Original

A comparative evaluation of the clinical effects of systemic and local doxycycline in the treatment of chronic periodontitis

Ferda Alev Akalın[§], Esra Baltacıoğlu[§], Dilek Şengün[§], Süeda Hekimoğlu[†], Müge Taşkın[†], İlker Etikan[‡] and İnci Fişenk[*]

[§]Department of Periodontology, Faculty of Dentistry,
[†]Department of Pharmaceutical Technology, Faculty of Pharmacy,
Departments of [‡]Biostatistics and [*]Microbiology, Faculty of Medicine,
Hacettepe University, Ankara, Turkey

Abstract: In this study, the clinical efficacies of systemic doxycycline (SD) and local doxycycline (LD) in the treatment of chronic periodontitis were compared. Forty-five patients were studied in 3 main groups with 5 treatments: SD alone, SD+scaling-root planing (SD+SRP), LD alone, LD+SRP and SRP alone. Antibiotic-treated patients were given doxycycline treatment alone in 1 quadrant of their upper jaws, and doxycycline+SRP was given in the contralateral quadrant. The areas included at least 4 teeth with ≥ 5 mm pockets. Probing depth (PD), clinical attachment level, gingival index, sulcular bleeding index and plaque index values were recorded at baseline and the 7th week. The results were statistically analyzed. All of the clinical parameters were significantly reduced by all treatments ($P \leq 0.05$). The SD and LD treatments alone provided significant clinical healings. The significant differences among the groups were only in PD at the 7th week. The LD treatment provided significantly higher PD reduction than the SD treatment ($P \leq 0.05$). No significant difference was found between the SD+SRP and the LD+SRP treatments. There was no significant difference between SD+SRP and SRP alone treatment ($P > 0.05$). The SD group showed lower PD reduction than SRP group ($P \leq 0.05$), while no significant difference was found between LD and SRP treatments. The LD alone treatment seemed more effective than SD alone treatment on PD reduction, but no significant difference was found between them when combined with the SRP. LD may be more preferable than SD as an adjunct to mechanical treatment since LD seems more effective than SD on PD reduction and does not have the side effects of SD. (J. Oral Sci. 46, 25-35, 2004)

Introduction

Currently, periodontal disease is accepted as an infection of the periodontium since the primary etiologic factor is bacteria, which triggers the host immune response and the consequent tissue destruction. Because of its infectious nature, in a biological view, the main target for periodontal treatment must be the suppression of the effective bacteria (1,2). In light of this conceptual development, it recently has been considered that mechanical treatment alone is insufficient in the periodontal treatment strategy. Antimicrobial therapy, especially antibiotic treatment, is of special importance as an adjunct to mechanical periodontal treatment (1,3,4).

To date, the most widely used antibiotics in the treatment of periodontal disease have been tetracyclines since they show the highest concentrations in gingival crevicular fluid (GCF) and are highly effective on *Actinobacillus Actinomycetemcomitans* (Aa) (5,6). Recently, some non-

Correspondence to Dr. F. Alev Akalın, Department of Periodontology, Faculty of Dentistry, University of Hacettepe, 06100 Ankara, Turkey
Tel: +90 312 312 76 92
Fax: +90 312 310 44 40
E-mail : akalin@hacettepe.edu.tr

antimicrobial properties of tetracyclines have also been demonstrated in addition to their antimicrobial effects. Studies have shown that the non-antimicrobial properties of the drug have a therapeutic potential. These agents can inhibit pathologic collagenolysis by blocking mammalian collagenases and other matrix-degrading metalloproteinases and thereby inhibit connective tissue breakdown (7,8). In one of the studies, patients with moderate chronic periodontitis were administered doxycycline for 2 weeks prior to a full-thickness flap procedure. The gingival extracts were analyzed for collagenase activity and the results showed that doxycycline significantly reduced collagenase activity in gingiva and GCF of periodontal pockets (7). It has been shown that MMPs in inflamed gingival tissue and GCF of adult periodontitis patients, originating from PMNs, can be directly inhibited by doxycycline (8).

Tetracycline was first isolated from a streptomices species in 1948 and the semi-synthetic new versions were produced in minocycline and doxycycline forms (9). Although antibiotics (especially tetracyclines) traditionally have been preferred for the treatment of early onset types of periodontitis, in recent years the concept of using them in the treatment of adult periodontitis has evolved (10-13). Regarding the side effects of systemic antibiotic treatments, local delivery systems have been developed in the last quarter of the 20th century (3,4). Many studies on clinical effects of both systemic and local tetracyclines have been performed. In some of these studies, tetracyclines made no statistically significant difference on probing depths and clinical attachment levels (10,11,14-19) while in others successful clinical results were obtained by tetracycline and minocycline treatments (20-28). These studies evaluated only systemic or local antibiotic treatments with or without mechanical periodontal treatment.

To our knowledge, the literature indicates that no study has been performed that compares the clinical effects of systemic and local doxycycline alone and/or combined with mechanical therapy in the treatment of periodontal disease.

Therefore, the purpose of the present study was to compare the effects of systemic and local doxycycline alone and combined with mechanical periodontal treatment on clinical parameters in patients with chronic periodontitis, and also to compare the effects of doxycycline alone and combined with scaling-root planing versus scaling-root planing alone.

Materials and Methods
Patient selection and clinical studies

The study was performed on 45 subjects (24 females and 21 males) who were clinically and radiographically diagnosed with chronic periodontitis (CP) according to the criteria currently accepted (29). The subjects were selected from patients who sought periodontal treatment at Hacettepe University, Faculty of Dentistry, Department of Periodontology. None of the patients had a systemic disease and none had received antibiotics nor any other medicines or periodontal treatment during the previous 6 months. All of the patients were non-smokers. No periodontal treatment or plaque removal was performed and no oral hygiene instruction was given to the patients that might have changed their periodontal status before the baseline clinical measurements. Plaque removal and oral hygiene procedures were performed after the baseline measurements and continued after the treatments. The patients had at least 16 teeth in their mouth and at least 4 teeth with ≥ 5 mm of probing depths in each quadrant of their upper jaws.

Since the study was designed to compare the effects of systemic and local doxycycline, the subjects were randomly divided into 3 main groups of 15 patients each: systemic doxycycline treatment (SD) group, local doxycycline treatment (LD) group, and the scaling-root planing (SRP) group as controls. In order to compare the antibiotic treatments with and without mechanical treatment, the patients receiving the antibiotic had 2 treatment models: doxycycline treatment alone in 1 quadrant of the upper jaw and doxycycline + SRP treatment in the contralateral quadrant.

With this design the study included 5 treatments in 3 main groups, each including 15 patients: SD treatment alone, SD + SRP, LD treatment alone, LD + SRP, and SRP treatment alone.

Clinical measurements: In order to determine the periodontal status of the patients, probing depth (PD)*, clinical attachment level (CAL), gingival index (GI) (30), sulcular bleeding index (SBI) (31), and plaque index (PI) (32) values were recorded at baseline and repeated 7 weeks after the treatments. Full mouth periapical radiographs were taken from the patients to determine the periodontal bone loss at baseline.

SD and SD + SRP group: This group included 8 females and 7 males with an age range of 30 to 57 years with the mean age of 41.7 years. Before the mechanical treatment, SD was given to these patients at a dosage of 100 mg × 2 the first day and 100 mg × 1 for 14 days. The SRP treatment site was a randomly selected right or left maxillary quadrant from the incisors to 1st molars which had at least 4 teeth with ≥ 5 mm of probing depth and moderate bone loss.

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* Williams periodontal probe, Hu-Friedy, Chicago, IL.

The contralateral quadrant was used to evaluate the results of SD treatment alone and no mechanical treatment was performed. Thus, the patients in this group had 2 study sites: one quadrant for SD treatment alone, and the contralateral quadrant for SD + SRP treatment. SRP was performed under local anesthesia at the end of the 15 days of SD treatment. The area was covered by periodontal dressing for 1 week.

LD and LD + SRP group: Seven females and 8 males, ranging in ages of between 30 to 57 years, and with a mean age of 42.4, were included in this group. The study sites in this group had the same criteria as the SD treatment group. LD gel was injected into the bases of the pockets with special carpule syringes and needles in a randomly selected right or left maxillary quadrant, from incisors to 1st molars. In the contralateral quadrant, the LD + SRP treatment model was performed. LD was applied into the bases of the pockets with special carpule syringes and needles after SRP treatment was completed under local anesthesia. The areas were covered by periodontal dressing for 1 week.

SRP group: This group included a total of 15 patients, 9 females and 6 males, ranging in age from 33 to 61 years old, with a mean age of 42.2 years. These CP patients received only SRP treatment under local anesthesia on a randomly selected maxillary quadrant with the same criteria. The areas were covered by periodontal dressing for 1 week.

After the treatments, the patients were instructed again to perform oral hygiene procedures and professional plaque removal (polishing) was also performed 3 weeks after the treatments.

At the end of 7 weeks, after the measurements were completed, SRP treatments were performed in the quadrants which had received only SD and LD treatments.

Preparation of doxycycline hyclate gel

For this study, a stable controlled-release formulation of doxycycline hyclate for the treatment of periodontal pockets was developed. A gel formulation of doxycycline hyclate, a derivative of tetracycline, was prepared in the laboratory of Hacettepe University, Faculty of Pharmacy, and Department of Pharmaceutical Technology.

In order to protect the stabilization of doxycycline hyclate, an anhydrous carrier formulation was developed in the laboratory. It was formulated as a suspension that was transformed into a release controlled, liquid crystalline semi-solid form when it came into contact with gingival fluid. The system was based on the ability of mixtures of monoglycerids and triglycerids to form a liquid crystalline semi-solid system when coming into contact with gingival crevicular fluid.

In this study, a mixture of glycerile monooleate (GMO) and sesame oil was selected as an anhydrous and nontoxic delivery system for doxycycline hyclate, based on its use in a previous study in which GMO and sesame oil mixture was used as a delivery system for metronidasole (33). Sesame oil, a triglyceride with a low melting point, was used in order to modulate the consistency of the product. The polar swelling lipid GMO forms a highly ordered cubic phase in water which can be used to sustain the release of the drugs (34) and to protect the drugs from chemical instability reactions such as hydrolysis and oxidation (35).

GMO gel is a biodegradable and stable formulation which is administered by a syringe and is transformed into a semi-solid form in the periodontal pocket, adheres to the mucosa and fits well in the pocket. It is a controlled release vehicle for some drugs (33). To prepare doxycycline hyclate gel in GMO and sesame oil mixture, 5% sesame oil was added to 95% of the melted GMO at 60-70°C with continuous stirring. After the vehicle was cooled to room temperature, 10% of doxycycline hyclate was added to the vehicle until a homogenous gel was obtained. Syringes ready for clinical use were then filled with the 10% doxycycline hyclate gel.

Determination of the concentration of doxycycline hyclate gel

After the application of LD to the pockets, GCF samples were harvested at 24 hours and at 7 days. The LD concentrations in these samples were inferred by using a modified disk diffusion assay. *Bacillus cereus* (NCTC 10320) was grown in Mueller-Hinton Broth (MHB) at 35°C in aerobic conditions for approximately 2.5 hours in order to obtain the logarithmic growth phase of the bacteria. Bacterial inoculum was adjusted to obtain turbidity comparable to 0.5 McFarland that was further diluted 1:100 with MHB. This suspension was inoculated on the surface of Mueller-Hinton agar medium. The filter paper strips containing standard antibiotic solutions of LD and GCF samples were placed on the surface of inoculated plates. All of the plates were incubated in aerobic conditions for 18 hours at 35°C. The inhibition zones, which were elyptic, were measured from the long axis. To provide a standard curve, 10 different concentration values were correlated with their corresponding inhibition zone diameters. Approximate concentrations of LD in GCF samples were inferred from this regression curve (36,37). The concentrations of LD were determined to be 225 ± 10 µg/ml at 24 hours, and 20 ± 5 µg/ml at 1 week.

Statistical analysis

The differences of clinical parameters within the time intervals in each group were determined using a *t*-test for paired samples.

In order to compare the groups independently, the comparisons were made among the SD, LD and SRP groups, and the SD + SRP, LD + SRP and SRP groups. The distinct groups of three were used since in the doxycycline groups the upper jaws were symmetrically studied (1 quadrant for doxycycline alone and the contralateral quadrant for doxycycline + SRP), and they were dependent groups. The differences among the groups were determined by one way analysis of variance (one way ANOVA). The homogeneity of variance was tested by the Levenee test. All of the variances were homogenous. When the differences among the groups were significant according to the ANOVA, a post hoc test (Tukey HSD test) was used to bilaterally compare the groups.

Results

Comparisons of clinical parameters between the baseline and 7th week in each group

The mean ± standard error values of the clinical parameters and the significant differences found at the measured time points in all of the groups are given in Table 1. At the 7th week, significant clinical healing was obtained with all treatments. In all of the groups, the mean values of PD, CAL, GI, SBI and PI were significantly reduced compared to the baseline values ($P \leq 0.05$).

SD group

PD and CAL: At baseline the mean PD and CAL values were 4.80 ± 0.19 and 5.37 ± 0.14, respectively. The values were significantly lower at the 7th week compared to baseline (3.67 ± 0.13 and 4.68 ± 0.15) ($P \leq 0.05$).
GI, SBI and PI: At baseline the mean values were 1.82 ± 0.18, 3.16 ± 0.15 and 1.43 ± 0.11, respectively. The scores

Table 1. The comparisons of clinical parameters between the baseline and 7th week in groups (n = 15)

		Baseline X ± SEM	7th week X ± SEM	Mean Difference	SD	SEM	t	p
	PD	4.80 ± 0.19	3.67 ± 0.13	1.13	0.41	0.11	10,606	0.0001
	CAL	5.37 ± 0.14	4.68 ± 0.15	0.69	0.31	0.08	8,677	0.0001
SD	GI	1.82 ± 0.18	1.18 ± 0.10	0.64	0.40	0.10	6.253	0.0001
	SBI	3.16 ± 0.15	2.48 ± 0.12	0.69	0.59	0.15	4,470	0.001
	PI	1.43 ± 0.11	0.85 ± 0.07	0.58	0.38	0.10	5,955	0.0001
	PD	4.82 ± 0.14	2.91 ± 0.10	1.91	0.66	0.17	11.251	0.0001
	CAL	5.47 ± 0.17	4.26 ± 0.12	1.21	0.47	0.12	10.055	0.0001
SD+SRP	GI	1.71 ± 0.17	1.06 ± 0.08	0.66	0.52	0.13	4,889	0.0001
	SBI	3.05 ± 0.14	2.21 ± 0.13	0.84	0.48	0.12	6.732	0.0001
	PI	1.48 ± 0.12	0.75 ± 0.07	0.73	0.47	0.12	5.993	0.0001
	PD	4.56 ± 0.13	3.21 ± 0.09	1.35	0.32	0.08	16.388	0.0001
	CAL	5.47 ± 0.26	4.19 ± 0.20	1.28	0.61	0.16	8.071	0.0001
LD	GI	2.01 ± 0.11	1.13 ± 0.08	0.88	0.55	0.14	6.196	0.0001
	SBI	3.36 ± 0.13	2.34 ± 0.09	1.02	0.48	0.12	8.280	0.0001
	PI	1.59 ± 0.12	0.90 ± 0.04	0.69	0.40	0.10	6.639	0.0001
	PD	4.98 ± 0.17	2.79 ± 0.12	2.19	0.77	0.20	11.027	0.0001
	CAL	5.74 ± 0.25	3.96 ± 0.19	1.77	0.66	0.17	10.371	0.0001
LD+SRP	GI	2.07 ± 0.11	1.05 ± 0.06	1.02	0.39	0.10	10.076	0.0001
	SBI	3.45 ± 0.11	2.16 ± 0.09	1.29	0.31	0.08	16.272	0.0001
	PI	1.55 ± 0.15	0.85 ± 0.05	0.70	0.47	0.12	5.805	0.0001
	PD	4.62 ± 0.16	2.89 ± 0.13	1.72	0.63	0.16	10,534	0.0001
	CAL	5.39 ± 0.20	4.30 ± 0.18	1.10	0.50	0.13	8,436	0.0001
SRP	GI	1.61 ± 0.13	1.07 ± 0.09	0.54	0.49	0.13	4.220	0.001
	SBI	3.02 ± 0.13	2.17 ± 0.06	0.85	0.50	0.13	6,643	0.0001
	PI	1.29 ± 0.09	0.90 ± 0.05	0.40	0.34	0.09	4,534	0.0001

"*t*-test for paired samples": All of the clinical parameters showed significant differences in the 7th week compared to baseline ($P \leq 0.05$). SD: standard deviation, SEM: standard error of mean

were significantly reduced at the 7th week (1.18 ± 0.10, 2.48 ± 0.12, 0.85 ± 0.07) ($P \leq 0.05$) (Table 1).

SD+SRP treatment

PD and CAL: The mean values were 4.82 ± 0.14 and 5.47 ± 0.17 at baseline. At the 7th week, the scores significantly were reduced to 2.91 ± 0.10 and 4.26 ± 0.12, respectively ($P \leq 0.05$).

GI, SBI and PI: The mean scores of these parameters (1.71 ± 0.17, 3.05 ± 0.14, 1.48 ± 0.12 at baseline, respectively) were significantly reduced at 7 weeks after the treatments (1.06 ± 0.08, 2.21 ± 0.13, 0.75 ± 0.07) ($P \leq 0.05$) (Table 1).

LD group

PD and CAL: In this group, at baseline the mean PD and CAL scores were 4.56 ± 0.13 and 5.47 ± 0.26, respectively. At the 7th week the scores were significantly lower than the baseline (3.21 ± 0.09 and 4.19 ± 0.20) ($P \leq 0.05$).

GI, SBI and PI: At baseline, the mean values of these parameters were 2.01 ± 0.11, 3.36 ± 0.13 and 1.59 ± 0.12, respectively. The scores significantly were reduced to 1.13 ± 0.08, 2.34 ± 0.09 and 0.90 ± 0.04 at the 7th week ($P \leq 0.05$) (Table 1).

LD+SRP Treatment

PD and CAL: At baseline the mean PD and CAL were 4.98 ± 0.17 and 5.74 ± 0.25 in this group. At the 7th week the

scores were 2.79 ± 0.12 and 3.96 ± 0.19, respectively. The changes were statistically significant ($P \leq 0.05$) (Table 1). GI, SBI, PI: The mean scores at baseline were 2.07 ± 0.11, 3.45 ± 0.11 and 1.55 ± 0.15, respectively. The scores were reduced to 1.05 ± 0.06, 2.16 ± 0.09 and 0.85 ± 0.05 at the 7th week. The changes were statistically significant ($P \leq 0.05$) (Table 1).

SRP Group

PD and CAL: At baseline, the mean values were 4.62 ± 0.16 and 5.39 ± 0.20, respectively. The scores significantly were reduced to 2.89 ± 0.13 and 4.30 ± 0.18 at the 7th week ($P \leq 0.05$).

GI, SBI and PI: In this group the mean baseline scores were 1.61 ± 0.13, 3.02 ± 0.13 and 1.29 ± 0.09, respectively. At the 7th week the scores were significantly lower compared to baseline (1.07 ± 0 .09, 2.17 ± 0.06 and 0.90 ± 0.05) ($P \leq 0.05$) (Table 1).

Comparisons of clinical parameters among the groups at the measure time points

When the SD, LD and SRP groups were compared, no significant difference in the clinical parameters was found among the groups at baseline ($P > 0.05$) (Table 2). At the 7th week the only clinical parameter which showed significant differences was PD ($P \leq 0.05$). The other clinical parameters, CAL, GI, SBI and PI did not show any statistically significant difference among these groups (P

Table 2. The comparisons of clinical parameters among the groups at baseline and 7th week

	Groups	Baseline				7th week				Tukey HSD	
	n=15	SD	SEM	F	p	SD	SEM	F	p		p
PD	SD	0.72	0.19			0.49	0.13				
	LD	0.50	0.13	0.626	0.539	0.34	0.09	11.571	0.0001	SD-LD	0.019*
	SRP	0.61	0.16			0.49	0.13			SD-SRP	0.0001*
CAL	SD	0.55	0.14			0.59	0.15				
	LD	1.01	0.26	0.066	0.936	0.77	0.20	2.084	0.137		
	SRP	0.76	0.20			0.68	0.18				
GI	SD	0.70	0.18			0.38	0.10				
	LD	0.44	0.11	1.887	0.164	0.30	0.08	0.420	0.660		
	SRP	0.51	0.13			0.34	0.09				
SBI	SD	0.57	0.15			0.46	0.12				
	LD	0.50	0.13	1.520	0.231	0.33	0.09	2.686	0.080		
	SRP	0.51	0.13			0.25	0.06				
PI	SD	0.43	0.11			0.28	0.07				
	LD	0.47	0.12	1.935	0.157	0.16	0.04	0.283	0.755		
	SRP	0.34	0.09			0.19	0.05				

"One way ANOVA" test was used for the comparisons. At baseline, no significant difference was found in any parameter ($P > 0.05$). Therefore "Tukey HSD" test was not used. At 7th week, significant differences were found in PD. *The differences are significant between SD and LD and between SD and SRP groups ($P \leq 0.05$). The other differences are not significant ($P > 0.05$). SD: standard deviation, SEM: standard error of mean

> 0.05). The least PD reduction was obtained by SD alone treatment. LD provided significantly higher PD reduction than SD ($P \leq 0.05$). The difference between SD alone and SRP was also significant. PD reduction, obtained by the SD alone treatment, was significantly lower than SRP alone treatment ($P \leq 0.05$). On the other hand, the difference between LD and SRP alone treatment was not statistically significant at the 7th week ($P > 0.05$) (Table 2). The comparisons of the SD + SRP, LD + SRP and SRP treatments indicated a significant difference between LD + SRP and SRP treatments at baseline. SBI was significantly higher in the LD + SRP group than the SRP alone group ($P \leq 0.05$). The other clinical parameters showed no statistically significant difference among these groups at baseline ($P > 0.05$) (Table 3). At the post-treatment 7th week, no significant difference in any clinical parameter was found among the SD + SRP, LD + SRP and SRP groups ($P > 0.05$) (Table 3).

Discussion

In the present study, significant clinical healings were obtained with all treatment models. PD and CAL values showed significant decreases between the baseline and the 7th week with all treatments. GI, SBI and PI scores also showed significant decreases, often consistent with each other.

The finding that SD and LD alone provided significant decreases even in PD and CAL values indicates the clinical efficacy of SD and LD on clinical healing without mechanical treatment. This finding confirms previous studies, which used systemic or local tetracycline treatments alone and obtained favorable clinical results. Studies with only systemic doxycycline (38), or with only systemic tetracycline treatment in localized juvenile periodontitis patients (39,40) and in adult periodontitis patients (12) obtained reduced pocket depth and/or clinical attachment levels and improved clinical parameters.

In general the data indicate that tetracycline fibers used as a monotherapy without adjunctive scaling and root planing are effective at reducing probing depths and gaining clinical attachment (17,23). Similar findings have been obtained by local doxycycline treatment (27,28). In the present study, the clinical efficacy of the drug (both systemic and local) seems to be a result of the antimicrobial properties of tetracycline/doxycycline. It has been noted that the beneficial effects of systemic antibiotics in progressive periodontitis is most likely due to the suppression of specific periodontal pathogens such as A. a. (1). The antibiotics administered via serum readily reach the microorganisms at the depth of diseased periodontal sites and also reach possible organisms residing within gingiva (6). According to the present findings in

Table 3. The comparisons of clinical parameters among the groups at baseline and 7th week

| | Groups | Baseline | | | | Tukey HSD | 7th week | | | |
	n=15	SD	SEM	F	p	p	SD	SEM	F	p
PD	SD+SRP	0.54	0.14				0.37	0.10		
	LD+SRP	0.64	0.17	1,369	0.266		0.45	0.12	0.315	0.731
	SRP	0.61	0.16				0.49	0.13		
CAL	SD+SRP	0.65	0.17				0.47	0.12		
	LD+SRP	0.96	0.25	0.759	0.475		0.73	0.19	1.248	0.297
	SRP	0.76	0.20				0.68	0.18		
GI	SD+SRP	0.65	0.17				0.32	0.08		
	LD+SRP	0.43	0.11	3,041	0.058		0.23	0.06	0.018	0.982
	SRP	0.51	0.13				0.34	0.09		
SBI	SD+SRP	0.53	0.14				0.51	0.13		
	LD+SRP	0.44	0.11	3.446	0.041	LD+SRP-SRP 0.044*	0.33	0.09	0.068	0.935
	SRP	0.51	0.13				0.25	0.06		
PI	SD+SRP	0.47	0.12				0.26	0.07		
	LD+SRP	0.60	0.15	1,170	0.320		0.21	0.05	1.806	0.177
	SRP	0.34	0.09				0.19	0.05		

"One way ANOVA" test was used for the comparisons. At baseline, significant difference was found in SBI. *The difference is statistically significant between LD + SRP and SRP groups ($P \leq 0.05$). The other differences are not significant ($P > 0.05$). At 7 weeks, no significant difference was found in any parameter ($P > 0.05$). Therefore "Tukey HSD" test was not used. SD: standard deviation, SEM: standard error of mean

the LD group, this healing may be a result of the strong effect of the drug due to its concentrated localization in the area.

In the present study, SD treatment combined with SRP also provided favorable healing that are consistent with previous findings. Systemic tetracycline/doxycycline treatment combined with mechanical treatment has been shown to improve clinical parameters, reduce probing depth, and gain clinical attachment in adult or refractory periodontitis patients (13,41-46). A recent study has shown that the supplementation of fullmouth subgingival debridement with a host-modulating agent, subantimicrobial dose doxycycline (SDD), provides clinically and statistically significant benefits in the reduction of deep pockets in patients with severe periodontitis (47). However, other studies have shown good results without the use of an adjunctive antibiotic (48,49).

The present results of LD treatment combined with SRP are also consistent with some of the previous studies, which obtained favorable clinical results with locally applied tetracycline combined with mechanical treatment in maintenance patients who did not respond to scaling and root planing (25) or in patients who had non-responsive sites (50,51).

Comparisons of the groups indicated no significant difference among the groups at baseline. At the post-treatment 7th week, the significant differences found among the groups were only in the PD values. SD alone provided the least pocket reduction during this period. Pocket reduction obtained by SD alone was significantly lower than LD alone and SRP alone. On the other hand, there was no significant difference between LD alone and SRP alone, between SRP alone and SRP combined with SD or LD. The latter finding suggests that there is no significant difference in PD reduction between mechanical treatment alone and mechanical treatment combined with doxycycline. These findings are consistent with the findings of several previous studies in which no significant difference could be found between mechanical treatment combined with tetracycline or minocycline and mechanical treatment alone (10,11,16). However, contrary findings have also been reported. In these studies systemic tetracycline treatment combined with scaling, reduced pocket depth, attachment level or microbial parameters better than scaling alone (6,42,52).

Conflicting data have also been reported for local tetracycline treatments. Our findings are in accordance with those that indicated no advantage to adjunctive local tetracycline or no significant difference in pocket depth reduction when compared to scaling alone (15,17). On the

point of comparing local antibiotic/doxycycline treatment alone to mechanical treatment, our findings are in contrast with those which showed that tetracycline fibers alone provided better results than scaling alone (19) but in accordance with those which showed that there was no statistically significant difference between the doxycycline polymer alone and root planing alone (53) or that local tetracycline alone was equally effective as scaling alone (54) with regards to reducing probing depth and gaining clinical attachment. It must be added here that the successful clinical healing results obtained both by SD and LD alone and combined with SRP may also be attributed to non-antimicrobial properties of doxycycline. In several studies, the inhibitor effects of doxycycline on matrix degrading MMP activities have been demonstrated (7,8). The results have indicated that this host-modulating antibiotic as an adjunct to SRP has also provided more successful clinical healing results than SRP alone (47,55). Recently, one of these studies has shown that improvements in PD and CAL were significantly greater with adjunctive SDD than with adjunctive placebo and it was concluded that the adjunctive use of doxycycline with SRP is more effective than SRP alone, which is in contrast to our findings (55). However, in those studies, low-dose doxycycline treatments were used for much longer time periods (6-9 months).

When the clinical effects of SD and LD alone were compared, PD values in the LD group were significantly lower than the SD group indicating a higher PD reduction with LD. However, no significant difference was found between systemic and local administrations of the drugs when combined with SRP, indicating the stronger effect of mechanical periodontal treatment on clinical healing. To date, 4 studies have compared the efficacy of local drug delivery and administration of systemic antibiotics (56-59). In one of these studies, no significant difference was found between treatments with respect to probing depth reduction and increase of clinical attachment (58). Similarly, others found that there was no difference in clinical results when application of local metronidazole was compared to systemic metronidazole (56). Purucker et al. (59) have compared the clinical effects of systemic amoxicillin/clavulanic acid treatment versus local tetracycline therapy 3 months after SRP treatment and concluded that the local delivery of tetracycline by a fiber or the systemic administration of amoxicillin/clavulanic acid produced similar clinical outcomes. However, similar to our findings, in another study local metronidazole provided better results than systemic metronidazole with regard to bone deposition when assessed by subtraction radiography (57).

In the present study, the higher PD reduction with LD

alone compared to SD alone may be due to its concentrated localization in the area resulting in a stronger antimicrobial effect. It is known that the local route of antibiotic administration can accomplish much higher therapeutic doses in subgingival sites than those possible by systemic therapy (1,3,4,60). It has also been noted that the substantivity of tetracycline to root surfaces is responsible for the prolonged presence of tetracycline in the periodontal pocket (61).

However, on the other hand, millimetric measurement of pocket depth is far from showing the biochemical, microbiological and immunological aspects of the pocket environment and periodontal tissues. The microbial composition of subgingival flora is one of the most important factors that affects periodontal disease activity in patients. It is necessary to perform a post-treatment microbiological analysis of the subgingival microflora. This is particularly important when treating progressive periodontitis (1). It has been shown that systemic tetracycline administration is capable of eradicating periodontal A. a. (6) but locally administered tetracycline is not (38). In the present study, microbial analysis before and after treatments were not included in the study design since the purpose was to evaluate the clinical results only. The reason for including antibiotic treatments alone in the present study was to demonstrate and compare the capabilities of the drugs to promote clinical healing. From this point of view, doxycycline treatment alone is not a treatment model but is a means of measuring the clinical efficacy of SD and LD alone.

In conclusion, the results indicated that the only clinical parameter which showed statistically significant differences among different treatments was PD. SD alone provided the lowest PD reduction. When SD and LD were compared, LD provided significantly higher PD reduction than SD. However, when combined treatments were compared, no significant difference was found between the SD + SRP and LD + SRP treatments. There was also no significant difference between mechanical treatment alone and mechanical treatment combined with doxycycline. SD showed lower PD reduction than SRP alone while no significant difference was found between LD alone and SRP alone, suggesting that LD alone seems to be as effective as mechanical treatment on PD reduction.

According to the present findings it seems clear that mechanical treatment is essential for periodontal therapy. However, it has been noted that if the microbiological or clinical analyses indicate persistent pathogenic infection, antibiotic therapy should be considered. Although LD therapy seems to be more effective than SD on PD reduction, based on the present study it is unknown whether local therapy affects pathogens located within the periodontal tissues. It has been suggested that chronic periodontitis patients that demonstrate continuing breakdown despite mechanical/surgical therapy often stabilize clinically after appropriate systemic antibiotic administration (1). Antibiotic therapy combined with systematic mechanical treatment generally has been noted to be a beneficial therapeutic approach in refractory or recurrent patients/sites previously unsuccessfully treated with solely conventional therapy (2).

In summary, our results suggest that LD + SRP may be a more preferable treatment model in moderate or recurrent chronic periodontitis than SD + SRP when the side effects of systemic treatment are also considered.

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