The Effect of Locally Delivered Controlled-Release Doxycycline or Scaling and Root Planing on Periodontal Maintenance Patients Over 9 Months

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Background: This research report evaluates clinical changes resulting from local delivery of doxycycline hyclate (DH) or traditional scaling and root planing (SRP) in a group of patients undergoing supportive periodontal therapy (SPT).

Methods: In all, 141 patients received either DH (67) or SRP (74) treatment in sites ≥5 mm on one-half of their dentition at baseline and month 4.

Results: Clinical results were determined at month 9. Baseline mean probing depth recordings were similar between the two groups (DH = 5.9 mm; SRP = 5.9 mm). Mean month 9 results showed similar clinical results for attachment level gain (DH 0.7 mm; SRP 0.8 mm) and probing depth reduction (DH 1.3 mm; SRP 1.1 mm). Percentage of sites showing ≥2 mm attachment level gain at month 9 was 24.7% in the DH group and 21.2% in the SRP group. Thirty-nine percent (39%) of DH sites and 38% of SRP sites showed ≥2 mm probing depth reduction. When treated sides of the dentition were compared to untreated sides, DH showed a difference in disease activity (≥2 mm attachment loss) from 19.3% (untreated) to 7.2% (treated); and SRP from 14.3% (untreated) to 8.1% (treated).

Conclusions: Results show that both DH without concomitant mechanical instrumentation and SRP were equally effective as SPT in this patient group over the 9-month study period. *J Periodontol 2000;71:22-30.*

KEY WORDS

Periodontal diseases/therapy; periodontal diseases/drug therapy; planing; scaling; comparison studies; doxycycline/therapeutic use.

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The goal of supportive periodontal therapy (SPT) following active periodontal treatment is to prevent recurring disease episodes and maintain the level of periodontal health achieved during the active treatment phase. Numerous studies have demonstrated and emphasized the importance of SPT in maintaining susceptible patients' periodontal health (for a review, see reference 1).

Very little data are available to determine the appropriate SPT interval for an individual periodontal patient. In the absence of specific protocols to individualize intervals, patients are usually seen every 3 to 6 months for repeat scaling and root planing. Approximately 3 of 4 patients respond well to this treatment.[2-7] Therefore, while routinely delivered mechanical maintenance is effective, approximately 20% to 25% of patients have significant additional periodontal breakdown despite treatment.

A second concern with SPT is patient compliance with proposed SPT treatments. Research reports have indicated that 34% to 42% of treated patients fail to return for their first recall appointment following active treatment.[8,9] Compliance decreases over time following treatment[8-10] as well as with the complexity of treatment.[11] A number of factors have been suggested that negatively affect compliance including skepticism, unfavorable treatment benefit, treatment complexity, time involved, economics, and stress.[12] Unfortunately, the most effective and conscientious periodontal therapy is sometimes rendered ineffective because of patients' non-compliance with SPT.

The purpose of this study was to evaluate and compare the clinical outcomes of two separate SPT treatments in periodontal maintenance patients. The first of these treatments was scaling and root planing; the second was locally delivered controlled-release doxycycline without concomitant mechanical instrumentation.

MATERIALS AND METHODS

This group of patients represents an SPT subgroup from two previously reported randomized, blinded, multicentered trials evaluating the safety and effectiveness of locally delivered controlled-release doxycycline. Clinical outcomes following doxycycline treatment in these two parallel-design, 9-month studies were compared to scaling and root planing (SRP), oral hygiene (OH), and vehicle control (VC).[13] In these trials, clinical outcomes following doxycycline hyclate (DH) and SRP treatments were superior to OH and VC. Therefore, data from the OH and VC groups are not included in this report.

This SPT subgroup of patients was identified by a self-reported history of previous definitive periodontal treatment defined as scaling and root planing by quadrant and/or periodontal surgery. In addition, patients had to have undergone SPT for a minimum of 2 years post-definitive treatment, with consistent recall intervals ≤6 months over that period. Specifics of the designs of the trials from which these patients were selected have been previously published.[13,14]

Patients were included if they gave informed consent, were 25 to 75 years of age, and had generalized moderate to severe periodontitis. To qualify, patients had at least 2 quadrants which each contained a minimum of 4 periodontal pockets ≥5 mm, that bled on probing. Two of the qualifying sites were required to have a probing depth ≥7 mm. Other details of the exclusion/inclusion criteria have been published previously.[14]

DH and Treatment Procedures

The test formulation‖‖‖‖ containing doxycycline hyclate was a solution containing 8.5% wt/wt doxycycline and 37% wt/wt poly(DL-lactide) (PLA) dissolved in a biocompatible carrier of 63% wt/wt N-methyl-2-pyrrolidone (NMP). In the case of DH, the two components of the formulation were provided in two separate syringes that were coupled together just prior to use and mixed for 100 cycles. Once mixed, the doxycycline-containing test product was allowed to sit at room temperature for 15 minutes and then mixed for another 10 cycles before use. A 23-gauge cannula was attached to the delivery syringe, and the test product was expressed into the periodontal pocket. Any overflow material was gently packed into the pocket with a wetted curet. Quadrants treated with DH were covered with a periodontal dressing.¶¶¶ Patients treated with DH returned at day 7 for removal of the dressing and DH (subsequent studies have shown that removal of DH is unnecessary; unpublished data). DH was applied to each qualifying pocket on the treated side of the mouth at the baseline and month 4 visits. Patients in the DH treatment group were instructed not to perform oral hygiene on the treated side of the mouth during each 7-day period following treatment. No concomitant mechanical instrumentation was provided. No therapy other than OH was provided on the untreated side of the mouth throughout the 9-month study period.

Patients randomized to the SRP group received a single episode of SRP on the treated side of the mouth at baseline and month 4. Therapists were instructed to continue SRP until the treated root surfaces felt hard and smooth to a dental explorer. Patients were given local anesthesia on request. No time restraints were placed on the SRP therapist; instead, treatment proceeded until the therapist was satisfied with the endpoint. SRP therapists were either periodontists or dental hygienists chosen by the principal investigator. The untreated side of the mouth did not receive any treatment other than OH throughout the study. Patients were instructed to begin oral hygiene on the treated side of the mouth the day following SRP.

Patients in both the DH and SRP groups received identical OH instructions. They were instructed in both the Bass brushing technique and proper use of dental floss to be performed 2 times a day. Compliance was queried at each subsequent visit, and further instruction was provided as necessary.

Treatment Assignment and Blinding

All patients were randomized to treatment groups according to a computer-generated random code. This was a single-blind evaluation; the examiners at each center were blinded to treatment. A double-blind design was not possible because of the dissimilar treatments between groups.

‖‖‖‖ Atridox, Block Drug Corporation, Inc., Jersey City, NJ.
¶¶¶ Coe-Pak periodontal dressing, GC America, Inc., Chicago, IL.

Table 1.

Schematic Outline of Study Procedures

	Treatment Day								
	Screen	Baseline	Interim Visit	Day 7	Month 1, 2	Month 4	Interim Visit	Day 7 Post-Reapplication	Months 5, 6, 8, 9
Informed consent	X								
Admission criteria	X	X							
Pregnancy test		X				X			X
Demographics	X								
Medical history	X								
Blood pressure and pulse rate	X	X				X			
Clinical photographs		X	X	X	X	X	X	X	X
Periodontal history	X								
Plaque index		X			X	X			X
Periodontal examination	X	X			X	X			X
Administer treatments		X				X			
Oral hygiene instruction		X		X	·	X		X	
Removal of periodontal dressing				X	·	X		X	
Removal of test articles				X				X	
Clinic visit	X	X	X	X	X	X	X	X	X

Evaluations

A schedule of the evaluation timepoints and data collection at each timepoint are outlined in Table 1. Measurements of probing depth, bleeding on probing, clinical attachment level, and plaque index[15-17] were made at these timepoints. Probing depth measurements were made at 6 location points on all teeth in the dentition (treated and untreated locations) using a periodontal probe,### graduated in 1 mm increments with readings made to the nearest millimeter. Four or five sites in each of the 4 quadrants (treated and untreated) that qualified for the study (≥5 mm with BOP) were selected for attachment level measurements using the cemento-enamel junction (CEJ) or other nearby landmark. These attachment level sites on the treated one-half of the dentition were a subset of the total sites evaluated for probing depth, bleeding score, and plaque score changes. There were continuous evaluations of both the treated and untreated sides of the dentition throughout the study, which allowed assessment of the benefits of treatment on disease progression. Concomitant medications and safety evaluations were recorded at each visit. Any suspected adverse events or allergic reactions were evaluated carefully by the investigator. Further details concerning these evaluation appointments have been published previously.[14]

Statistical Methods

The patient groups from the two studies were combined for this analysis after an ANOVA for study by treatment interactions revealed no significant interactions when the DH and SRP groups from the two studies were combined. The efficacy endpoints were mean change in attachment level and probing depth. Means were calculated by using the sum of the treated and untreated site measurements for a patient divided by the number of treated and untreated sites. For all parameters, the patient mean was the basis of the statistical analysis, not the sites alone.[18,19] Efficacy results for qualifying treated and untreated sites for attachment level and probing depth were analyzed statistically by analysis of variance (ANOVA) on differences from baseline values between groups. All statistical tests were conducted at a significance level of $P \leq 0.05$. All tests were two-tailed.

Exclusion of Tooth Sites

Sites on both the treated and untreated halves of the dentition were excluded from the study at the discre-

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tion of the principal investigator when they demonstrated ≥2 mm attachment level loss from baseline at two consecutive evaluations. Excluded sites were treated with SRP and monitored at each subsequent visit to be certain they were stable.

Procedures and criteria for study monitoring, prestudy training, data management, and exclusion of patients or investigators/centers have been described previously[14] and will not be reviewed in this report.

RESULTS

The efficacy parameters evaluated were mean change in attachment level and mean change in probing depth. ANOVA analyses are presented for data combined from all centers in each study for each parameter and treatment group. The number of patients per group available for analysis varied at each analysis timepoint based on a blinded determination of whether they were efficacy-evaluable at that particular study timepoint. Patients were eliminated at various efficacy timepoints when they presented outside the predetermined evaluation timepoints or had concomitant treatment, e.g., antibiotic therapy that may have altered the results. Plaque score changes are presented as a measurement of compliance. Bleeding on probing reductions are also included. A total of 141 patients qualified for the study – 67 DH-treated patients and 74 SRP-treated patients. Sixty of the patients were female, and 81 were male. Median age was 50 years old.

Plaque Scores (PS) and Bleeding on Probing (BOP)

Baseline plaque scores were similar between treated and untreated areas of the dentition and between DH and SRP groups. Baseline PS ranged between 0.9 and 1.1. Reduction at month 9 ranged between 0.1 and 0.2. Reductions between treated and untreated areas of the mouth and between treatments were not statistically different ($P > 0.05$). Baseline BOP ranged from 1.5 to 1.6 for both treated and untreated areas of the dentition. Reductions at month 9 ranged from 0.4 to 0.6. Reductions between treated and untreated areas were statistically significant in favor of the treated DH and SRP groups.

Attachment Level Gain (ALG)

Table 2 shows ALG for all evaluated sites in the treated and untreated halves of the dentition and for subgroups of moderate (5 to 6 mm) and deep (≥7 mm) sites. Results show no differences between SRP and DH groups at either 4 or 9 months. Mean month 9 ALG for all sites was 0.72 mm for DH and 0.75 mm for SRP; for sites initially 5 to 6 mm, means were 0.65 mm for DH and 0.58 mm for SRP; and for sites initially ≥7 mm, these means were 0.96 mm for DH and 1.02 mm for SRP. Treated halves of the dentition show more improvement than untreated areas. These differences were usually significant ($P \leq 0.05$), and mean improvements were somewhat larger for untreated areas in DH patients compared with untreated areas in SRP patients.

Probing Depth (PD)

Table 3 shows PD reduction for all evaluated sites in the treated and untreated halves of the dentition and for subgroups of moderate (5 to 6 mm) and deep (≥7 mm) sites. Results show no differences between DH and SRP groups at 4 months. At month 9, DH showed statistically better PD reduction in all sites and sites 5 to 6 mm ($P \leq 0.05$). Although statistically different, these differences were not clinically relevant. Mean month 9 PD reduction for all sites was 1.28 mm for DH and 1.13 mm for SRP. DH sites with baseline PD 5 to 6 mm showed 1.11 mm reduction, and SRP showed 0.92 mm reduction. Sites initially ≥7 mm showed 1.76 mm reduction in the DH group and 1.67 mm in the SRP group. Again, treated areas of the dentition showed significantly greater improvement ($P \leq 0.05$) than untreated areas, and untreated areas in DH patients showed somewhat more improvement than untreated areas in SRP patients.

ALG and PD Reduction ≥2 mm

Tables 4 and 5 show the number of sites and percentage of sites that experienced significant clinical change at month 9. Comparisons between DH and SRP in both Table 4 (ALG) and Table 5 (PD reduction) show similar outcomes between the groups. Approximately 30% of treated sites in both groups showed ≥2 mm ALG. Approximately 40% in both groups showed ≥2 mm PD reduction. These values are generally double those of the untreated sides of the dentition.

Sites Losing ≥2 mm Attachment Level

Table 6 compares the frequency and percentage of sites with ≥2 mm attachment level loss in DH and SRP treated groups. These values are compared to untreated halves of the dentition in the same patient groups. These data combine sites that were exited for attachment level loss ≥2 mm during the study and sites that showed this amount of loss at month 9. The percentage of treated sites losing ≥2 mm of attachment during the study was similar between DH and SRP groups (7.2% and 8.1%, respectively). Treated halves of the dentition showed a substantial reduction in percentage of sites losing ≥2 mm attachment compared to untreated sides. In this intra-treatment group comparison, SRP showed a 43% reduction, and DH showed a 63% reduction.

DISCUSSION

Results of this retrospective analysis of patients undergoing supportive periodontal treatment (SPT) are consistent with the overall response seen in the large mul-

Table 2.

Evaluation of Maintenance Patients—Attachment Level Gain (mean and SE)

All Sites	Baseline	Change at Month 4	Change at Month 9
DH			
Treated sites	6.04 (0.30)	0.59 (0.12)	0.72 (0.13)
	n = 67	n = 59	n = 59
Untreated sites	5.16 (0.23)	0.33 (0.07)	0.46 (0.09)
	n = 67	n = 59	n = 59
SRP			
Treated sites	5.51 (0.20)	0.60 (0.08)	0.75 (0.09)
	n = 74	n = 67	n = 70
Untreated sites	5.34 (0.24)	0.30 (0.08)	0.34 (0.08)
	n = 74	n = 67	n = 70
DH vs. SRP		0.7995	0.4891
DH vs. untreated		0.0317	0.0354
SRP vs. untreated		0.0072	0.0002
5 to 6 mm Baseline Probing Depth			
DH*			
Treated sites	5.23 (0.27)	0.54 (0.10)	0.65 (0.11)
	n = 65	n = 57	n = 56
Untreated sites	4.88 (0.25)	0.23 (0.07)	0.44 (0.09)
	n = 65	n = 57	n = 56
SRP			
Treated sites	4.87 (0.20)	0.44 (0.08)	0.58 (0.09)
	n = 74	n = 67	n = 70
Untreated sites	5.07 (0.23)	0.29 (0.08)	0.34 (0.09)
	n = 74	n = 67	n = 70
DH vs. SRP		0.7230	0.2830
DH vs. untreated		0.0085	0.1018
SRP vs. untreated		0.1587	0.0228
≥7 mm Baseline Probing Depth			
DH**			
Treated sites	7.32 (0.35)	0.65 (0.16)	0.96 (0.17)
	n = 64	n = 55	n = 55
Untreated sites	6.47 (0.28)	0.61 (0.18)	0.57 (0.18)
	n = 47	n = 41	n = 42
SRP			
Treated sites	6.94 (0.29)	0.82 (0.13)	1.02 (0.14)
	n = 71	n = 66	n = 66
Untreated sites	6.83 (0.39)	0.34 (0.16)	0.54 (0.16)
	n = 45	n = 42	n = 42
DH vs. SRP		0.2160	0.6022
DH vs. untreated		0.7718	0.1406
SRP vs. untreated		0.0013	0.0205

* Two patients in the DH group did not have AL sites with pockets measuring 5 to 6 mm at baseline.

** Three patients in the DH group did not have AL sites with pockets measuring ≥ 7 mm at baseline.

Table 3.

Evaluation of Maintenance Patients—Probing Depth Reduction (mean and SE)

All Sites	Baseline	Change at Month 4	Change at Month 9
DH			
Treated sites	5.93 (0.05)	–0.98 (0.09)	–1.28 (0.09)
	n = 67	n = 59	n = 59
Untreated sites	5.68 (0.07)	–0.46 (0.07)	–0.66 (0.09)
	n = 64	n = 59	n = 59
SRP			
Treated sites	5.86 (0.05)	–1.00 (0.09)	–1.13 (0.09)
	n = 74	n = 67	n = 70
Untreated sites	5.58 (0.05)	–0.55 (0.06)	–0.55 (0.07)
	n = 74	n = 67	n = 70
DH vs. SRP		0.6306	0.0294
DH vs. untreated		0.0001	0.0001
SRP vs. untreated		0.0001	0.0001
5 to 6 mm Baseline Probing Depth			
DH			
Treated sites	5.36 (0.02)	–0.86 (0.08)	–1.11 (0.08)
	n = 67	n = 59	n = 59
Untreated sites	5.28 (0.03)	–0.37 (0.07)	–0.57 (0.09)
	n = 67	n = 59	n = 59
SRP			
Treated sites	5.33 (0.02)	–0.83 (0.07)	–0.92 (0.08)
	n = 74	n = 67	n = 70
Untreated sites	5.26 (0.02)	–0.53 (0.07)	–0.52 (0.07)
	n = 74	n = 67	n = 70
DH vs. SRP		0.4268	0.0302
DH vs. untreated		0.0001	0.0001
SRP vs. untreated		0.0018	0.0001
≥7 mm Baseline Probing Depth			
DH			
Treated sites	7.54 (0.07)	–1.22 (0.14)	–1.76 (0.14)
	n = 67	n = 58	n = 58
Untreated sites	7.44 (0.09)	–0.78 (0.14)	–1.02 (0.17)
	n = 50	n = 44	n = 44
SRP			
Treated sites	7.56 (0.09)	–1.51 (0.15)	–1.67 (0.15)
	n = 74	n = 66	n = 68
Untreated sites	7.44 (0.08)	–0.77 (0.10)	–0.90 (0.13)
	n = 48	n = 45	n = 45
DH vs. SRP		0.7429	0.1574
DH vs. untreated		0.0266	0.0008
SRP vs. untreated		0.0001	0.0001

Table 4.

Evaluation of Maintenance Patients—Attachment Level Change ≥2 mm

	Treated Sites N	Treated Sites %	Untreated Sites N	Untreated Sites %
≥2 mm improvement				
DH	157	31.2	107	24.7
SRP	177	29.4	110	21.2
≥2 mm loss				
DH	29	5.8	29	6.7
SRP	27	4.5	40	7.7
Total sites				
DH	504		434	
SRP	603		518	

Table 5.

Evaluation of Maintenance Patients—Probing Depth Change ≥2 mm

	Treated Sites N	Treated Sites %	Untreated Sites N	Untreated Sites %
Reduction 2 mm				
DH	405	39.2	150	19.6
SRP	460	37.5	177	19.9
Gain 2 mm				
DH	7	0.7	16	2.1
SRP	14	1.1	16	1.8
Total sites				
DH	1032		765	
SRP	1228		891	

ticenter trials from which this patient subset was derived. In these two multicenter trials, outcomes between DH and SRP groups were clinically equivalent[13] as they were in this analysis. There were no clinical and only minor statistical differences in ALG, PD reduction, and BOP reduction when SPT was accomplished by DH treatment without concomitant instrumentation or by traditional SRP.

Of particular importance was the impact of each of these therapies on the rate of disease progression in the patient's dentition. The study design allowed intra-

Table 6.

Sites Losing ≥2 mm Attachment Level

	Total Sites	Losing Sites*	%
DH			
Treated	512	37	7.2
Untreated	502	97	19.3
SRP			
Treated	627	51	8.1
Untreated	558	80	14.3

* Combined sites with ≥2 mm attachment loss at month 9 and sites exited from study because of ≥2 mm attachment loss.

patient comparisons of disease activity in monitored sites on treated and untreated halves of the dentition over the 9-month study period. Disease progression was defined as sites that showed a loss of attachment level ≥2 mm over the 9-month study period. There was an approximate 63% difference in activity comparing treated and untreated areas of the dentition following DH, and a 43% difference following SRP treatment. In this patient population, overall disease activity was higher than expected.[20-22] This may relate to the population being evaluated. These were patients who had received definitive periodontal care and had been compliant with SPT visits (≤6-month intervals) for at least 2 years. Despite this, they qualified to enter the study by having at least 2 quadrants that each had 4 or more sites ≥5 mm that bled on probing. Two of these sites had to be ≥7 mm. This likely represents an increased disease activity compared to a general SPT population.[20-22] Additionally, the rate of disease activity in both the treated and untreated halves of the dentition may have been influenced by not treating the entire dentition. Several recent research reports indicate that full-mouth treatment, rather than a quadrant or split-mouth approach, results in a more positive clinical response overall which may be due to the decreased overall bacterial load.[23,24] These data are strong evidence of the benefit of frequent SPT in similar patient populations.

Research indicates that tetracyclines may be used in conjunction with SRP in SPT patients[25,26] or as a monotherapy in refractory SPT patients[27] with considerable success. These data indicate that DH may have potential use as an alternate treatment to SRP at SPT visits where root planing is not required. These DH treatments, used periodically when clinical conditions indicate, may improve the generally poor visit compliance seen in SPT patients.[8-11] Lack of visit compliance negatively affects outcomes following definitive periodontal treatment.[22,28,29] It is unknown whether

use of treatment alternatives to routine root planing will improve visit compliance in SPT patients. Additional studies are necessary to demonstrate any improvements in compliance.

Treatment with DH seemed to result in a modest crossover effect to untreated halves of the dentition, despite the somewhat higher incidence of sites losing ≥2 mm of attachment level in the DH group. Generally, mean improvement in ALG and PD reduction was slightly greater in untreated areas of DH patients compared with SRP patients. This may be a result of crossover of DH from treated to untreated areas of the dentition. A recent pharmacokinetic study has shown modest levels of doxycycline in the saliva following DH treatment of half the dentition.[30] This reinforces the importance of a parallel rather than split-mouth design when evaluating similar products.

One drawback of the study is its 9-month design with repeat treatment at month 4. This provides no information regarding whether DH treatment may prolong the SPT interval as has been suggested following use of tetracycline-impregnated fibers.[26] In addition, 9-month data with only two treatments provide little information regarding long-term effects of DH treatment. One recent report has shown little long-term benefit following use of tetracycline fibers.[31] However, this report contained relatively few patients and, as the authors suggested, the data may have been skewed by patients in the fiber group that showed unusually high rates of disease activity. This illustrates the necessity of properly powered evaluations to assess outcomes. Other reports have demonstrated long-term stability following tetracycline fiber application.[32] Finally, stability of outcomes following any type of periodontal therapy is SPT dependent.[1,7] It is assumed that DH-treated patients in routine clinical practice will eventually require root planing as a part of ongoing SPT. Therefore, significantly longer-term results that do not include root planing as part of SPT may not be available.

In conclusion, this study demonstrates that SPT using DH (without concomitant mechanical treatment) is as effective as SRP in reducing the clinical signs of periodontitis over 9 months. This suggests that DH treatment may be an effective SPT treatment in patients who do not require root planing at their SPT visit. Additional studies are necessary to demonstrate the feasibility of this treatment routine and whether it will improve SPT compliance. Both DH and SRP demonstrated positive effects on the rate of disease progression compared with untreated areas in patients' dentition. This emphasizes the importance of frequent SPT visits and compliance with these visits in maintaining periodontal health.

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