more females and Chinese (Table 1). Three patients from the control group were excluded from analysis as they had dropped out of the study after baseline and no post-baseline data were contributed. At baseline, both groups presented with similar PPD, number of sites with PPD ≥ 5 mm, number of sites with PPD ≥ 5 mm and positive BOP, full mouth BOP scores, PAL, plaque scores and number of smokers.

Both groups demonstrated a decreasing mean PPD over time. A significantly greater reduction in mean PPD was observed in the intervention group at 9 months (mean difference [d] = -0.36; 95% CI -0.53 to -0.20; effect size = -1.06) and 12 months (d = -0.37; 95% CI -0.54 to -0.19, effect size = -1.07) compared to the control group. Similar to PPD, the intervention group showed a greater reduction in the number of sites with PPD ≥ 5 mm at 9 months (d = -5.50; 95% CI -7.74 to -3.25; effect size = -0.70) and 12 months (d = -5.36; 95% CI -7.08 to -3.64; effect size = -0.69) compared to the control group. No meaningful differences between the groups were noted at 3 and 6 months for mean PPD and number of sites with PPD ≥ 5 mm (|effect size| <0.5) (Table 2).

Both groups showed comparable reduction in the number of sites with PPD ≥ 5 mm and positive BOP, full mouth BOP scores and PAL at all time points, with no meaningful differences between groups (|effect size| <0.5) (Table 2).

Consistent with the PPD outcomes, there was an increase in the number of sites with PPD reduction ≥ 2 mm from baseline at post-baseline time-points among deep sites (baseline PPD ≥ 5 mm) in the intervention group compared to the control group, with a significant increase at 9 month (d = 3.21; 95% CI 1.22 to 5.20) and 12 months (d = 3.24; 95% CI 0.99 to 5.50). Similarly, the intervention group demonstrated higher numbers of sites with PAL reduction of ≥ 2 mm from baseline across all post-baseline time-points among deep sites when compared to the control group, with a significant increase at 9 months (d = 3.28; 95% CI 0.41 to 6.15) (Table 3).

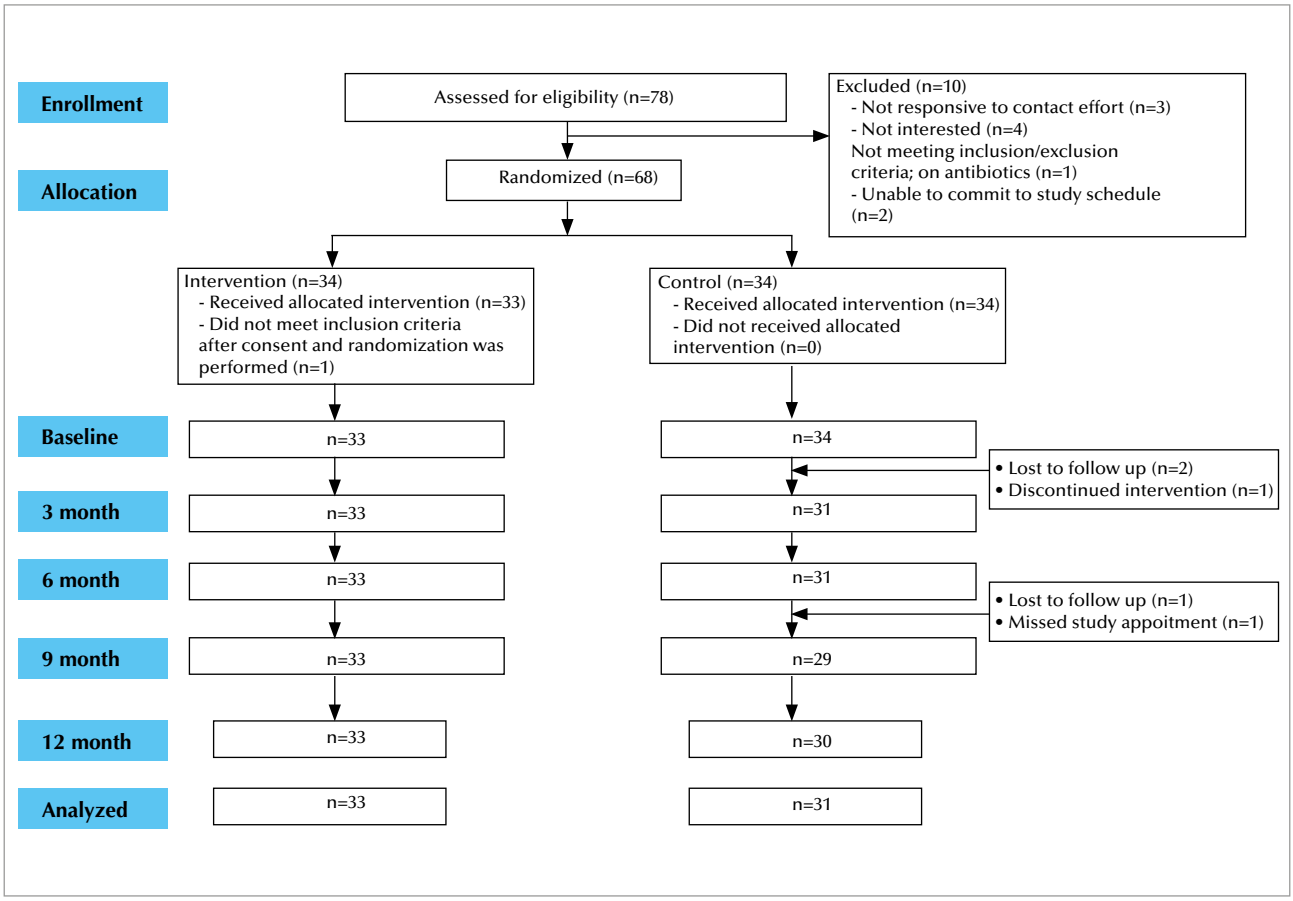


***Figure 2. CONSORT diagram showing the flow of participants through each stage of the trial.***

**Table 1.** Baseline characteristics of the patients.

| Characteristics | Intervention (n = 33) | Control (n = 31) |
|---|---|---|
| Age in years, Mean (SD) | 55.8 (7.7) | 57.8 (9.3) |
| Female, n (%) | 15 (45.5) | 11 (35.5) |
| Ethnicity, n (%) | | |
| Chinese | 30 (90.9) | 25 (80.7) |
| Others | 3 (9.1) | 6 (19.4) |
| Smoking status, n (%) | | |
| Non-smoker | 25 (75.8) | 25 (80.7) |
| Past smoker | 5 (15.2) | 2 (06.5) |
| Current smoker | 3 (9.1) | 4 (12.9) |
| PPD (mm), Mean (SD) | 3.89 (0.35) | 3.84 (0.34) |
| Number of sites with PPD ≥5 mm, Mean (SD) | 16.20 (6.57) | 15.80 (9.23) |
| Number of sites with BOP & PPD ≥5 mm, Mean (SD) | 12.50 (5.84) | 11.30 (5.36) |
| Full mouth BOP (%), Mean (SD) | 31.10 (14.20) | 30.50 (14.60) |
| PAL (mm), Mean (SD) | 4.77 (0.80) | 4.74 (0.73) |
| Full mouth Plaque scores (%), Mean (SD) | 21.4 (15.0) | 20.7 (15.2) |

PPD = Probing pocket depth. BOP = Bleeding on probing. PAL = Probing attachment level.

**Table 2.** Mean change from baseline in the primary and secondary outcomes. Mean values were estimated from a linear regression model adjusted for baseline value of the outcome.

| | Intervention | | Control | | Difference (95% Confidence interval) | Effect size |
|---|---|---|---|---|---|---|
| | n | Mean (SE) | n | Mean (SE) | | |
| **Change in PPD (mm)** | | | | | | |
| At month 3 | 33 | -0.48 (0.05) | 31 | -0.35 (0.05) | -0.13 (-0.28, 0.02) | -0.37 |
| At month 6 | 33 | -0.56 (0.06) | 31 | -0.43 (0.06) | -0.13 (-0.30, 0.03) | -0.39 |
| At month 9 | 33 | -0.67 (0.06) | 29 | -0.31 (0.06) | -0.36 (-0.53, -0.20)*** | -1.06 |
| At month 12 | 33 | -0.72 (0.06) | 30 | -0.36 (0.06) | -0.37 (-0.54, -0.19)*** | -1.07 |
| **Change in number of sites with PPD ≥5 mm** | | | | | | |
| At month 3 | 33 | -6.99 (0.74) | 31 | -4.02 (0.76) | -2.97 (-5.08, -0.86)** | -0.38 |
| At month 6 | 33 | -7.77 (0.85) | 31 | -4.50 (0.88) | -3.27 (-5.72, -0.82)* | -0.42 |
| At month 9 | 33 | -9.67 (0.77) | 29 | -4.17 (0.82) | -5.50 (-7.74, -3.25)*** | -0.7 |
| At month 12 | 33 | -10.87 (0.59) | 30 | -5.51 (0.62) | -5.36 (-7.08, -3.64)*** | -0.69 |
| **Change in number of sites with BOP & PPD ≥5 mm** | | | | | | |
| At month 3 | 33 | -6.10 (0.65) | 31 | -4.02 (0.67) | -2.07 (-3.94, -0.20)* | -0.24 |
| At month 6 | 33 | -6.76 (0.82) | 31 | -4.84 (0.84) | -1.92 (-4.26, 0.43) | -0.23 |
| At month 9 | 33 | -8.00 (0.67) | 29 | -4.24 (0.71) | -3.77 (-5.74, -1.80)*** | -0.44 |
| At month 12 | 33 | -8.47 (0.55) | 30 | -5.38 (0.57) | -3.09 (-4.68, -1.50)*** | -0.36 |
| **Change in full mouth BOP (%)** | | | | | | |
| At month 3 | 33 | -3.84 (1.89) | 31 | -5.87 (1.95) | 2.03 (-3.39, 7.46) | 0.14 |
| At month 6 | 33 | -4.57 (2.06) | 31 | -9.38 (2.12) | 4.81 (-1.10, 10.72) | 0.34 |
| At month 9 | 33 | -7.06 (1.72) | 29 | -7.82 (1.84) | 0.76 (-4.29, 5.80) | 0.05 |
| At month 12 | 33 | -10.71 (1.52) | 30 | -7.87 (1.60) | -2.84 (-7.26, 1.58) | -0.2 |
| **Change in PAL (mm)** | | | | | | |
| At month 3 | 33 | -0.37 (0.10) | 31 | -0.44 (0.10) | 0.07 (-0.20, 0.34) | 0.1 |
| At month 6 | 33 | -0.44 (0.10) | 31 | -0.50 (0.10) | 0.07 (-0.21, 0.34) | 0.09 |
| At month 9 | 33 | -0.58 (0.10) | 29 | -0.33 (0.10) | -0.25 (-0.54, 0.03) | -0.33 |
| At month 12 | 33 | -0.66 (0.10) | 30 | -0.40 (0.11) | -0.26 (-0.56, 0.04) | -0.34 |

* p<0.05; ** p<0.01; *** p< 0.001. PPD: Probing pocket depth. BOP: Bleeding on probing. PAL: Probing attachment level. SE: Standard error.

**Table 3.** Mean number of sites with reduction ≥2 mm from baseline for sites with baseline measurements ≥5 mm (exploratory outcomes).

| | Intervention | | Control | | Difference (95% Confidence interval) |
|---|---|---|---|---|---|
| | n | Mean (SE) | n | Mean (SE) | |
| **Number of sites with reduction in PPD ≥2 mm** | | | | | |
| At month 3 | 33 | 5.91 (0.63) | 31 | 4.80 (0.53) | 1.10 (-0.55, 2.76) |
| At month 6 | 33 | 7.33 (0.82) | 31 | 5.68 (0.67) | 1.66 (-0.47, 3.79) |
| At month 9 | 33 | 8.21 (0.76) | 29 | 5.00 (0.62) | 3.21 (1.22, 5.20)** |
| At month 12 | 33 | 8.58 (0.80) | 30 | 5.33 (0.79) | 3.24 (0.99, 5.50)** |
| **Number of sites with reduction in PAL ≥2 mm** | | | | | |
| At month 3 | 33 | 7.82 (0.95) | 31 | 6.77 (0.74) | 1.04 (-1.38, 3.47) |
| At month 6 | 33 | 8.82 (1.03) | 31 | 8.10 (0.90) | 0.72 (-2.03, 3.47) |
| At month 9 | 33 | 10.24 (1.06) | 29 | 6.97 (0.95) | 3.28 (0.41, 6.15)* |
| At month 12 | 33 | 10.36 (1.01) | 30 | 7.67 (1.14) | 2.70 (-0.35, 5.74) |

* p<0.05; ** p<0.01; *** p< 0.001. PPD: Probing pocket depth. PAL: Probing attachment level. SE: Standard error.

## Discussion

In the present study, the periodontal conditions of patients with residual deep sites who received minocycline gel application during supportive periodontal treatment achieved a clinically significant increased reduction in the mean probing depths and number of sites with residual PPD ≥ 5 mm at 9 and 12 months. They also achieved more sites with baseline PPD ≥ 5 mm and PPD reduction of ≥ 2 mm at 9 and 12 months.

The clinical results of the present study are in agreement with those of van Steenberghe *et al*. (van Steenberghe *et al*., 1999). In the double blind parallel comparative study, 104 patients with moderate to severe periodontitis were randomized to receive either the 2% minocycline gel or a placebo gel at various treatment timepoints. Standard clinical measures and microbial sampling were collected up till 15 months. The results showed a significant gain in clinical attachment and mean probing depth reduction in the intervention group. The subjects in the study were however recruited at initial periodontal therapy.

Recent studies in patients on SPT failed to show additional benefit of adjunctive local minocycline delivery (McColl *et al*., 2006; Killeen *et al*., 2016; Killeen *et al*., 2018). One major difference, which is also the strength of the present study is the use of a placebo gel, which was absent in those studies . This minimized the possibility of the Hawthorne effect. Furthermore, in one study (McColl *et al*., 2006), the minocycline group did not receive mechanical root debridement in addition to the application of the minocycline gel. This might have led to an inadequate disruption of the subgingival biofilm, resulting in limited efficacy of the minocycline gel (Loesche, 1999). On the other hand, Killeen and co-workers (Killeen *et al*., 2016; Killeen *et al*., 2018) used 6 monthly recall intervals instead of 3 monthly intervals used in this current study. Shorter recall intervals have been shown to overcome the effects of poor oral hygiene in reducing bacterial recolonization of previously treated pockets (Ramfjord, 1987).

The ability of minocycline to maintain periodontal stability through the reduction of teeth and sites with residual deep probing depths and positive BOP can be attributed to the bacteriostatic properties of minocycline, which is effective against periodontal pathogens, such as Prevotella intermedia and *Aggregatibacter actinomyctemecomitans* (Hagiwara *et al*., 1998) and red complex bacteria such as Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola (Goodson *et al*., 2007). Lower levels of these pathogens were associated with significant clinical improvements (Haffajee *et al*., 2006).

Alternatives to locally delivered antibiotics include systemic antibiotics, systemic and local antiseptics and access flap procedures. However, the use of systemic antiobiotics has the risk of adverse side effects, such as gastrointestinal problems, and the risk of developing antimicrobial resistance.

The use of adjunctive locally delivered antibiotics in the treatment of deeper pockets (≥ 5 mm) had been favoured over other alternatives, particularly when there are relatively few residual pockets, such as non responding sites or disease recurrence during SPT. Their usage has been proven effective (Tonetti *et al*., 2012; Chackartchi *et al*., 2019). A potential application is when patients are not keen on surgical intervention, or there are medical contraindications to surgeries, such as bleeding disorders. Another application is the presence of residual pockets in the esthetic zone and surgical intervention may potentiate further recession and compromise the esthetics of the area.

Although the full mouth plaque scores were not measured at subsequent visits after the baseline, comparable reduction of full mouth BOP scores for both intervention and control groups was observed, indicating similar levels of oral hygiene amongst both groups. This demonstrates the additional benefits of adjunctive minocycline gel application in improving clinical outcomes in SPT, even in patients with similar levels of oral hygiene.

Most of the differences in the clinical improvements between the intervention and control groups were observed at the 9 and 12 month visits. This suggests a need for sustained clinical applications of the minocycline gel for 6 months or more to produce significant benefits. Studies investigating the use of locally delivered adjuncts may consider a longer follow up period of beyond 12 months to observe the longer term clinical benefits of the adjuncts.

Due to the relatively small sample size, the results obtained from this study could possibly be significant due to a potentially inflated type-I statistical error. These results should be further confirmed in a study with a larger sample size. Within the limitations of the study, the subgingival application of 2% minocycline gel in residual deep pockets of patients undergoing SPT can be a viable alternative to surgical treatment and other adjuncts. In addition, this study may be replicated in other patient populations, such as smokers and diabetics, to understand if these benefits can be applicable to them.

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### *Conflict of Interest and Sources of Funding*

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