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Supportive periodontal therapy using mechanical instrumentation or 2% minocycline gel: a 12 month randomized, controlled, single masked pilot study

E. McColl[1], K. Patel[1], G. Dahlen[2], M. Tonetti[1,3], F. Graziani[1], J. Suvan[1] and L. Laurell[1]

[1]Department of Periodontology, Eastman Dental Institute, University College London, London, UK; [2]Department of Oral Microbiology, Faculty of Odontology, Sahlgrenska Academy at Göteborgs University, Göteborg, Sweden; [3]Division of Periodontology, Department of Oral Health and Diagnostic Sciences, University of Connecticut Health Center, Farmington, CT, USA

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Abstract

Objective: To compare the short-term performance of subgingival local delivery of 2% minocycline gel and conventional subgingival debridement in supportive periodontal therapy (SPT) patients.

Methods: Forty adult patients having completed active treatment for moderate to advanced chronic periodontitis were included in a randomized, controlled, single masked maintenance care pilot study. Sites with residual pocket probing depths $\geqslant 5$ mm and bleeding on probing were treated with either minocycline gel (*minocycline-group*) or scaling and root planing only (*debridement-group*) at baseline, 3, 6, and 9 months. Clinical and microbiological examinations were performed at baseline, 3, 6, 9, and 12 months.

Results: Full-mouth plaque and bleeding scores remained $<10\%$ and $<20\%$, respectively, for both groups throughout the study. In both groups there was a persistent reduction in number of teeth and sites with probing pocket depths $\geqslant 5$ mm ($p<0.05$) with no significant differences between the groups. The prevalence of *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, and *Prevotella nigrescens*, remained at levels $\leqslant 10^5$ in the majority of patients and sites in both groups.

Conclusion: This pilot study failed to show a difference between local delivery of 2% minocycline gel as mono-therapy and traditional subgingival debridement in patients on SPT.

Key words: clinical trial; maintenance; microbiology; periodontal disease; supportive care

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Periodontal diseases are inflammatory diseases caused by Gram-negative bacteria (Haffajee & Socransky 1994). Thus, the treatment of periodontal diseases aims at eliminating the infection that caused the disease. Usually treatment of advanced forms of periodontitis is performed in three phases (Lindhe & Nyman 1984). (1) the initial or cause-related therapy, (2) the corrective therapy performed 3–6 months after initial therapy by which residual pockets $\geqslant 5$ mm are surgically treated by means of open flap debridement, pocket elimination/reduction surgery or regenerative procedures and (3), continuous maintenance care also referred to as supportive periodontal therapy (SPT).

The importance of high-quality SPT to maintain treatment results achieved through active periodontal therapy has been clearly demonstrated (e.g. Nyman et al. 1975, Rosling et al. 1976, Nyman et al. 1977, Axelsson & Lindhe 1981,

Kerr 1981, Becker et al. 1984, Sanz & Herrera 1998). In addition, studies showing long-term successful treatment outcome of moderate-to-advanced periodontitis are all based on SPT every 3 months (e.g. Badersten et al.1984, Lindhe & Nyman 1984, Ramfjord et al 1987, Renvert et al. 1990, Kaldahl et al. 1996, Tonetti et al. 1998a, b, Rosling et al. 2001, Serino et al. 2001). Accordingly the periodontal patient on regular maintenance care is likely to spend 4 h or more per year receiving SPT (Wilson 1996a, b). Over the long term, such regular SPT may result in some adverse events. Frequent and excessive scaling and root planing can remove tooth structure and produce tooth sensitivity (von Troil et al. 2002, Chung et al. 2003) and ''hour glass appearance'' at the root crown interface (Riffle 1952). Clearly this can be a problem in maintenance care. The patient who has increased tooth sensitivity following non-surgical/surgical therapy may find further instrumentation painful. This may affect long-term compliance and also may increase the time involved in each maintenance visit.

In a systematic review on maintenance care, Heasman et al. (2002) concluded, that further research is necessary to establish the ideal regimen for periodontal maintenance care. Such trials should try to determine which regimen will (1) lead to improvement in clinical outcomes, (2) lead to stability of periodontal disease in the long term, (3) be most likely to lead to a microbial flora that is consistent with periodontal health or stability, (4) be the most cost effective to deliver and (5) cause the fewest adverse effects (e.g. root sensitivity) in the long term.

During the last decade the use of various antibiotic formulations locally delivered into periodontal pockets as adjuncts to scaling and root planing have been evaluated (for a review see Drisko 1996, Rams & Slots 1996, Tonetti 1997). Although not conclusive, short and medium term clinical trials tend to show an additional effect of scaling and root planing plus local application of some antibiotic products over scaling and root planing alone (*Tetracycline HCL fibers*, Goodson et al. 1991, Flemmig et al. 1996, Vandekerckhove et al. 1997, Wilson et al. 1997; *Doxycycline*, Polson et al. 1997, Garret et al. 1999, Wennstrom et al. 2001, Eickholz et al. 2002, Salvi et al. 2002; *Metronidazole*, Stelzel & Flores-de-Jacobi 1996, Riep et al. 1999, Griffiths et al. 2000; *Minocycline*, Graca et al. 1997, Vandekerckhove et al. 1998, van Steenberghe et al. 1999, Williams et al. 2001).

Although the evidence is limited, the studies by e.g. Van Steenberghe et al. (1999), Garrett et al. (2000) and Meinberg et al. (2002) indicate that there may be a place for local delivery monotherapy in SPT particularly if time, ease of use and patient centered outcomes are considered.

The aim of this 12-month randomized-controlled single masked pilot study was to compare clinically and microbiologically the effect of local application of 2% minocycline gel to that of subgingival mechanical instrumentation in patients on periodontal maintenance care following completion of active periodontal therapy.

Material and Methods

Subjects

Forty adult participants were recruited from the patients who had completed treatment for moderate-to-advanced chronic periodontitis at the Department of Periodontology, Eastman Dental Institute. The number of subjects was not based on sample size calculations but represented a convenience sample to assess variability and to be able to properly size a subsequent study. Ethical approval was obtained from the Eastman Dental Institute and University College London Hospitals Joint Ethics Committee. Informed consent was obtained from all the subjects to be entered in the study. The study was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects. The subject's medical history and concomitant medication use was rechecked at each visit. Side effects or unexpected occurrences were dealt with according to the standard of medical and dental practice.

Inclusion exclusion criteria

To be *included* in the study, the patient had to (i) be 40 years or older, (ii) be in general good health, (iii) have completed active periodontal therapy (non-surgical and/or surgical) not more than 6 months prior to study enrolment, (iv) have at least four teeth presenting with probing depths $\geqslant 5$ mm and bleeding on probing (BOP) following completion of active treatment, (v) have full-mouth plaque score (FMPS) $<25\%$ (Lang et al. 1990, 1996), (vi) not be pregnant or lactating, (vii) have given written informed consent and (viii) be willing and able to attend to 3 months follow-up appointments.

Patients were *excluded* if they (i) had a medical history that may have an impact on periodontal disease susceptibility and/or treatment, i.e. diabetes mellitus, rheumatoid arthritis, HIV, cardiovascular disease, (ii) had a known allergy to tetracyclines or the pharmaceutical composition of the carrier gel, (iii) had used any antibiotic medication within the last 3 months or (iv) were on a medication that may influence periodontal disease progression, i.e. NSAID, steroids, cyclosporine A.

The clinical characteristics of a typical study patient are shown in Fig. 1.

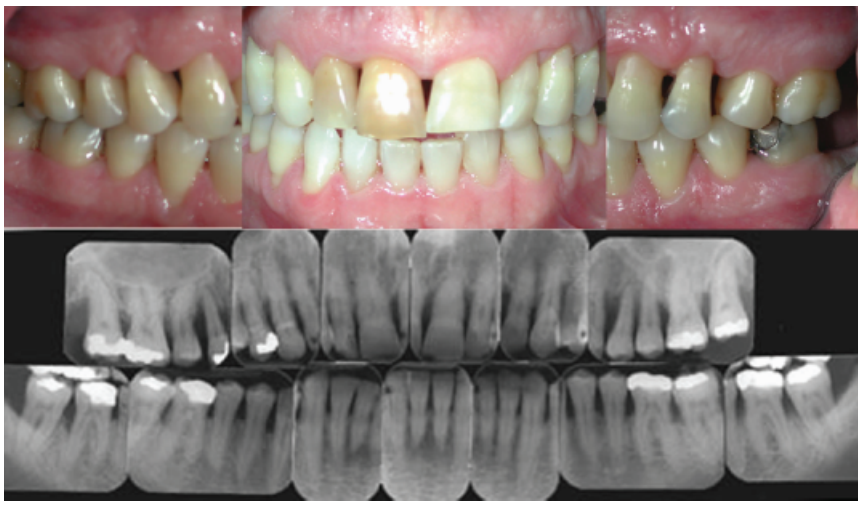

Fig. 1. Clinical characteristics of a typical study patient.

Clinical examination

Clinical examination was performed by a single calibrated masked examiner at baseline (i.e. at least 6 months after completion of active treatment), and at 3, 6, 9, and 12 months and included: plaque presence or absence (FMPS % was calculated), probing pocket depth (PPD), probing attachment level (PAL). Intra-examiner calibration indicated a 98% reproducibility within 2 mm for PAL and 98% within 1 mm for PPD. The cemento-enamel junction was used as reference point for PAL measurements. If not detectable another suitable landmark was used as reference and noted accordingly (e.g. crown margin, restoration margin, etc.). BOP to the bottom of the pocket (present or absent after waiting 15 s full-mouth BOP score %) was calculated.

Full-mouth measurements and registrations were done at six sites of each tooth – mesio-buccal, mid-buccal, disto-buccal, disto-lingual, mid-lingual and mesio-lingual. Measurements were done using an UNC 15 mm periodontal probe and values were rounded up to the nearest millimeter.

Microbiological examination

One microbiological sample was taken at each of the four teeth with the deepest probing depths at the baseline examination. Two sterile paper points were inserted into the site with the deepest probing depth. These sites were used as the reference sites for the microbiological sampling at 3, 6, 9 and 12 months. The samples were transferred to 100 μl TE buffer (10 mM Tris HCl, 1 mM EDTA, pH 7.6) and 100 μl 10.5 M NaOH were added and the suspensions were boiled for 5 min. After boiling 800 μl 5 M ammonium acetate were added to each tube and the samples were processed with the checkerboard methodology according to standardized procedures (Socransky et al. 1994, Papapanou et al. 1997). Immobilization of bacterial samples onto nylon membranes was completed within 2 weeks from sample collection.

Digoxigenin-labelled, whole-genomic probes were prepared by random priming using the High-Prime labeling kit (Boehringer-Mannheim, Ingelheim, Germany) from the following 12 microbial strains: *Porphyromonas gingivalis* (FDC381), *Prevotella intermedia* (ATCC 25611), *Prevotella nigrescens* (ATCC 33563), *Tannerella forsythia* (ATCC 43037), *Actinobacillus actinomycetemcomitans* (FDC Y4), *Fusobacterium nucleatum* (ATCC 10953), *Treponema denticola* (OMGS 3271), *Micromonas (Peptostreptococcus) micros* (OMGS 2852), *Campylobacter rectus* (ATCC 33238), *Eikenella corrodens* (ATCC 23834), *Selemonas noxia* (OMGS 3119), *Streptococcus intermedius* (ATCC 27335). The hybrids formed between the bacterial DNA and the probes were detected by application of an anti-digoxigenin antibody conjugated with alkaline phosphatase and incubation with a chemiluminiscent substrate (CSPD, Boehringer-Mannheim). Evaluation of the signal was performed with a LumiImager™ workstation (Boehringer-Mannheim) by comparing the obtained signals with those of pooled standard samples containing 10^6 (high standard) or 10^5 (low standard) of each of the 18 bacterial species. The sensitivity and specificity of whole-genomic probes constructed as above have been described previously (Socransky et al. 1994, 2004), and a comparison between checkerboard hybridization and culture in the identification of subgingival microbiota has also been published (Papapanou et al. 1997). In addition, the probes were cross-tested against the 12 species of the panel in order to distinguish cross-hybridizations. The obtained chemiluminiscent signals were transformed into a scale of scores from 0 to 5 according to Papapanou et al. (1997) as follows: 0 = not detected, 1 = $<10^5$, 2 = 10^5, 3 = $>10^5$, 4 = 10^6, 5 = $>10^6$.

The occurrence of individuals positive for each of the investigated bacterial species was described at two different cut-off levels, score 2 and score 3. Cut-off level ($\leqslant 10^5$) was selected to contrast ''low-colonized'' (scores 0–2) *versus* ''heavily colonized'' sites, i.e. associated with cut-off level ($>10^5$) (scores 3–5).

The clinical examinations as well as the bacteriological sampling were carried out by one masked and calibrated examiner being unaware of what treatment the patient had. The microbiological assessment and analysis was also performed masked.

Primary outcome variables included change in number of sites with PPD $\geqslant$ 5 mm, change in composition of subgingival micro-flora and patient comfort.

Randomization

Subject numbers were assigned in ascending order at the enrollment visit. The participants were randomly assigned by computer-generated table to either test or control treatment, i.e. parallel group design with 20 patients in each group. A balanced random permuted block approach (4-unit block size) was used to prepare the randomization tables in order to avoid unequal balance between the 2 treatments. Treatment allocation using minimization was performed by an independent registrar allocating patients according to number of sites with PPDs $\geqslant$ 5 mm (Altman & Bland 2005). Treatment allocation was concealed in an opaque envelope until completion of oral hygiene instructions during the treatment session.

Treatment

Treatment was performed by a graduate student in his third and final year. Following clinical examination and bacterial sampling oral hygiene was reinforced as needed. The opaque envelope containing the treatment assignment information was then opened.

Test treatment

In patients assigned to the test treatment *minocycline group* (*M-group*) all sites $\geqslant$ 5 mm showing BOP received 2% minocycline gel as mono-therapy. The medication was administered into the pocket with the applicator provided by the manufacturer to fill the pocket up to the gingival margin (van Steenberghe et al. 1999) (Fig. 2). No mechanical root instrumentation was performed.

Control treatment

In patients assigned to the control group *debridement group* (*D-group*) all sites $\geqslant$ 5 mm showing BOP were subjected to subgingival debridement only (Rosling et al. 2001), with a piezo-ceramic scaler (EMS) and curettes (LM instruments) as deemed necessary by the clinician.

Treatment/re-treatment at 3, 6 and 9 months included all sites, i.e. residual or ''new'' sites that at the respective examination time point exhibited probing depths $\geqslant$ 5 mm with BOP according to the initial randomized treatment assigned. Oral hygiene was reinforced as required.

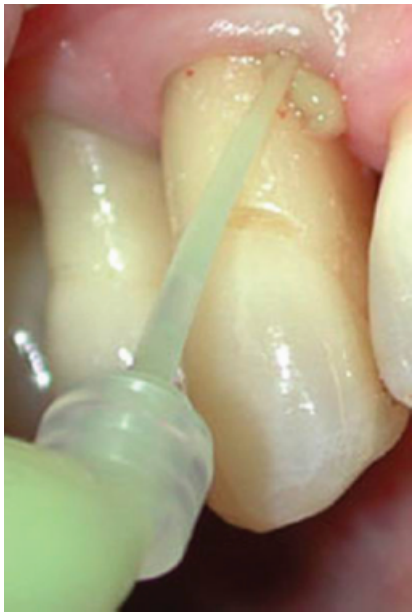

Fig. 2. Application of 2% minocycline gel.

Treatment time and patient perception

The time needed for treatment at each appointment (OH instruction excluded) was recorded using a stop watch. Total treatment time was assessed by summing up the time recorded at each appointment. After each treatment session a questionnaire (see Table 5) with a self adressed return envelope was given to the patient to be answered and returned within a week. The questionnaire consisted of a visual analogue scale. The patients perception was presented on a 100 mm straight line where the left end point represented no and the right end point severe discomfort, pain, etc. The patients were asked to place a mark in the appropriate position on the line. The distance from the no-point was then measured with millimeter ruler.

Patient protection

Patients were monitored for any deterioration in periodontal health during the study or reaction to medication. An increase in probing depth of at least 2 mm or loss of clinical attachment of at least 2 mm defined the site to be retreated with active periodontal therapy as deemed appropriate.

Statistical analysis

Data were entered into an Excel (Microsoft office 2000) database and were proofed for entry errors. The database was subsequently locked, imported into SPSS for Windows (SPSS Inc., version 11.0) formatted and analysed. A subject-level intention-to-treat analysis was performed by carrying last visit forward for drop-outs. Subject-level variables were computed (full-mouth or at different PPD categories) for each of the parameters. Numerical data were summarized as means and SD, categorical data were summarized as frequency distribution. Changes in the clinical variables between groups as well as within groups were analysed using ANOVA and Student's *t*-tests. χ^2 square analysis was used to test the hypothesis of no difference in prevalence of individuals and sites with bacterial counts $>10^5$. Differences were considered significant at the $p \leqslant 0.05$ level.

Table 1. Full-mouth plaque scores (%) at baseline and at the various re-examinations for the minocycline and the debridement groups (mean values and SD)

	2% minocycline	Debridement	*p*-value
Baseline	7.8 ± 7.4	7.2 ± 8.2	0.81
3 months	6.2 ± 4.3	8.5 ± 6.6	0.21
6 months	8.5 ± 7.0	7.5 ± 4.9	0.61
9 months	8.4 ± 5.2	8.3 ± 5.8	0.95
12 months	10.7 ± 12.1	5.8 ± 4.3	0.11

Table 2. Full-mouth bleeding scores (%) at baseline and the various re-examinations for the minocycline and the debridement groups (mean values and SD)

	Minocycline 2% gel	Debridement	*p*-value
Baseline	17.9 ± 6.7	18.3 ± 6.3	0.84
3 months	11.8 ± 6.6*	11.8 ± 5.6*	0.98
6 months	16.8 ± 4.4	13.1 ± 4.6*	0.01
9 months	21.1 ± 5.9	15.0 ± 5.5*	0.002
12 months	8.8 ± 6.7*	10.3 ± 4.9*	0.43

*Value different from baseline at $p<0.01$.

Results

Patients

Of the 40 patients recruited, 38 completed the study, 19 patients (seven males, 12 females) in the M-group and 19 patients (six males and 13 females) in the D-group (two patients were lost to follow-up for personal non-study-related reasons). The mean age of patients in the M-group was 48 ± 7 years and in the D-group 45 ± 7 years ($p>0.05$) There were two smokers in the M-group and five smokers in the D-group. The mean number of teeth amounted to 24 ± 2 and 24 ± 3 in the M-group and D-group respectively. Over the course of the study one patient in the D-group lost three teeth and one patient also in the D-group lost two teeth, both within the first three months of starting the study. These teeth had been scheduled for extraction during the preceding period of active therapy.

There were no adverse reaction at any time to the 2% minocycline gel nor were there any sites losing attachment that required further treatment during the study.

Plaque scores

FMPS at baseline and the various re-examination time points are presented in Table 1. At baseline, the FMPS amounted to 8 ± 7% in the M-group and 7 ± 8% in the D-group. The FMPS remained low throughout the duration of the study in both groups.

Bleeding score

Full-mouth bleeding scores (FMBS) at baseline and the various re-examination time points are presented in Table 2. There was a significant reduction in FMBS between baseline and 3months in both groups. In the D-group the FMBS remained low and stable throughout the study whereas in the M-group there was a fluctuation in the FMBS between re-examination time points. At the 12 month examination, however, FMBS were low in both groups without significant differences between groups.

Number of teeth and sites with PPDs ⩾5 mm (Table 3)

At baseline, the number of teeth with pockets ⩾5 mm amounted to 13 ± 4 in both the M-group and the D-group corresponding to 15.5 ± 6% and 16.9 ±

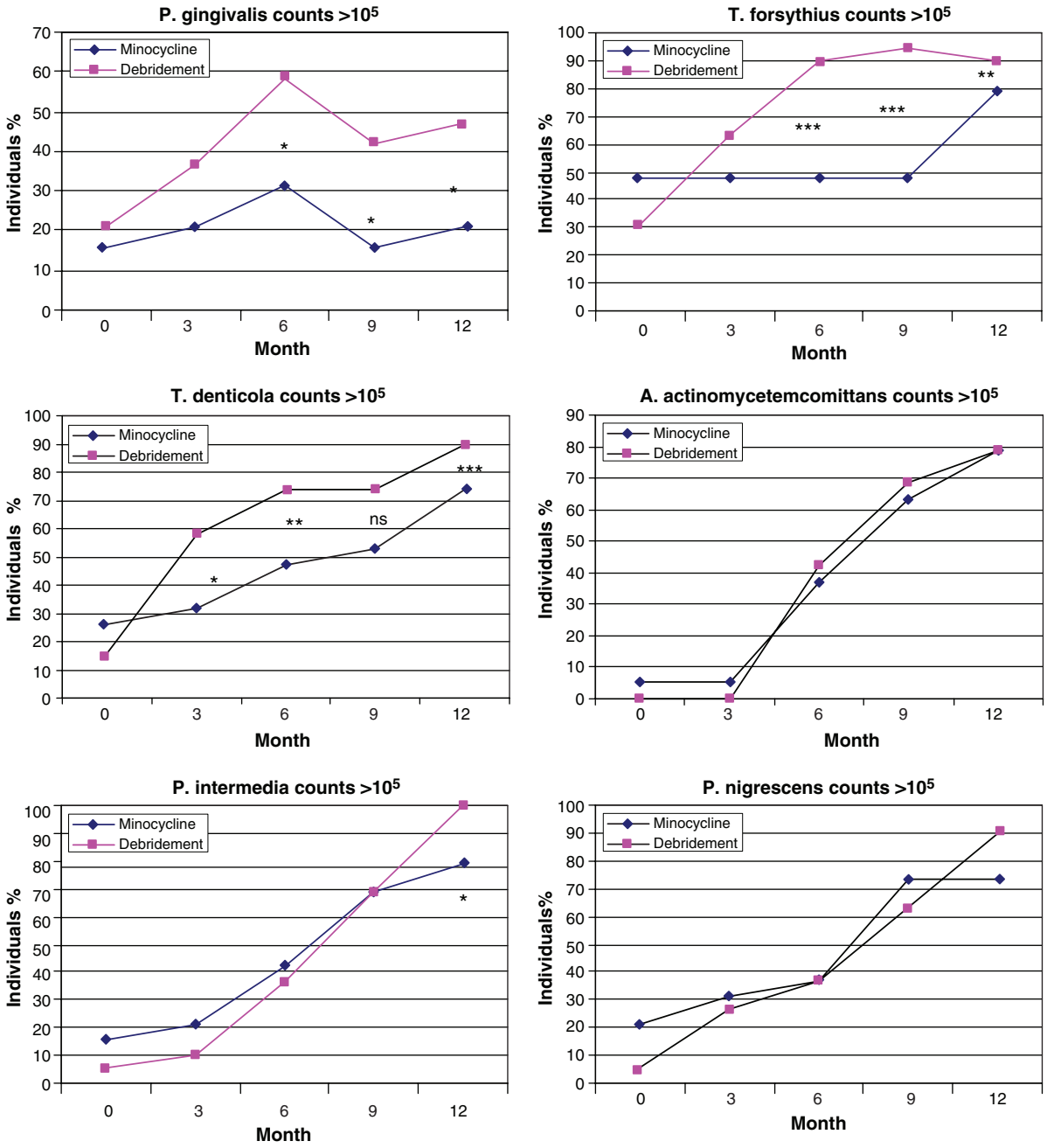

Fig. 3. Prevalence (%) of individuals with *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, and *Prevotella nigrescens*, counts $>10^5$ in the minocycline and debridement groups as analyzed by ''Checker board'' DNA–DNA hybridization technique. * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$, ns = not significant.

6%, respectively of available sites. At 3 months a significant ($p<0.05$) reduction in the number of such teeth had occurred in both groups. This decrease remained throughout the study with no significant difference between the groups. Likewise, the number of sites as well as the percentage number of sites with PPDs $\geqslant 5$ mm showed a significant ($p<0.05$) reduction between baseline and 3 months. Again there was no difference between the groups and the number of sites $\geqslant 5$ mm remained stable throughout the study.

Sites with PPDs $\geqslant 7$ mm

Sites with probing depths $\geqslant 7$ mm were found in 14 M-group patients and 12 D-group patients at baseline. In the M-group the number of such sites averaged 2.4 ± 1.9 and in the D-group 3.1 ± 2.0. At 12 months the numbers were reduced to 1.7 ± 1 and 2.8 ± 2.0 in the *M*- and D-group*s* respectively, with no significant difference between groups.

Microbiological findings

The prevalence of individuals with one or more sites with high bacterial counts, i.e. counts $>10^5$ are depicted in Fig. 3. There was a general pattern of increasing prevalence of bacterial pathogens with increasing time in both the M-group and the D-group. However, from

?*Table 3*. Number of teeth, number of sites and percentage of sites with probing pocket depths ⩾5 mm in the minocycline (M) and the debridement group (D) at baseline and at the various re-examination time points (mean values and SD)

	Number of teeth		Number of sites		% sites	
	M-group	D-group	M-group	D-group	M-group	D-group
Baseline	13 ± 4	13 ± 4	23 ± 2	25 ± 8	15.5 ± 6.1	16.9 ± 6.1
3 months	9 ± 3*	9 ± 3*	14 ± 7*	15 ± 6*	9.7 ± 4.7*	10.4 ± 3.8*
6 months	9 ± 3*	10 ± 4*	16 ± 8*	20 ± 8*	11.1 ± 5.5*	13.6 ± 5.5*
9 months	9 ± 3*	10 ± 4*	18 ± 8*	19 ± 7*	12.7 ± 5.7*	13.3 ± 5.4*
12 months	9 ± 5*	10 ± 4*	16 ± 9*	18 ± 8*	11.0 ± 6.4*	13.0 ± 6.7*

*$p<0.05$ as compared with baseline.

6 months on, there were significantly more patients in the D-group with high counts of *P. gingivalis*, *T. forsythia* and *T. denticola* than in the M-group. No such difference was found for *A. actinomyctemcomitans, P. intermedia* and *P. nigrescens*.

The prevalence of ''heavily colonized'' sites, Fig. 4, i.e. the percentage of sites with bacterial counts $>10^5$ increased over time to encompass 25% of the sites with *P. gingivalis* and about 50% of the sites with the other bacteria

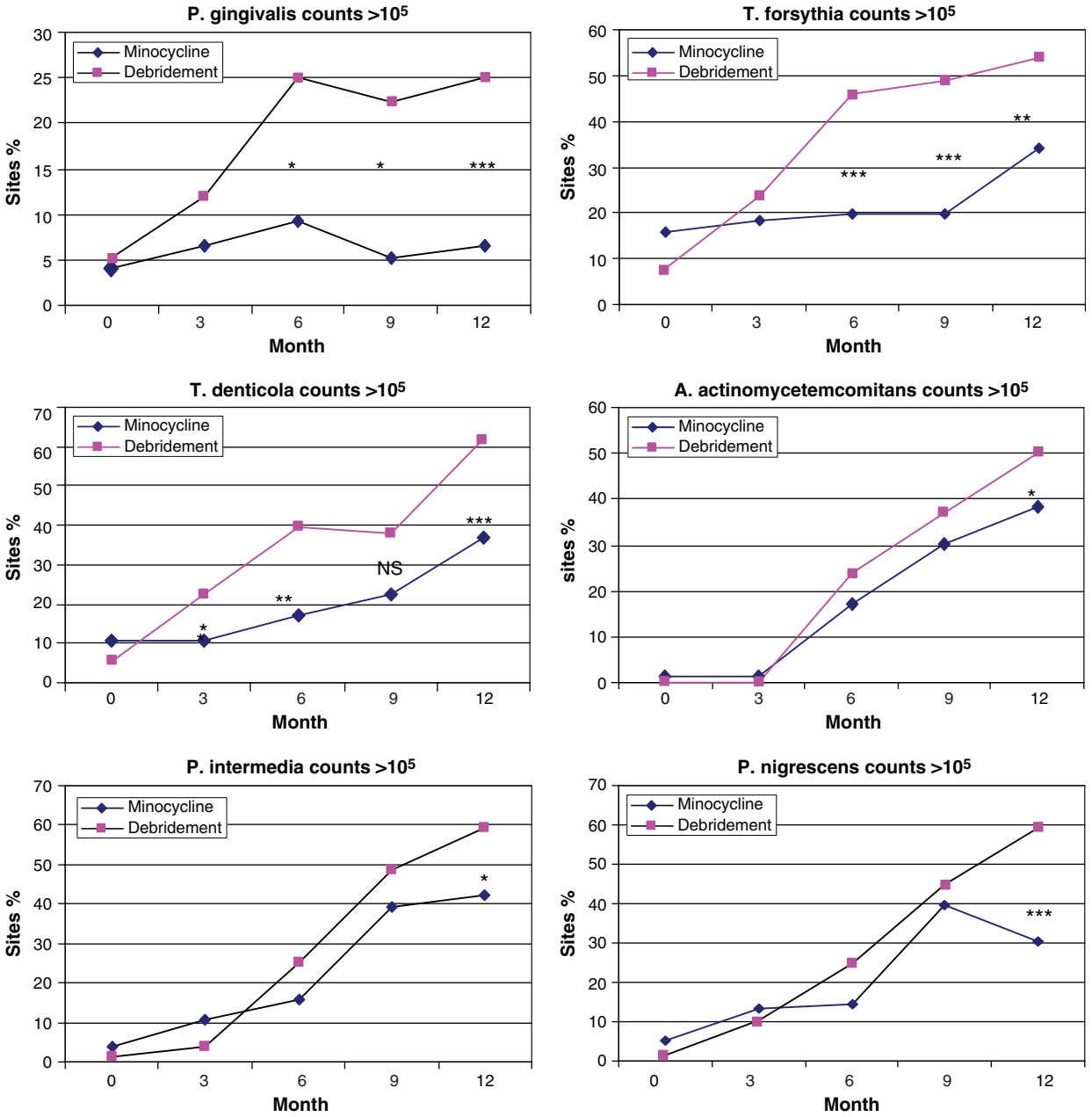

Fig. 4. Prevalence (%) of sites with *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, and *Prevotella nigrescens*, counts $>10^5$ in the minocycline and debridement groups as analysed by ''Checker board'' DNA–DNA hybridization technique. *$p<0.05$, **$p<0.01$, ***$p<0.001$, NS, not significant.

Table 4. Treatment time in the minocycline and the debridement groups at the various treatment sessions and total treatment time (mean values and SD)

	Minocycline	Debridement	Difference
Baseline	17 ± 3	25 ± 5	$p<0.01$
3 months	19 ± 6	26 ± 5	$p<0.05$
6 months	21 ± 2	27 ± 5	$p<0.05$
9 months	21 ± 2	28 ± 6	$p<0.05$
Total	79 ± 7	106 ± 21	$P<0.05$

Table 5. Response to questionnaire as assessed on a visual analogue scale (mean values and SD)

Question	M-group	D-group	*p*-value
Did you feel pain during the procedure	3 ± 3	46 ± 11	<0.0001
Did you have discomfort (other than pain) during or after the procedure	3 ± 2	26 ± 18	<0.0001
Did you have any sensitivity in the treated areas following the procedure	2 ± 3	11 ± 9	<0.001

M-group, minocycline; D-group, debridement.

in the *D-group*. However from month 6 on, there was a significantly lower prevalence, about 50%, of sites harbouring high counts of *P. gingivalis, T. forsythius* and *T. denticola* in the M-group than in the D-group. For *A. actinomyctemcomitans, P. intermedia* and *P. nigrescens* the difference was only significant at 12 months.

At 12 months 58% of the individuals in the M-group and 68% in the D-group had one or more sites with at least two species of the *Red Complex* (Socransky et al. 1998) at counts $>10^5$. The corresponding percentage of the sites amounted to 22.4% and 35.9%, respectively.

Treatment time (Table 4)

The time needed for treatment was recorded at each visit. At all sessions the treatment with minocycline 2% gel was significantly less time consuming than routine non-surgical maintenance therapy. Over the four sessions of treatment (i.e. 0, 3, 6, and 9 months) the mean treatment time in the M-group receiving the Minocycline 2% gel was 79 ± 7 min. while for the D-group total mean treatment time was 106 ± 21 min. Thus a difference in mean chair time of 27 min. was apparent in favour of the M-group ($p<0.05$).

Patient perception

Patient perception of treatment was recorded using a visual analogue questionnaire scale. The following questions were answered with the patient marking on the 10 cm line to give a value 0–100 after each treatment session: (1) Did you feel pain during the procedure, (2) Did you have discomfort (other than pain) during or following the procedure and (3) Did you have any sensitivity in the treated areas following the procedure?

For each question and patient the mean value from each of the four treatment session was calculated and used for the further statistical analysis. The numerical values are depicted in Table 5. The M-group suffered significantly ($p<0.0001$) less from pain, discomfort, and sensitivity than the D-group.

Discussion

The aim of this 12-month randomized-controlled single masked study was to compare clinically and microbiologically the effect of local application of 2% minocycline gel to that of subgingival mechanical instrumentation in patients on SPT following completion of active periodontal therapy. Like all other tetracycline related drugs, minocycline is bacteriostatic. It has been demonstrated that the concentration of minocycline in gingival fluid following application of the 2% minocycline gel is reduced from about 2000 μg/ml at baseline to 5 μg/ml after 72 h (Satomi et al. 1987). However a concentration of 5 μg/ml is higher than the MIC_{90} for a number of periodontitis related microorganisms such as *P. gingivalis*, *T. forsythia*, *P. intermedia* and *A. actinomyctemecomitans* (Hagiwara et al. 1998).

The present study failed to detect a difference between treatments over a 12-month period clinically. In both groups there was a reduction in number of teeth and sites with PPD ⩾5 mm between baseline and 3 months and this reduction was maintained until the 12-month final examination. At 3 months the difference between treatments in the reduction in the number of such sites was 0.95 and at 12 months 0.63 sites. A post hoc power calculation analysis revealed that, at 3 or 12 months, the minimal detectable difference between the two treatments was five sites or almost a third of the sites presenting with a problem at baseline. This indicates that this study did not have adequate power to detect a clinically relevant difference between the two approaches if a real difference existed.

Of crucial importance to successful STP is the patients own infection control (Kornman 1994). The patients in this study had all completed active treatment for moderated to severe generalized chronic periodontitis. Both groups of patients maintained extremely low plaque scores (Table 1) throughout the duration of the study and this may have had a significant impact in maintaining periodontal stability. However, despite a high level of infection control with plaque and bleeding scores below 20%, the patients in both groups presented with a mean of 13 out of 24 teeth with 15% of available sites showing residual pockets ⩾5 mm 6 months after completion of active treatment. The majority of these sites had a PPD of 5 mm. There could be several reasons for this high number. Patient own infection control could have been unstable causing disease recurrence. Treatment could have been insufficient leaving several pockets remaining. It could also be that the patients in this study were susceptible to periodontal disease and prone to further periodontal breakdown. A recent systematic review concluded that residual PPDs ⩾6 mm are associated with further disease progression on a subject level (Renvert & Persson 2002). In the present study, 12 M-group patients and 14 *D-group* patients had one or more sites with PPD of >6 mm (M-group 2.4+1.9 and D-group 3.1+2.0).

The clinical results of the present study are difficult to compare with those of other studies as there are few studies designed to evaluate SPT per se. In a multi-centre controlled randomized clinical trial on 104 patients, van Steenberghe et al. (1999) evaluated the clin-

ical and microbiological effect of locally delivered 2% minocycline gel (Dentomycin Blackwell Supplies Ltd, Gillingham, UK) as an adjunct to scaling and root planing. Following non-surgical periodontal therapy either a 2% minocycline gel (test group) or a placebo (control group) was locally administered into periodontal pockets $\geqslant 5$ mm. Repeated application was performed at 2 weeks and at 1, 3, 6, 9, and 12 months in all sites initially selected for the study. These sessions could be considered as SPT sessions. All sites were also rescaled at 6 and 12 months. From 6 months on, the sites having received the 2% minocycline gel showed significantly greater mean PPD reduction and mean PAL gain than the control sites.

In a multi-centre study (Garrett et al. 2000) 141 patients on SPT received either scaling and root planing or subgingivally applied doxycycline hyclate (Atridox, Block Drug Corporation Inc., Jersey City, NJ, USA) at baseline and at 4 weeks. Both treatments were equally effective as evaluated at 9 months with overall probing depth reduction of around 1.2 mm. However, this treatment protocol included the use of a surgical dressing to improve retention of the delivery device which makes it extra time consuming.

The clinical results of the present study are also in agreement with those of Meinberg et al. (2002) who compared conventional SPT *versus* the use of subgingival minocycline microspheres (Arestin, Oral Pharma Inc., Warminster, PA, USA) in patients diagnosed with moderate to advanced chronic periodontitis. Forty-eight patients had non-surgical periodontal therapy followed by SPT every 3 months for 1 year. Twenty-four patients were maintained on a regular SPT, while the other 24 patients had subgingival application of 1 mg minocycline only into each site measuring $\geqslant 5$ mm that bled on probing. The minocycline application was repeated 1, 3 and 6 months after active therapy without adjunctive instrumentation. After 1 year the M-group showed an additional PPD reduction of 0.5 mm.

In the present study, the microbiological analysis focused on some putative perio-pathogenic microorganisms and presented at two count levels; less than or equal to 10^5 as low counts and more than 10^5 as heavily colonized. Perio-pathogens can most likely not be completely eradicated by conventional periodontal therapy but proportions $\leqslant 10\%$ of the total flora and counts $< 10^5$ have been associated with periodontal health (e.g. Socransky et al. 1991, Ximénes-Fyvie et al. 2000). However the prevalence of high counts were more frequent in the present study than in the study by van Steenberghe et al. (1999).

In the present study, around 20% of the individuals and around 10% of the sites had high counts of the tested microorganisms at baseline. Over time both the prevalence of individuals with heavily colonized sites as well as the percentage number of such sites increased. This increase seemed to be more pronounced in the D-group having had the subgingival instrumentation than in the M-group in which the patients had subgingival administration of 2% minocycline gel only. The difference was most apparent for *P. gingivalis*, *T. forsythia* and *T. denticola* from 6 months on. The difference between treatments should, however, be interpreted with caution as there was no difference in clinical outcome between treatments at any time point. The reason for the gradual increase in the prevalence of heavily colonized sites can only be speculated upon. It could be explained by the fact that microbial sampling was always taken at the same four sites which at baseline were the deepest sites. Following treatment, the PPD in these sites may have decreased below 5 mm by the next examination and therefore were not treated, as treatment according to the protocol was only given to sites 5 mm or deeper with BOP as measured at each examination appointment. (It should be remembered that the number of such sites decreased significantly between baseline and 3 months.) As a consequence, the subgingival microbiota may have been undisturbed until increased probing depth made the site eligible for re-treatment.

Although the evidence is limited, the current study and the above studies indicate that there may be a role for local delivery mono-therapy in SPT. If one considers patient-centred outcomes, this treatment modality may become even more favourable. In this study, patient-centred outcomes indicated that as well as being less time consuming to perform (a mean difference in chair time of 27 min. in favor of the M-group over a 9-month period.) the patients in the M-group experienced significantly less post-operative pain and discomfort. With the power limitations discussed above, if one then considers, that there appears to be no difference in treatment outcome between SPT using subgingival debridement or 2% minocycline gel as a mono-therapy a discussion of the implications for practice may help assessing the potential of future research in this area.

Obviously there are cost implications of using a local delivery agent, which will be more expensive than standard subgingival debridement. However, if sufficient time were saved, this cost differential may be reduced. Perhaps the most relevant use of this therapy is in patients with extreme sensitivity following active therapy. In patients where sensitivity makes the repeated subgingival instrumentation in regular SPT extremely difficult and painful, local application of an antimicrobial agent may give clinicians another tool in their SPT armamentarium. Instead of 3 monthly sessions of subgingival debridement for life, possibly the intervals between debridement could be increased with the use of locally delivered 2% minocycline gel supplementing this, so that subgingival instrumentation be carried out once a year with the antimicrobial agent at intervening 3-month visits. Investigation of such a regime should be considered in the design of future trials. ''The available evidence presently suggests that local delivery may be most beneficial in the control of localized ongoing disease in otherwise stable patients. Maintenance patients with a few non-responding sites may therefore benefit most from local antimicrobial therapy'' (Mombelli 1997).

Another issue of concern to the clinician, however, is the risk of bacterial resistance to long-term use of local delivery antimicrobials. The issue of bacterial resistance following application of the 2% minocycline gel was not investigated in this study and would be worthy of consideration in a future study. Preus et al. (1995) established that although resistant bacterial strains may develop following local antibiotic delivery these seem to disappear after 3–6 months. So far, however, little hard data are available on possible effects of subgingival local delivery antibiotics on the microbiota of the gastrointestinal tract. This lack of data has spurred speculations and concerns of the possible spread of bacterial resistance and even increases in the chance of the transfer of multi-drug resistance after local application of antibiotics (Greenstein & Tonetti 2000).

Conclusions

Although there are concerns about the long-term use of local delivery antibiotics and bacterial resistance, the results of this study failed to detect a difference in the effect of local delivery of 2% minocycline gel as a mono-therapy in SPT and subgingival debridement over a 12-month period. The pilot nature of the trial and the insufficient power to detect clinically relevant differences, however, require caution in making specific conclusions. The data, however, seem to be consistent with the concept that local drug delivery as a mono-therapy may be clinically useful as an alternative to root debridement. Clearly patient selection is essential and the patient's plaque control must be of high standard. Patients who have problems with sensitivity may be ideal candidates for this type of therapy increasing the time interval between painful subgingival instrumentation by interspersing with the use of locally delivered antibiotic. Further investigations are needed with a larger patient population and an increased duration of clinical and microbiological monitoring to investigate this possibility.

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Address:
Maurizio Tonetti
Division of Periodontology
Department of Oral Health and Diagnostic Sciences
School of Dental Medicine
University of Connecticut Health Science Center
263, Farmington Ave
Farmington, CT 06030
USA.
E-mail: mtonetti@uchc.edu

Clinical Relevance

Background: Repeated subgingival scaling over many years causes root damage and sensitivity. This pilot study compared subgingivally applied minocycline gel to conventional subgingival debridement in 40 maintenance patients over 1 year.

Principal findings: The periodontal status remained stable in both groups and no difference between treatments was detected. Patients, however, seemed to prefer the minocycline gel.

Clinical Implications: Definitive clinical conclusions cannot be drawn at this stage since this pilot study did not have sufficient power to detect clinically relevant differences between the two regimens. A future study needs to definitively assess the potential of this treatment approach, especially in patients complaining with root sensitivity.