



Evaluation the Effect of Systemic Azithromycin Adjunctive Therapy in Moderate to Severe Chronic Periodontitis

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Abstract

Background: Chronic periodontitis is an inflammatory disease of periodontal tissues. This disease occurs due to accumulation of subgingival microbial biofilm resulting in pocket formation and bone loss. Because of bacterial invasion, therapeutic role of antibiotics is an important part of periodontitis treatment. The aim of the current study was to evaluate the effect of adjunctive azithromycin therapy in nonsurgical treatment of moderate to severe chronic periodontitis.

Methods: In this double blind placebo-controlled, randomized clinical trial, 40 patients with moderate to severe chronic periodontitis were randomly divided into 2 groups. After full-mouth scaling and root planing (SRP), azithromycin 500 mg was given once a day from the first day of SRP in the SRP group and the control group were given placebo tablets. Gingival index (GI), plaque index, probing depth (PD), and clinical attachment loss (CAL) were evaluated at baseline and 2 weeks, one month and 3 months later. *T* test and Mann-Whitney test were used to do data analysis.

Results: Azithromycin had no effect on plaque index. Statistically significant effects could be seen on gingival index at first week, Clinical attachment loss at 2 weeks and probing depth at 1 month.

Conclusions: Azithromycin may have positive therapeutic effects and can be used as adjunctive therapy in nonsurgical treatment of moderate to severe periodontitis.

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Background

Chronic periodontitis is an inflammatory disease of periodontal tissues. It is developed by sub-gingival biofilm microorganisms and results in pocket formation and bone loss (1). Chronic periodontitis is a multifactorial disease but bacteria play a more important role in its pathogenesis. Pathogenic bacteria of microbial plaque are known as the main cause of periodontitis (2-4). Mostly gram-negative rods and sprockets exist in deep periodontal pockets, whereas gram-positive bacteria exist in normal sulcus (5).

The basic treatment plans for treatment of chronic periodontitis is oral hygiene instruction (OHI) and elimination of local irritation factors such as plaque and calculus via mechanical scaling and root planing (SRP) of teeth. This treatment returns the sulcus microbial flora to normal microflora and promotes periodontal health by reducing probing pocket depth and improving attachment levels (6,7). However SRP has certain limitations in areas such as furcation and deep pockets and with respect to complete elimination of tissue invasive bacteria (8). Antibiotic therapy is considered as an important and necessary adjunctive treatment in some patients because of bacterial invasion into gingival tissues. Therefore

Highlights

- ▶ Azithromycin could be considered as an antibiotic of choice and an adjunctive therapy for nonsurgical phase of treatment in periodontitis.

mechanical and chemical therapies are sometimes necessary for treatment of chronic periodontitis (9). Systemic antibiotic prescription as an adjunctive treatment of periodontitis has been demonstrated to improve healthy clinical periodontal parameters (9,10). Some of these agents can secret in gingival crevicular fluid from oral administration. Tetracycline group of antibiotics and combination of amoxicillin and metronidazole are the most commonly prescribed antibiotics for non-surgical therapy by clinicians (11,12). However, recently as meta-analysis has confirmed the effectiveness of amoxicillin-metronidazole as an adjunctive therapy to SRP in chronic periodontitis patients so that this treatment has become the first choice for most dentists (13). However, because the drugs should be taken four times a day for 2 weeks, this treatment requires high patient compliance and may

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result in emergence of resistant species and unwanted side effects.

Azithromycin is a member of the azalides, a class of macrolide antibiotics, and is used in the treatment of many bacterial infections such as middle ear infections and pneumonia (14-16). This antibiotic has many useful properties that may probably be important to make it a treatment of choice for periodontal infections. It has a wide spectrum of effects including those on anaerobes and gram-negative bacteria (17). Azithromycin also penetrates well into dental biofilm (18,19). It has been shown that the concentration of azithromycin in periodontally diseased tissue is significantly higher than that in normal gingival tissues (20). It is slowly released into the tissue, and has a long half-life in periodontal tissues (20). It leads to lower resistance in comparison to other antibiotics for chronic periodontitis and can be prescribed once daily for 4-7 days (21). It has also been shown that neutrophils and macrophages uptake it in inflamed tissues so drug concentration is preserved in these areas even after decreased serum concentration (22,23). Azithromycin has few side effects that are generally mild such as interaction with warfarin. It should also be prescribed with caution in patients predisposed to cardiovascular disease (24-27). Currently the reports are conflicting on the efficacy and appropriate doses of this antibiotic as an adjunct to periodontal therapy.

The aim of this study was to investigate the effect of azithromycin adjunctive therapy to SRP in comparison with SRP alone in the treatment of moderate to severe chronic periodontitis.

Materials and Methods

The ideal sample size to ensure adequate power for a randomized clinical trial was calculated based on previous studies as 17 subjects for each group to provide an 80% power with an α of 0.05. Accordingly, a total of 40 patients were randomized to 2 groups given the potential exclusion and dropouts during the trial.

Patients were enrolled according to the following inclusion and exclusion criteria and after signing informed consent to participate in the study. Inclusion criteria were lack of smoking, minimum age of 18 years, healthy systemic condition, presence of at least 20 teeth, and diagnosis of moderate to severe chronic periodontitis, presence of at least one pocket with pocket probing depth (PPD) >5 mm per quadrant with bleeding on probing (BOP). The exclusion criteria were history of subgingival periodontal therapy, pregnancy, breastfeeding, poor patient compliance, antibiotic therapy in the last 3 months, allergic reactions to macrolides, compromised immunity system, warfarin or cyclosporine consumption, plaque index of more than 35% and any antibiotic therapy during the study.

All patients signed an informed consent form to participate in the study. Subgingival scaling was performed

in a single session for all the patients and OHI was given to all, including correct Flossing and Modified Bass brushing technique. The patients were asked not to use any type of mouthwash during the study. Sample randomization was performed by a person who did not contribute to the study, azithromycin or placebo capsules were placed in envelopes with a code written on it. Randomized codes were given to patients. SRP and systemic adjunctive azithromycin treatment was considered as test group receiving three 500 mg azithromycin capsules once a day for 3 consecutive days. The control group received SRP with 3 placebo capsules.

Clinical periodontal parameters of probing depth (PD), gingival index (GI) and clinical attachment loss (CAL) were examined at baseline and the data recorded by a blinded examiner using a six-point scale for each tooth (mesiobuccal, buccal, distobuccal, mesiooral, oral, and distooral) with a standard William's periodontal probe. Plaque index was recorded by disclosing agent in each follow-up session. GI was coded as 1, 2 or 3 according to BOP and gingival inflammation

Periodontal examinations were conducted at two weeks, 1 month and 3 months after treatment and beginning of antibiotic therapy. In all sessions, patients were asked if they had used any other type of antibiotics and were excluded from the study if they had used.

t-test and Mann-Whitney test were used to analyze the data. SPSS software version 18 was used to conduct data analysis at a significance level of 0.05.

Results

Forty patients were enrolled in this study with a mean age of 33.7 ± 10.7 in the control group and 35.8 ± 12.7 in the test group. 45% of the control group and 50% of the test group were male.

Gingival Index

Mean GI was 1.65 in the control group and 1.58 in the test group at baseline, with no significant difference. GI was significantly lower in the test group at 1-month and 3-month follow-ups (Table 1, Figure 1).

Clinical Attachment Loss

There was no significant difference in CAL between the studied groups at baseline according to the Mann-Whitney test results. Significantly lower levels in the test group was recorded at 2-week, 1-month and 3-month follow-ups ($P < 0.05$, Table 2, Figure 2).

Probing Depth

Significant differences were seen in PD at 1-month and 3-month follow-ups between the 2 groups ($P < 0.05$, Table 3, Figure 3).

Discussion

Chronic periodontitis is a destructive disease of

Table 1. Comparison of Gingival Index in the Studied Groups in Different Evaluation Times

Time	Group	Mean	SD	P Value
Baseline	Control	1.65	0.4	0.087
	Test	1.58	0.2	
Two weeks	Control	1.45	1.4	0.229
	Test	1.23	1.2	
One month	Control	1.41	0.2	0.052
	Test	1.08	0.1	
Three months	Control	1.45	0.3	<0.001
	Test	0.91	0.2	

Table 2. Comparison of Clinical Attachment Loss in the Studied Groups in Different Evaluation Times

Time	Group	Mean	SD	P Value
Baseline	Control	1.81	0.84	0.063
	Test	1.27	0.80	
Two weeks	Control	0.74	0.68	0.049
	Test	0.31	0.49	
One month	Control	0.49	0.66	0.046
	Test	0.08	0.28	
Three months	Control	0.44	0.58	0.013
	Test	0.03	0.13	

Table 3. Comparison of Probing Depth in the Studied Groups in Different Evaluation Times

Time	Group	Mean	SD	t	P Value
Baseline	Control	2.46	0.31	-0.870	0.723
	Test	2.56	0.33		
Two weeks	Control	2.16	0.21	1.479	0.740
	Test	2.03	0.30		
One month	Control	2.11	0.34	2.951	0.045
	Test	1.81	0.26		
Three months	Control	2.25	0.23	7.615	<0.001
	Test	1.69	0.21		

periodontal supporting tissues caused by sub-gingival bacterial biofilm. SRP and mechanical debridement is the basic treatment for this condition but additional treatments are sometimes needed because of bacterial invasion into the surrounding tissues (1-3). Azithromycin seems to be an appropriate choice for periodontitis adjunctive therapy because of certain advantages such as longer half-life time, short consumption period, and anti-inflammatory effect. We investigated azithromycin's effect in non-surgical periodontal therapy in periodontal patients in a double-blind clinical trial.

The results indicated a significant effect of adjunctive

use of azithromycin on GI at 1 week, CAL after 2 weeks and PD after 1 month. No allergic reactions or drug side effects were reported during the study.

Our results were in accordance with previous studies; a systematic review by Zhang et al has also confirmed the positive effect of azithromycin used as an adjunct to SRP on reducing PD, BOP and improving attachment level, particularly in initially deep PD sites (28). Mascarenhas et al have conducted a study on smokers suffering from periodontitis. PD and CAL were improved significantly whereas GI showed no significant changes that can be related to absence of obvious gingival inflammation in smokers (29).

Pradeep et al also evaluated the effect of azithromycin on PD and CAL. In their study mean PD was obtained 2.13 ± 0.35 for control group and 2.53 ± 0.52 for test group. CAL was 0.6 ± 0.6 for control and 1.07 ± 0.7 for test group which are similar to our results (30). Gomi et al also evaluated GI, CAL and PD variables and achieved the same results as our study's (31).

However Sampaio et al found no significant differences in PD and CAL after 1 year. This inconsistency can be related to poor patient compliance, different drug doses and inclusion of a group with no deep pockets (32).

Saleh et al in a study to compare SRP alone with SRP and adjunctive amoxicillin and metronidazole (A+M) and SRP with azithromycin, observed that A+M caused a higher reduction in PPD compared to azithromycin in all sites studied (33).

Although systemic azithromycin is a drug with well-known antibacterial properties, it also possesses additional anti-inflammatory and immune-modulating effects making it a drug of choice for treatment of periodontitis (34). By influencing the production of cytokines, systemic azithromycin has a dampening effect on the pro-inflammatory response. Furthermore, the majority of cells involved in both the innate and adaptive immune responses are influenced when systemic azithromycin is administered (35).

Azithromycin has few side effects and low bacterial resistance. More importantly better patient compliance can be achieved by its prescription once a day and it can be more easily used as adjunctive therapy for moderate to severe nonsurgical phase of treatment in periodontitis patients. We suggest conducting additional studies to compare the results of azithromycin versus other antibiotics used in periodontitis as adjunctive therapy (36).

Conclusions

Azithromycin has few side effects, low risk of bacterial resistance and better patient compliance. Based on our results adjunctive use of azithromycin could result in positive outcomes compared to SRP alone in PD, GI and CAL.

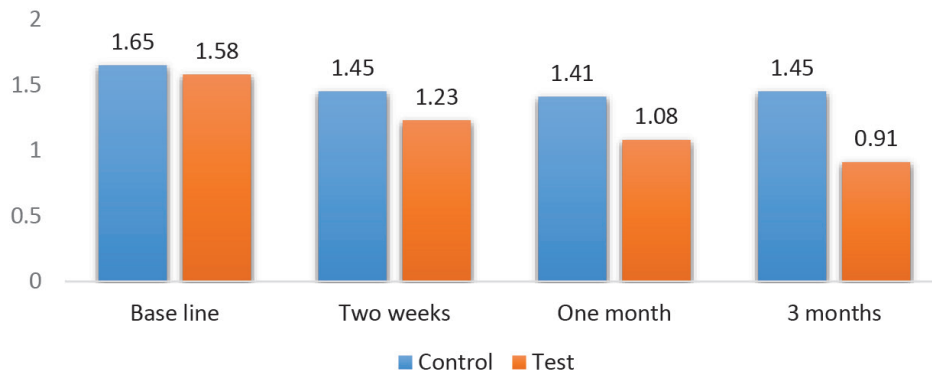


Figure 1. Comparison of Gingival Index in the Studied Groups Due to Evaluation Time.

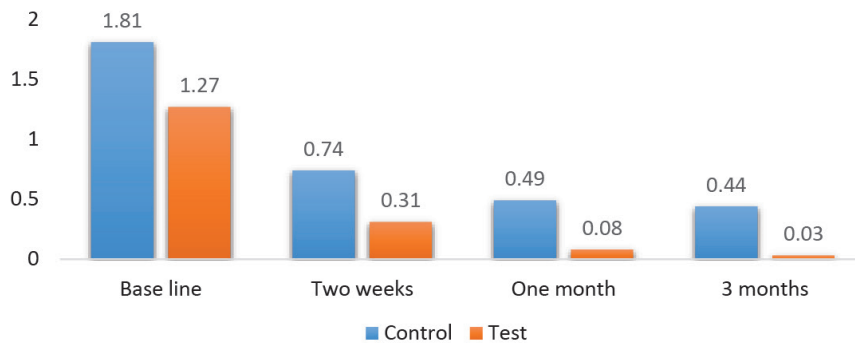


Figure 2. Comparison of Clinical Attachment Loss in the Studied Groups Due to Evaluation Time.

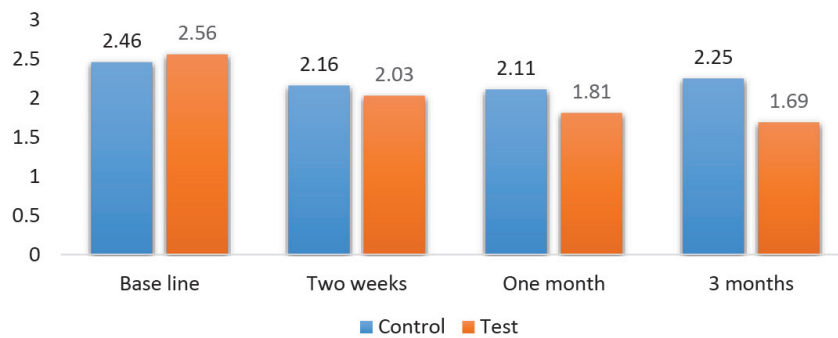


Figure 3. Comparison of Probing Depth in the Studied Groups Due to Evaluation Time.

Authors' Contribution

LG: study conduct, supervisor, article edition. SM: study implementation, data analysis. NR: manuscript preparation. OT: article edition.

Ethical Statement

The protocol of the present study was approved by the Ethics Committee of the University and has been registered in the Iranian Registry of Clinical Trials (Registry number: iRCT2014071518493N1).

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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