Comparison of the Efficacy of Short-Term and Long-Term Azithromycin Regimen with Metronidazole and Amoxicillin for Treatment of Moderate Chronic Periodontitis in Adults

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Abstract

Objective: Administration of amoxicillin and metronidazole along with scaling and root planning (SRP) is an effective adjunctive therapy for chronic periodontitis. Studies have shown that administration of azithromycin is also effective for treatment of chronic periodontitis. This study aimed to compare the effect of short-term and long-term azithromycin regimen with amoxicillin and metronidazole for treatment of moderate chronic periodontitis in adults.

Methods: This experimental study was carried out on 75 patients with moderate chronic periodontitis aged 35-50 yrs. with at least one pocket with a probing depth of 4-6 mm and attachment loss of 3-4 mm in each quadrant. Loe and Silness Gingival Index (GI), Modified Papillary Bleeding Index (MPBI) of Barnett, Loe and Silness Plaque Index (PLI), Probing Pocket Depth (PPD) and Attachment Loss (AL) were calculated at 0, 2 and 4 days, 6 weeks and 2 and 3 months after therapy. The patients underwent SRP and assigned to three groups. Group one received 250 mg metronidazole plus 250 mg amoxicillin 3 times a day for 7 days. Group 2 received 500 mg azithromycin twice daily for 7 days and group 3 received 250 mg azithromycin once a day for one month. Data were analyzed using ANOVA and Repeated Measures ANOVA.

Results: PLI, MPBI, GI, PPD and AL parameters showed a significant reduction in all groups at all understudy time points ($p<0.05$). The reduction in BI, GI and PLI parameters was greater in group 3 compared to groups 1 and 2 ($p<0.05$); but, no significant difference was observed between groups 1 and 2 in this respect. A greater reduction in PPD was noted in groups 2 and 3 compared to group 1 ($p<0.05$). AL showed a significant reduction in group 3 compared to groups 1 and 2 only in the final follow-up session ($p=0.042$).

Conclusion: Antibiotic therapy regimens were all effective for treatment of chronic periodontitis but the magnitude of improvement was greater in long-term azithromycin group compared to others.

Key words: Adjunctive periodontal therapy, Amoxicillin, Chronic periodontitis, Long-term azithromycin, Metronidazole, Short-term azithromycin.

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Introduction:

Chronic periodontitis is the most common form of periodontitis causing bone loss and attachment loss. This disease has a slow progression and is more prevalent in adults (1). Calculus and bacterial plaque are among the etiologic factors; thus, treatment is mainly comprised of removal of supra- and sub-gingival calculus to reduce bacterial content. However, despite this treatment, progressive attachment loss continues in some patients indicating that mechanical treatment is not successful in reducing some periodontal pathogens. Therefore,

antibiotic therapy is recommended to reduce the number of these resistant pathogens (2). Metronidazole-amoxicillin regimen is an effective systemic antibiotic therapy for chronic periodontitis (3, 4). Metronidazole is a bactericidal antibiotic effective against anaerobes (3). Amoxicillin belongs to penicillin family and has a broad-spectrum of action against gram-positive and gram-negative bacteria (3). MoeinTaghavi *et al.* in 2007 reported a significantly greater improvement in patients subjected to 7 days of treatment with metronidazole-amoxicillin regimen compared to the control group receiving placebo (2). Rooney *et al*. in 2002 compared the therapeutic effects of metronidazole-placebo (MP), amoxicillin-placebo (AP), metronidazole-amoxicillin (AM) and placebo alone (PP). The best results were obtained in the AM group. Also, the results of AP and MP groups were better than PP (4). Kaner *et al*. in 2007 showed that in adults with generalized aggressive periodontitis, treatment with metronidazole-amoxicillin was associated with more favorable clinical outcome compared to chlorhexidine chips (5). Valenza *et al*. in 2009 stated that combination of metronidazole-amoxicillin was effective for treatment of chronic periodontitis but its effect on some bacterial strains was transient (6).

In the recent years, due to higher patient compliance tomono-drug regimens and lower frequency of drug intake per day, use of azithromycin for treatment of periodontitis has attracted some attention. Azithromycin is a macrolide effective against anaerobes and gram-negative bacilli. Furthermore, its therapeutic effects remain for a long time after drug intake in the gingival crevicular fluid. Thus, it may be administered along with SRP and after it for treatment of periodontitis (3). Gomi *et al*. in 2007 evaluated the effective concentration of azithromycin in the gingival crevicular fluid and demonstrated that after a 3-day treatment course, drug concentration was still effectively high in gingival crevicular fluid and lasted until day 14 (7).

Considering the fact that azithromycin can be administered as monotherapy and several studies have shown the long-lasting presence of its therapeutic concentrations in the gingival sulcus, the present study aimed to evaluate the effect of long-term azithromycin regimen on patients with chronic periodontitis and compare it with short-term azithromycin and metronidazole-amoxicillin therapeutic regimens.

Methods:

This experimental study was conducted on 75 patients aged 35-50 yrs. presenting to the Periodontology Department of Babol University of Medical Sciences, School of Dentistry. Patients were selected by non-randomized convenient sampling. The study design was approved in the Ethics Committee of Babol University of Medical Sciences. The inclusion criteria were suffering from moderate chronic adult periodontitis with at least one pocket with 4-6 mm depth and 3-4 mm attachment loss in each quadrant. The exclusion criteria were smoking, systemic diseases, drug intake and periodontal abscess. PPD, PLI, MPBI, GI and AL were measured in patients' Ramfjord teeth (8). After obtaining a written informed consent from patients, Bass technique of brushing was instructed to patients to create a reference index and eliminate the confounding effect of PLI. Patients were provided with Oral B toothbrush and Crest toothpaste. After two weeks, patients were visited again and if their PI was less than 30%, they entered the study. The mentioned indexes were once again measured and patients received SRP. Patients were non-randomly assigned to 3 groups receiving different antibiotic regimens. Patients in group 1 comprised 12 females and 13 males with a mean age of 43.7 yrs. and received 250 mg metronidazole (Tehran Chimie Pharmaceutical

Co., Tehran, Iran) and 250 mg amoxicillin (Kosar Pharmaceuticals, Tehran, Iran) 3 times a day for 7 days. The second group included 11 females and 14 males with a mean age of 42.5 yrs. and received 500 mg azithromycin (Farabi Pharmaceuticals, Tehran, Iran) twice a day for 7 days. Group 3 comprised 11 females and 14 males with a mean age of 40.9 yrs. and received 250 mg azithromycin (Tolid Daru, Co., Tehran, Iran) once a day for one month. At 2, 4 and 6 weeks and 2 and 3 months the mentioned clinical parameters were measured again in patients' Ramfjord teeth. Obtained data were compared between different groups using ANOVA and Repeated Measures ANOVA.

Results:

Table 1 shows the PLI values in understudy groups at different time points.

Table 1- The mean and standard deviation of PLI in the understudy groups at different time points

Time/Treatment	Day 0	Day 14 (initiation of treatment)	Day 28 (2 weeks)	Day 42 (4 weeks)	Day 56 (6 weeks)	Day 74 (2 months)	Day 104 (3 months)
Met-Amoxi (1)	1.13 (0.32)	0.56 (0.13)	0.5 (0.11)	0.57 (0.12)	0.57 (0.14)	0.57 (0.13)	0.63 (0.18)
Az short (2)	0.13 (0.39)	0.53 (0.08)	0.55 (0.09)	0.58 (0.103)	0.55 (0.07)	0.6 (0.12)	0.64 (0.11)
Az long (3)	1.3 (0.35)	0.44 (0.11)	0.38 (0.14)	0.38 (0.12)	0.45 (0.14)	0.44 (0.17)	0.41 (0.15)

At all time points, a significant difference was noted between the long-term azithromycin and metronidazole-amoxicillin and short-term azithromycin groups ($p<0.05$). But no significant difference was found between the metronidazole-amoxicillin and short-term azithromycin. Significant differences were found between different groups at different time points ($p<0.0001$ for intragroup and $p<0.001$ for inter-group comparisons). A significant reduction was observed in PLI in long-term azithromycin compared to metronidazole-amoxicillin and short-term azithromycin groups (0.89±0.39 versus 0.50± 0.34 and 0.49±0.43, respectively; $p>0.0001$). According to the results of Table 2, no significant difference was found in GI between different groups at the onset of treatment and 2 weeks post-therapy. However, at 2 months, a significant difference was noted between the two groups of metronidazole-amoxicillin and short-term azithromycin ($p<0.05$). Furthermore, according to the results of Repeated Measures ANOVA, significant differences existed between different groups and also within groups at different time points ($P<0.0001$ for intragroup and $p<0.006$ for intergroup comparisons). A significant reduction was also observed in GI in long-term azithromycin group compared to metronidazole-amoxicillin and short-term azithromycin groups (0.90(0.35) versus 0.66(0.32) and 0.60(0.38), respectively; $p=0.011$).

Table 2- The mean and standard deviation of GI in the understudy groups at different time points

Time/Treatment	Day 0	Day 14 (initiation of treatment)	Day 28 (2 weeks)	Day 42 (4 weeks)	Day 56 (6 weeks)	Day 74 (2 months)	Day 104 (3 months)
Met-Amoxi (1)	1.4 (0.22)	1.3 (0.3)	0.9 (0.16)	0.8 (0.17)	0.8 (0.19)	0.8 (0.21)	0.7 (0.26)
Az short (2)	1.22 (0.32)	1.17 (0.19)	0.86 (0.14)	0.75 (0.13)	0.7 (0.15)	0.61 (0.15)	0.62 (0.17)
Az long (3)	0.34 (0.27)	1.34 (0.32)	0.75 (0.28)	0.65 (0.24)	0.53 (0.16)	0.49 (0.21)	0.43 (0.22)

MPBI (Diagram 1), at 2 weeks after treatment in long-term azithromycin group was significantly different than in short-term azithromycin and metronidazole-amoxicillin groups ($p<0.0001$ for both). However, this parameter was not significantly different at initiation of treatment and at 4 and 6 weeks. At 2 months post-treatment, a significant difference was only

detected between the two groups of short-term and long-term azithromycin (p<0.048) and at 3 months, the differences between all three groups were statistically significant in this regard (p<0.05).

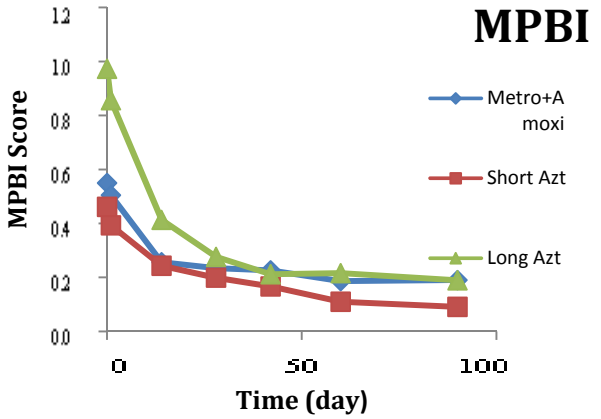

Diagram 1- The mean MPBI in understudy groups at different time points

According to Repeated Measures ANOVA, MPBI values were significantly different between the understudy groups at different time points (p<0.0001 for intragroup and p<0.006 for inter-group comparisons). A greater reduction was observed in MPBI in long-term azithromycin group than in metronidazole-amoxicillin and short-term azithromycin groups (0.78(0.37) versus 0.36(0.29) and 0.37(0.19), respectively; p>0.0001). As presented in Diagram 2, PPD was not significantly different at 2 and 3 months. A significant difference was noted in this parameter at the initiation of treatment and at 2 and 4 weeks between the metronidazole-amoxicillin group and short-term and long- term azithromycin groups (p<0.05). At 6 weeks, a significant difference was found only between metronidazole-amoxicillin and long-term azithromycin groups (p<0.05).

According to the results of Repeated Measures ANOVA, significant differences existed in PPD values between different groups and within each group at different time points (p<0.0001 for intragroup and p<0.005 for inter-group comparisons; p<0.005). Reduction in PPD was 0.43(0.34), 0.24(0.23) and 0.41(0.15) in long-term azithromycin, metronidazole-amoxicillin and short-term azithromycin groups, respectively.

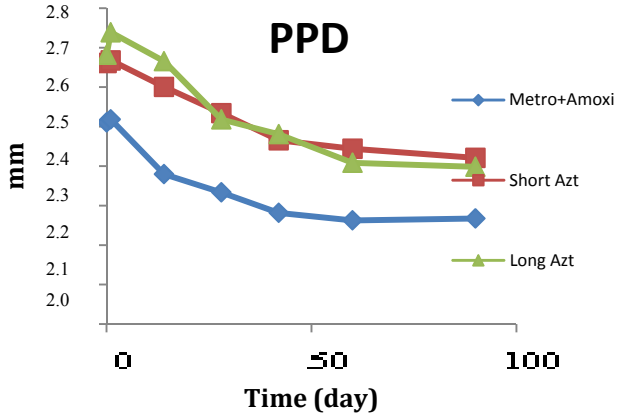

Diagram 2- The mean PPD in the understudy groups at different time points

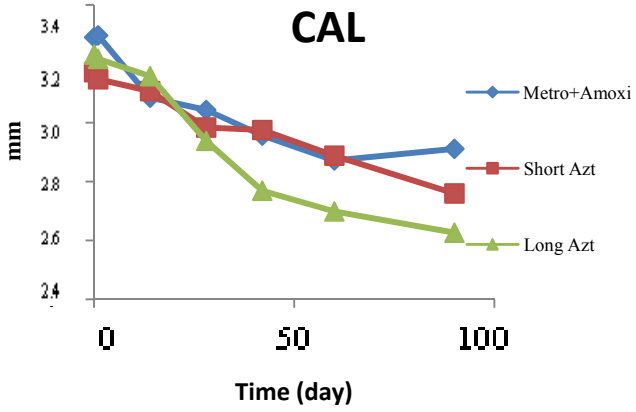

Diagram 3-The mean AL in understudy groups at different time points

According to the results of ANOVA, the only significant difference in AL was at day 104 between metronidazole-amoxicillin and long-term azithromycin groups (p<0.042). Furthermore, according to Repeated Measures ANOVA, no significant differences existed between different groups but the differences within each group at different time points was statistically significant in this regard (Diagram 3).

Discussion:

SRP alone is not sufficient for treatment of periodontitis and adjunctive therapiessuch as topical and systemic antibiotic administration are also required (8-10). The effect of different antibiotics on periodontitis has been extensively studied to find a more efficient monotherapy for this purpose to increase patient compliance. In our study, three different antibiotic regimens (metronidazole plus amoxicillin, short-term azithromycin and long-term azithromycin) along with mechanical treatment were compared. Based on the obtained results, in all three groups periodontal parameters improved; but, significant differences were found in this respect between the metronidazole+ amoxicillin and short-term and long-term azithromycin groups. In general, significant differences were noted between the three groups. It seems that all three regimens were effective against chronic periodontitis.

The mean PLI significantly decreased in all groups at different time points. The metronidazole+ amoxicillin and short-term azithromycin groupshad a significant difference in this regard with long-term azithromycin. In the latter group, greater improvement was observed. Considering the fact that similar oral health instructions were given to patients and they were provided with similar toothbrush and toothpaste, this reduction may be due to higher attention paid to plaque control due to the longer use of antibiotics or the more efficient inhibitory effect of long-term azithromycin on biofilm formation reducing the formation of bacterial plaque.

In terms of MPBI and GI, significant reductions were found in the understudy groups at different time points. Significant differences existed in this respect between the metronidazole-amoxicillin group and short-term and long-term azithromycin groups and the reductions were greater in the latter group.

PPD also decreased in all groups at different time points. The difference in this regard between the metronidazole-amoxicillin with short- and long-term azithromycin was statistically significant bot no such difference was noted between the short-term and long-term use of azithromycin. Reduction in clinical AL in each group at different time points was significant as well. But the difference between groups was not statistically significant. The only significant difference in this regard was noted at 3 months (the final follow up session) between the long-term azithromycin and metronidazole-amoxicillin groups that indicates the longer lasting effect of treatment with long-term azithromycin.

Haffajee *et al*. in 2008 evaluated different periodontal therapies (SRP alone, SRP+ azithromycin for 3 days, SRP+metronidazole for 14 days and SRP+ doxycycline for 3 months) for the treatment of chronic periodontitis. Clinical parameters improved in all groups but greater improvement was observed in SRP +3 days of azithromycin and SRP+14 days of metronidazole. Both regimens significantly reduced counts of red complex species at 2 weeks. Percentage of resistant species significantly increased in all treatment groups at 12 months (10). Smith *et al*. in 2002 performed 3 sessions of SRP at 0, 1 and 2 weeks. At 2 weeks, patients were assigned to two groups of azithromycin alone for 3 days and placebo. At 22 weeks, PPD and BOP significantly decreased in azithromycin group compared to SRP alone. This reduction was especially significant in areas with pockets deeper than 5 mm (8). In a study by Hass *et al*. in 2008 two groups of periodontitis patients receiving SRP+ placebo and SRP+ single dose azithromycin were compared for 3 days. The two groups were not significantly different in terms of reduction in PI, BOP and supra-gingival calculus but the clinical attachment level and PPD significantly decreased in both groups. These reductions were

greater in group 2. Thus, azithromycin administration is considered as an effective adjunctive therapy (11). No significant improvement in BOP and PI parameters in Hass *et al*. study (2008) in comparison to ours may be attributed to the longer treatment course with azithromycin in our study.

Some previous studies have yielded results similar to ours. Dastoor *et al*. in 2007 compared the efficacy of periodontal surgery+placebo with that of periodontal surgery plus azithromycin administration for 3 days in smoker moderate and severe periodontitis patients and showed that in each group, a significant reduction occurred in CAL, PPD and BOP in surgical sites but no significant difference existed between the two groups. However, they concluded that azithromycin could be effective for facilitating wound repair and reducing gingival inflammation and number of bacterial pathogens (12). The reason for insignificant reduction in CAL, PPD and BOP in the mentioned study may be conduction of surgery and selection of smoker patients; whereas, smoking was an exclusion criterion in our study. Our study results demonstrated that long-term azithromycin regimen was more effective than amoxicillin-metronidazole for treatment of chronic periodontitis. Also, patients usually prefer monotherapy. In a study by Bartold *et al*. in 2012, it was suggested that azithromycin could be effective as an adjunctive therapy for treatment of chronic periodontitis (13). However, it should be noted that long-term use of azithromycin has some drawbacks as well including the high cost for patients and risk of gastrointestinal side effects. Short-term azithromycin has a relatively similar and in some cases superior effect than amoxicillin-metronidazole regimen. Furthermore, patients usually prefer monotherapy with lower frequency of drug intake per day. Thus, short-term azithromycin is a suitable alternative to amoxicillin-metronidazole regimen.

Conclusion:

Based on the obtained results, all understudy therapeutic regimens were effective for treatment of chronic periodontitis but the magnitude of improvement was greater in long-term azithromycin group.

Conflict of Interest: "None Declared"

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