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Local minocycline as an adjunct to surgical therapy in moderate to severe, chronic periodontitis

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Abstract

Objective: The aim of the study was to evaluate the effects of minocycline microspheres on periodontal probing depth reduction when used in combination with surgery in adults with moderate to severe, chronic periodontitis.

Material and Methods: Sixty patients with a minimum of one non-molar periodontal site $\geqslant 6$ mm in two oral quadrants received either local minocycline microspheres at baseline, immediately following each of two surgical therapies (Weeks 2 and 3), and at Week 5 or surgery alone.

Results: The mean probing depth reduction at Week 25 at sites $\geqslant 5$ mm at baseline was 2.51 mm in the test group and 2.18 mm in the control group. Smokers in the test group had a significantly greater probing depth reduction (2.30 mm) than smokers in the control group (2.05 mm). The number of sites with probing depth reductions of $\geqslant 2$ and $\geqslant 3$ mm were significantly higher in the test group than in the control group.

Conclusion: Applications of local minocycline as an adjunct to surgery in adults with moderate to severe, chronic periodontitis were associated with statistically significant greater reductions in probing depth than surgery alone.

Key words: microspheres; minocycline; moderate; probing depth; severe periodontitis; smoking; surgical therapy

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Periodontal disease is characterized by formation of periodontal pockets, loss of periodontal support and resorption of alveolar bone (Williams 1990, Kinane & Lindhe 2003).

It is well documented that periodontitis is a multifactorial disease. Several risk and susceptibility factors have been proposed to explain the onset and progression of the disease (Page et al. 1997). However, most periodontal researchers agree that oral microorganisms are the primary aetiologic agents causing the destruction of the supporting periodontal tissues (Walker et al. 2004, Haffajee & Socransky 2005, Socransky & Haffajee 2005).

Periodontal therapy including either surgical and/or non-surgical methods usually results in improvements in periodontal health if good plaque control is obtained (Lindhe & Nyman 1975, Rosling et al. 1976, Nyman et al. 1977, Axelsson & Lindhe 1981, Lindhe et al. 1984, Westfelt et al. 1985, Rosling et al. 2001, Axelsson et al. 2004). Several clinical studies have shown that surgical procedures resulted in improved clinical outcomes for deep periodontal pockets. Heitz-Mayfield et al. (2002), in a meta-analysis of six randomized-controlled trials, demonstrated that surgical techniques resulted in a significantly greater reduction in pocket depths and greater clinical attachment gain for pockets exceeding 6 mm than in corresponding pockets treated with scaling and root planing (SRP) alone.

Use of antibiotics for the treatment of periodontal disease is an area of great research interest. Antibiotic therapy administered systemically or locally, either as a single therapy or in combination with non-surgical periodontal treatment, has been investigated (Listgarten et al. 1978, Lindhe et al. 1983, Berglund et al. 1998, Garrett et al. 1999, van Steenberghe et al. 1999, Ramberg et al. 2001, Wennström et al. 2001, Williams et al. 2001, Aimette et al. 2004). Several studies have reported

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that systemically or locally delivered antibiotics enhance the effect of subgingival scaling (Haffajee et al. 2003).

Minocycline is an antimicrobial tetracycline derivative which is active against a broad spectrum of Gram-negative and Gram-positive anaerobes including pathogens associated with adult periodontitis (Drisko 1996). Delivery of Arestin® (21-day, controlled, non-systemic release, bioresorbable polymer formulation of microspheres containing minocycline HCl), subgingivally administered, provides bactericidal action against anaerobes and facultative anaerobes residing in the periodontal pocket (Greenstein & Polson 1998). Williams et al. (2001) studied the adjunctive effect of Arestin® in a controlled multicentre trial including patients with moderate to severe periodontitis. Arestin®, along with SRP, demonstrated greater probing depth (PD) reduction (0.3 mm) when compared with Arestin® alone or SRP alone. Furthermore, Meinberg et al. (2002) and van Dyke et al. (2002) reported added beneficial effects of Arestin®, when used as a single treatment or in combination with non-surgical periodontal therapy (scaling). In a 12-month maintenance study (McColl et al. 2006), no clinical differences were observed in pockets $\geqslant$5 mm with residual bleeding on probing (BoP) between subgingivally administrated minocycline gel (2%) as mono-therapy and conventional non-surgical therapy. To date, the effect of locally delivered minocycline on periodontal healing in combination with periodontal surgery has not been evaluated.

The aim of the present clinical trial was to study the effect of local administration of minocycline HCl microspheres, 1 mg (Arestin®), on periodontal healing after modified Widman flap (MWF) surgical periodontal therapy. The effects of Arestin® as an adjunct in patients treated with SRP will be reported in a separate paper.

Material and Methods

Patient selection

Adults between the ages of 25 and 80 years and in good general health were screened at two study centres: Specialist Clinic in Uddevalla, Sweden (Centre A), and a private practice in Aurora, CO, USA (Centre B). The study was undertaken with the understanding and written consent of each patient. The study was reviewed and approved by the Regional Ethical Review Board at the University of Göteborg, Sweden, or the Western Institutional Review Board in Olympia, Washington, USA, and was conducted under current Good Clinical Practice Guidelines in full compliance with the World Medical Association Declaration of Helsinki.

Inclusion criteria

To be included in the study, the patients had to have at least 12 non-molar teeth with $\geqslant$3 non-molar teeth per quadrant with two or more periodontal sites with BoP and one or more sites with PD $\geqslant$6 mm.

Exclusion criteria

The exclusion criteria were as follows: pregnant or lactating females, use of medications known to affect periodontal conditions (e.g., phenytoin, cyclosporine), use of coumadin or non-steroidal anti-inflammatory agents, diagnosis of uncontrolled metabolic disease, use of antibiotics/allergic to tetracyclines, or use of dentifrice or mouth rinse containing chlorhexidine.

Study design

This was a randomized, stratified, single-blind, controlled, parallel-group design, 25-week study including two treatment groups. Sixty patients who met the inclusion/exclusion criteria were randomized into either MWF surgery only (SO) or MWF surgery plus minocycline microspheres (SMM) groups using numbered closed envelopes. Each envelope contained treatment allocation and two quadrants, one madibular and one maxillary, to be subjected to surgery. The remaining two quadrants were to receive scaling and root planing.

Before the randomization process, all patients were stratified for smoking status. Subjects who smoked cigarettes, cigars or pipes, or used smokeless tobacco, were defined as smokers.

A treatment clinician or principal investigator administered minocycline microspheres (MMs) treatments, and all questions or discussions with patients were directed to this non-blinded individual. A separate examining clinician at each centre remained blinded and performed all physical and clinical periodontal assessments.

Baseline examination

Radiographs were obtained, clinical periodontal assessments including PD, recession (R) used to calculate clinical attachment level (CAL), BoP and plaque index (PI) were performed, and study teeth were identified according to the inclusion criteria (Fig. 1).

Treatment procedure

Following periodontal assessments, SRP was performed on the two selected quadrants in each patient within 1 week. During the same time period, patients randomized to the SMM group were administered MM subgingivally to all periodontal pockets $\geqslant$5 mm. At Week 2, MWF surgery was performed on one of the assigned quadrants. MM was again administered to the SRP quadrants as well as the assigned surgery quadrant following flap repositioning and suturing. At Week 3, MWF was performed to the remaining surgery quadrant and MM was administered following flap repositioning and suturing. At Week 5, MM was re-administered to all selected pockets in the test group (Fig. 1). Each treatment site received a single unit dose of Arestin® (1 mg of minocycline). A dispenser fitted to a plunger was applied subgingivally until resistance was felt and slowly removed while continuing to dispense the minocycline microgranulae. All patients were instructed to rinse twice daily for 30 s with 15 ml of 0.12% chlorhexidine gluconate mouth rinse (Centre B) or 1 min. with 10 ml of 0.2% chlorhexidine gluconate (Centre A) during the 2 weeks following initial surgery and to perform effective oral hygiene measures, which were reinforced during their subsequent visits.

Clinical assessments were repeated at Weeks 13 and 25. Radiographs were again obtained at Week 25. Adverse event (AE) and concomitant medication information was collected at all visits.

Clinical and safety assessments

The primary efficacy assessment was the mean PD reduction at Week 25 using the patient as a measurement unit. Secondary clinical assessments of CAL, BoP, PI and radiographic bone level were also based on the patient as a

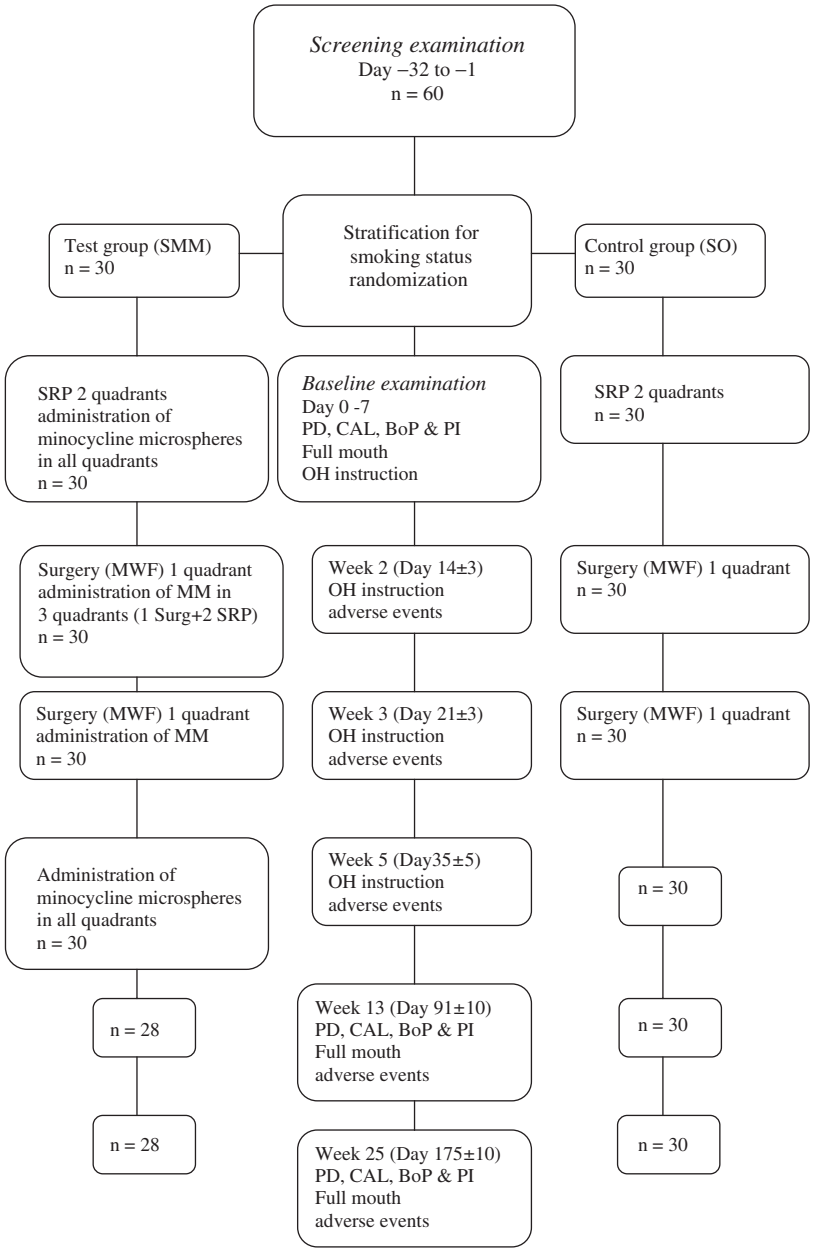

Fig. 1. Study outline. For a detailed information, see Material and Methods.

unit of measure. Secondary clinical assessment of dichotomized outcome measures (e.g., PD reduction $\geqslant 1$, $\geqslant 2$ and $\geqslant 3$ mm) was based on the periodontal site as the unit of measure. Clinical assessments were performed using a manual UNC-15 periodontal probe (HuFridey®, Chicago, IL, USA) at six periodontal sites per tooth (i.e., mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual). Before the study, the examiners were calibrated for accuracy and reproducibility.

PD was measured from the free gingival margin to the base of the pocket and recorded at the nearest millimetre.

Recession was measured to the nearest millimetre from the cemento-enamel junction (CEJ) to the gingival margin or from a restorative margin if the CEJ was not present. CAL was calculated as PD plus recession or minus recession if the gingival margin was coronal to the CEJ.

BoP was recorded as present or absent within 30 s of the PD measurements.

PI assessment was performed after staining with a disclosing solution and recorded as present or absent.

A set of intra-oral radiographs were obtained at Weeks 0 and 25 using a standardized parallel technique Eggen [1969; Rinn XCP® (extension cone paralleling)]. A clinician, blinded to patient study treatment, evaluated radiographs to determine changes in bone level; bone level was measured on a continuum.

Safety assessments consisted of monitoring and recording all AEs and determining their seriousness, expectedness and relatedness throughout the study. MedDRA (Medical Dictionary for Regulatory Affairs) Version 8.0 was used for coding and reporting of AEs.

Statistical analysis

A total of 30 patients per study group were estimated to provide 80% power at an α level of 0.05 (two-sided) to detect at least a 0.53-mm change in the mean PD at Week 25 using a two-sample *t*-test. A standard deviation of 0.72 was assumed based on previous study data (Williams et al. 2001).

Differences between study group characteristics for discrete and continuous variables at patient entry were examined using Fisher's exact tests and Students *t*-tests, respectively. Non-parametric Wilcoxon's statistics was used to validate the findings of the parametric *t*-test.

Univariate comparisons of patient-level clinical outcome measures at Weeks 0, 13 and 25 were based on two-sample *t*-tests. Homogeneity of variance was assessed using Levene's test.

The primary endpoint for the study was the change in mean PD from baseline to Week 25. This outcome measure was based upon averaged values within a patient, and thus the patient represents the unit of measure. This endpoint was analysed using covariance (ANCOVA) on non-molar periodontal sites $\geqslant 5$ mm with the following stratification factors: smoking status, centre and mean PD at baseline. The underlying assumptions of the ANCOVA were validated using non-parametric techniques. The intent-to-treat approach was used for all analyses. Missing data at interim time intervals were estimated by the last-observation-carried-forward (LOCF) method. The Gail and Simon test for qualitative interaction was performed to determine whether there was any evidence of treatment by centre interaction and to support the validity of pooling the results of the two study centres.

Secondary endpoints included changes in the mean CAL, per cent BoP, per cent PI and mean bone level.

These analyses of change were based on non-molar periodontal sites $\geqslant 5$ mm at baseline. Outcome measures were based upon averaged values within a patient, and thus the patient represents the unit of measure. Analyses of the secondary endpoints were similar to that described for mean change in PD.

Additional analyses included changes in PD, as well as CAL, $\geqslant 1$, $\geqslant 2$ and $\geqslant 3$ mm, and were based on the periodontal site as the unit of measure. Analyses of periodontal site-level data were accomplished using logistic regression models for correlated data, with adjustment for smoking status, centre and baseline PD. More specifically, the models were regenerated using alternating logistic regressions (ALR) applicable to multivariate binary data, where the within-subject periodontal site association is modelled as an odds ratio rather than a correlation (Carey et al. 1993).

Table 1. Baseline demographic characteristics of patients: by treatment group

Characteristic Periodontal sites*	SO, $N = 30$ 771	SMM, $N = 28$ 744	p-value
Gender			0.61
Male (%)	15 (50)	12 (43)	
Female (%)	15 (50)	16 (57)	
Smoking status			0.80
Never (%)	3 (10)	4 (14)	
Former (%)	10 (33)	7 (25)	
Present (%)	17 (57)	17 (61)	
Race or ethnicity			0.32
Caucasian (%)	29 (97)	24 (85)	
Asian (%)	0 (0)	1 (4)	
Black (%)	1 (3)	2 (7)	
Hispanic (%)	0 (0)	1 (4)	
Center			0.99
Sweden (%)	16 (53)	15 (54)	
USA (%)	14 (47)	13 (46)	
Age+ (years)	48.90 ± 8.7	53.30 ± 7.9	0.08
Clinical (per patient)			
Surgery quadrants			
PD* ± SD (mm)	5.75 ± 0.33	5.66 ± 0.37	0.35
CAL* ± SD (mm)	6.60 ± 0.96	6.71 ± 1.16	0.70
BoP* ± SD (%)	97 ± 21	94 ± 14	0.33
PI* ± SD (%)	44 ± 31	43 ± 30	0.73
Pockets $\geqslant 5$ ± SD (mm)	25.53 ± 10.14	26.25 ± 10.07	0.79

*Non-molar periodontal sites $\geqslant 5$ mm.
N, number of patients; BoP, bleeding on probing; CAL, clinical attachment level; SO, surgery only; SMM, surgery plus minocycline microspheres; PI, plaque index; PD, probing depth.

Results

Demographics

Thirty-one patients were randomized to the SO group and 29 to the SMM group. One patient was discontinued from the SO group due to protocol violation, and one patient was discontinued from the SMM group due to a non-serious AE of joint pain considered to be possibly related to MM.

Demographic and baseline characteristics (Table 1) were similar across the two study groups. Most patients were present smokers, 57% in the SO group and 61% in the SMM group or former smokers, 33% in the SO group and 25% in the SMM group. Most of the study patients were Caucasian, 97% in the SO group and 85% in the SMM group. The mean age was 48.9 ± 8.7 years in the SO group and 53.3 ± 7.9 years in the SMM group ($p = 0.08$). Clinical parameters (PD, CAL, BoP, PI and number of pockets $\geqslant 5$ mm) were not statistically significantly different between treatment groups at baseline. Patients were not exposed to any prohibited concomitant therapies during the study. Twelve patients lost a total of 14 teeth during the study; however, only three of these teeth were non-molars in surgery quadrants. The LOCF method of analysis was utilized for these three teeth.

Table 2. PD reduction (mm) from baseline to Weeks 13 and 25: by treatment group

Visit	Statistic	Probing depth reduction (mm)		p-value*
		SO, $N = 30$	SMM, $N = 28$	
Week 13	Mean ± SE	2.29 ± 0.09	2.48 ± 0.10	0.1519
	95% CI	2.11–2.48	2.29–2.68	
Week 25	Mean ± SE	2.18 ± 0.10	2.51 ± 0.10	0.0267
	95% CI	1.98–2.38	2.30–2.72	

*Based on ANCOVA and *F*-test.
CI, confidence interval; *N*, number of patients; SO, surgery only; SMM, surgery plus minocycline microspheres.

Efficacy findings

Before performing any statistical analyses, the Gail and Simon test was used to evaluate differences in treatment effect by centre. The observed consistency in treatment effect provided the necessary validation for the pooling of results across Centres A and B.

Table 2 presents the mean patient PD reduction for all patients at Weeks 13 and 25. Differences in the mean PD reduction at Week 13 for the SMM group (2.48 mm) and for the SO group (2.29 mm) were not statistically significant. At Week 25, this reduction was 2.51 mm for the SMM group and 2.18 mm for the SO group ($p = 0.0267$).

Table 3 presents the mean patient PD reduction by smoking status. At Week 25, non-smokers in both treatment groups demonstrated mean PD reductions throughout the study compared with baseline: 2.37 mm for the SO group *versus* 2.77 mm for the SMM group. The difference between the treatment groups was not statistically significant ($p = 0.2164$). Smokers in both treatment groups also demonstrated mean reductions in PD at Week 25. However, smokers in the SMM group demonstrated a statistically significantly ($p = 0.0443$) greater reduction (2.30 mm) than smokers in the SO group (2.05 mm).

PD reductions of $\geqslant 1$, $\geqslant 2$ and $\geqslant 3$ mm (using the periodontal site as the unit of analysis) are presented in Table 4. Non-smokers in the SMM group demonstrated a statistically

Table 3. PD reduction (mm) from baseline to Weeks 13 and 25: by treatment group and smoking status

Visit	Statistic	Probing depth reduction (mm)		*p*-value*
		SO	SMM	
		Non-smokers		
		$n = 13$	$n = 11$	
Week 13	Mean ± SD	2.41 ± 0.16	2.55 ± 0.18	0.5657
	95% CI	2.07–2.74	2.18–2.91	
Week 25	Mean ± SD	2.37 ± 0.22	2.77 ± 0.24	0.2164
	95% CI	1.91–2.82	2.27–3.27	
		Smokers		
		$n = 17$	$n = 17$	
Week 13	Mean ± SD	2.17 ± 0.11	2.40 ± 0.11	0.1592
	95% CI	1.94–2.40	2.17–2.63	
Week 25	Mean ± SD	2.05 ± 0.09	2.30 ± 0.09	0.0443
	95% CI	1.87–2.23	2.12–2.49	

*Based on ANCOVA and *F*-test.
CI, confidence interval; *n*, number of patients in each subgroup; SO, surgery only; SMM, surgery plus minocycline microspheres.

Table 4. Number and percentage of periodontal sites showing PD reductions (mm) from baseline to Weeks 13 and 25 of ⩾1, ⩾2 and ⩾3 mm: by treatment group and smoking status

Visit	Number (%) of periodontal sites		*p*-value*
	SO, $N = 771$	SMM, $N = 744$	
	Non-smokers		
	$n = 316$	$n = 308$	
Week 13			
⩾1	303 (96)	297 (96)	0.8661
⩾2	265 (84)	278 (90)	0.0187
⩾3	164 (52)	156 (51)	0.8962
Week 25			
⩾1	299 (95)	297 (96)	0.2368
⩾2	263 (83)	285 (93)	0.0039
⩾3	163 (51)	176 (57)	0.1178
	Smokers		
	$n = 455$	$n = 436$	
Week 13			
⩾1	433 (95)	423 (97)	0.2162
⩾2	338 (74)	368 (84)	0.0028
⩾3	175 (38)	205 (47)	0.0080
Week 25			
⩾1	424 (93)	421 (97)	0.0672
⩾2	338 (74)	372 (85)	0.0012
⩾3	146 (32)	196 (45)	<0.0001

*Based on logistic regression for correlated data.
N, total number of sites analysed per treatment group; *n*, number of sites analysed in each subgroup; SO, surgery only; SMM, surgery plus minocycline microspheres.

significantly greater percentage of periodontal sites with ⩾2 mm PD reduction than the SO group at both Week 13 (90% SMM *versus* 84% SO, $p = 0.01870$) and Week 25 (93% SMM *versus* 83% SO, $p = 0.0039$) (Table 4). However, when performing a corresponding analysis for sites with a PD reductions of ⩾1 or ⩾3 mm, no statistically significant differences were found. Smokers in the SMM group compared with smokers in the SO group showed statistically significantly greater PD reductions of ⩾2 and ⩾3 mm at Weeks 13 and 25. The percentage of sites with ⩾2 mm PD reduction for smokers in the SMM group was 85% compared with 74% for smokers in the SO group ($p = 0.0012$). The corresponding percentages of sites with ⩾3 mm PD reduction was 45% in the SMM group and 32% in the SO group ($p < 0.0001$).

For secondary variables, CAL, BoP, PI and radiographic bone level, no differences were found at Weeks 13 or 25 between the SMM group and the SO group. However, radiographs were only analysed for Centre A.

Table 5 presents ANCOVA results for BoP change from baseline to Weeks 13 and 25, according to treatment, after adjusting for baseline PD, smoking status and centre. The difference in mean percent BoP at Week 25 was 8% (95% CI: −1–18), with a 56% mean BoP reduction in the SO sites and a 64% mean BoP reduction in the number of SMM sites ($p = 0.0749$).

The BoP changes from baseline to Weeks 13 and 25 according to smoking status is presented in Table 6. Adjustment was made for baseline PD and centre. No significant difference in BoP reduction was observed at Week 13 for either non-smokers or smokers. However, for smokers, the difference in mean percent BoP reduction at Week 25 was 12% (95% CI: 0–24), with a 54% mean BoP reduction in the SO sites and a 66% mean BoP reduction in the SMM sites ($p = 0.0510$).

Safety findings

No serious AEs were reported. One patient in the SMM group was excluded from the study due to a non-serious AE of joint pain, which was determined to be possibly related to MM. A total of 148 non-serious AEs were reported 82 AEs (55%) from 19 patients (61%) in the SO group and 66 AEs (45%) from 19 patients (66%) in the SMM group. The most common non-serious AEs reported were pre-surgical anxiety, post-procedural experiences (i.e., discomfort, sensitivity and swelling) and headache. Post-procedural pain AEs ($p = 0.0565$, Fisher's exact) approached significance; however, there were no significant differences between treatment groups.

Discussion

This study demonstrates that use of adjunctive, subgingivally administered, Arestin® (minocycline HCl microspheres, 1 mg) therapy has an added

Table 5. Bleeding on probing (BoP) (%) reductions from baseline to Weeks 13 and 25: by treatment group

	Statistic	BoP reduction (%)		*p*-value*
		SO, $N = 30$	SMM, $N = 28$	
Week 13	Mean ± SE	62 ± 4	64 ± 4	0.7100
	95% CI	53–70	55–73	
Week 25	Mean ± SE	56 ± 3	64 ± 3	0.0749
	95% CI	49–62	57–71	

*Based on ANCOVA and *F*-test.
CI, confidence interval; *N*, number of patients.

Table 6. Bleeding on probing (BoP) (%) reductions from baseline to Weeks 13 and 25: by treatment group and smoking status

	Statistic	BoP reduction (%)		*p*-value*
		SO, $N = 30$	SMM, $N = 28$	
Non-smokers		$n = 13$	$n = 11$	
Week 13	Mean ± SD	60 ± 7	53 ± 7	0.5238
	95% CI	45–74	38–68	
Week 25	Mean	59 ± 6	62 ± 6	0.6986
	95% CI	47–70	49–74	
Smokers		$n = 17$	$n = 17$	
Week 13	Mean ± SD	64 ± 5	70 ± 5	0.3882
	95% CI	53–74	60–81	
Week 25	Mean ± SD	54 ± 4	66 ± 4	0.0510
	95% CI	46–62	57–74	

*Based on ANCOVA and *F*-test.
CI, confidence interval; *N*, number of patients; *n*, number of patients in each subgroup.

beneficial effect (0.33 mm) on pocket reduction when used with MWF surgery compared with MWF surgery alone. A similar beneficial effect has been reported with the use of subgingival MM therapy in non-surgical SRP (Williams et al. 2001). Furthermore, the use of MM in the SMM group resulted in a statistically significantly greater number of sites with PD reduction of $\geqslant 2$ and $\geqslant 3$ mm than in the SO group at Week 25. While the clinical significance of a mean gain in pocket reduction of 0.33 mm may be debated among practitioners, the significantly greater percentage of reduction of $\geqslant 2$ and $\geqslant 3$ mm are of relevance to routine clinical practice. Additionally, smoking persists in society despite its negative health effects. Consequently, any improvement in the treatment of periodontitis is a welcome addition to existing therapies. The statistically significantly greater reduction in PD for smokers receiving adjunctive MM treatment (0.25 mm) may be of importance in managing periodontal disease in this patient population.

As might be anticipated, the use of MM had no discernable impact on the patient's oral hygiene, showing no significant differences in PI between groups. In addition, no significant differences were noted in BoP between non-smokers in both treatment groups. This might be expected because of the type of surgery used, coupled with similarities in the patient's plaque control. However, for smokers, there were differences (although not statistically significant) in percentage of BoP reduction between treatment groups at Week 25 ($p = 0.0510$). This might partly be due to a smaller variability in PD reduction noted in smokers.

The lack of difference in CAL change between the two treatment groups would suggest the greater pocket depth reduction observed in the SMM group to be the effect of MM primarily caused by tissue shrinkage via reduction of inflammation in the more coronal area of the pocket. These results are in line with Williams et al. (2001), who also reported that there were no additional clinical attachment gain in the subjects who were treated with adjunctive Arestin®. It would be of interest to compare the results from the present study with similar studies using resective and regenerative techniques.

Other considerations for clinical use of adjunctive MM therapy include the cost of the material, the additional surgical time for its application and the lack of containment of the material (i.e. flap reflection in contrast to non-surgical pocket wall containment). Although the results of this study cannot be extrapolated to other surgical pocket reduction procedures, the results are encouraging as few adverse findings were observed.

While the clinical significance for application of this approach can only be determined for the individual patient, the statistical significance supports the adjunctive use of MM with MWF surgery as a valid addition to the current therapeutic armamentarium for the management of periodontitis.

Conclusions

This study demonstrated a statistically significant reduction in periodontal probing depths when locally administered MMs were used as an adjunct to MWF surgical therapy (SMM) compared with surgery alone (SO). This study further demonstrated statistically significantly greater percentage of pockets with PD reduction $\geqslant 2$ mm in the SMM group. Additionally, statistically significant reductions in mean PD were observed in smokers treated with SMM than surgery alone (0.25 mm) as well as a greater percentage of pockets with PD reductions $\geqslant 2$ and $\geqslant 3$ mm.

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Clinical Relevance

Scientific rationale for the study: Local antibiotic treatment with minocycline microspheres as an adjunct to mechanical non-surgical treatment improves the clinical outcome. To date, the effect of locally delivered minocycline on periodontal healing, in combination with periodontal surgery, has not been evaluated.

Principle findings: Subgingival applications of minocycline microspheres produced significantly greater reduction in mean probing depth in combination with periodontal surgery in adults with moderate to severe, chronic periodontitis than surgery alone in both smokers and non-smokers.

Practical implications: Minocycline microspheres may be a useful adjunct in the surgical treatment of moderate to severe, chronic periodontitis in adults.