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RESEARCH ARTICLE

AZITHROMYCIN VERSUS METRONIDAZOLE– AMOXICILLIN COMBINATION AS AN ADJUNCT TO NONSURGICAL PERIODONTAL THERAPY OF GENERALIZED AGGRESSIVE PERIODONTITIS

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ABSTRACT

Objective: This study evaluated the short-term clinical benefits of two systemic antibiotic regimes added to the nonsurgical periodontal treatment of generalized aggressive periodontitis. **Materials and Methods:** The patient records were reviewed and 45 patients were selected and divided into the following three groups: Scaling and root planning (SRP) only (group C); SRP plus azithromycin (AZT group); and SRP plus metronidazole and amoxicillin (M + A group). The periodontal indexes were recorded at baseline and 3-month posttherapy. **Results:** The periodontal parameters were improved in all groups 3-month posttherapy. The scores were decreased more in the AZT and M + A groups than the controls, but this difference did not reach significance. In addition, the decrease in the plaque index from baseline to 3-month in the AZT group was not significant. **Conclusion:** Nonsurgical therapy reduces the probing depth and clinical inflammation findings. This healing tendency was observed in the AZT group despite the baseline plaque scores. Therefore, AZT might be active against the bacteria in dental biofilms.

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INTRODUCTION

Generalized aggressive periodontitis (GAP) is a complex periodontal disease affecting the entire dentition with pronounced, rapid destruction of the periodontium and resulting loss of teeth (Armitage, 1999) Unlike chronic periodontitis, the amount of biofilm and calculus accumulation is consistent with the severity and progression of the periodontal destruction because of an inadequate host response to periodontopathogenic bacteria, (Parameter on aggressive periodontitis, 2000; Meng, 2007) and is characterized by the episodic, rapid destruction of periodontal tissues. The primary approach to the treatment of GAP is surgical and nonsurgical mechanical treatment. To enhance the outcome of nonsurgical therapy, including scaling and root planning (SRP), antimicrobial agents have been used as adjuncts to conventional periodontal therapy (Ramberg *et al*., 2001). There is a consensus that the use of adjunctive antibiotics results in greater attachment levels than mechanical therapy alone (Haffajee *et al*., 2003; Prakasam *et al*., 2012). However, there is little consensus on the optimum type, dosage, duration of treatment, and mix of antibiotics for combination therapy Hirsch, 2010). The combined use of amoxicillin (AMX) and metronidazole (MTZ) has been proposed to exhibit increased bactericidal, and spectral efficacy compared with monotherapy with either drug (Pavicic, 1994; Griffiths, 2011). The combination of MTZ and AMX in the treatment of aggressive periodontitis has gained recognition mostly due to its effectiveness against Aggregatibacteractinomycetemcomitans, a periodontal pathogen closely associated with the etiology of this infection (Winkel *et al*., 2001; Kaner *et al*., 2007). In addition to A. actinomycetemcomitans, this combination is active against Treponema denticola, Tannerella forsythia, Porphyromonasgingivalis, Fusobacterium nucleatum, and Prevotella intermedia (Lacroix, 1989; Haffajee *et al*., 1996; Van Winkelhoff, 1989). Azithromycin (AZT) is a macrolide antibiotic that has more potent activity against Gram-negative bacteria compared with erythromycin, can penetrate dental biofilms, and has good periodontal tissue penetration (Gomi *et al*., 2007; Botero *et al*., 2013). Higher concentrations persist in many tissues for 0–7 days using a simple dosage regimen (Gomi *et al*., 2007; Smith *et al*., 2002). The effectiveness of adjunctive AZT in the treatment of chronic and aggressive

periodontitis has been investigated (Mascarenhas, 2005; Gomi, 2007; Yashima, 2009). However, there is no clear protocol for the use of antibiotics as adjuncts to the nonsurgical treatment of GAP. Therefore, this retrospective study determined the clinical short-term effects of AZT and a combination of MTZ and AMX.

MATERIALS AND METHODS

The clinical records of GAP patients seen in the Department of Periodontics Govt Dental College Srinagar were reviewed to identify patients diagnosed with "GAP" according the criteria of Armitage (Armitage, 1999), who were nonsmokers, systemically healthy, with no medication use in the previous 6 months, and no previous periodontal treatment. The records of 93 patients were examined; 45 met the inclusion criteria. The following clinical parameters were scored at six sites per tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) at baseline and 12 weeks after SRP: Probing depth (PD), gingival index (GI), plaque index (PI), and bleeding on probing (BOP). The control group underwent full-mouth SRP only (group C), whereas the two test groups received one of the two systemic antibiotic regimens in addition to SRP. The first test group (AZT group; n = 15) was given AZT 500 mg, once per day, for 3 days, and the second group was given MTZ + AMX 500 mg each, 3 times/ day (M + A group; n = 15).

Statistical analysis: Parametric tests were used for further statistical comparisons. The gender and age distributions among the groups were analyzed using Pearson's Ch-square test and one-way analysis of variance (ANOVA), respectively. Intra-group differences were tested using paired t-tests. Initial values and the mean changes in the parameters examined were compared by one-way ANOVA. Tukey's honestly significant difference (HSD) test was performed as a post-hoc assessment of individual differences. All statistical analyses were performed using SPSS for Windows 8, version 13.0. Statistical significance was accepted at $P < 0.05$.

RESULTS

Table 1 presents the mean baseline clinical characteristics. There were no significant differences among groups in terms of age, gender, or clinical periodontal parameters, confirming that the groups were well matched. The mean per-group average change in periodontal parameters from baseline to 3 months after SRP is shown in Table 2.

Table 1. Characteristics of the subjects at baseline

	AZT (n=15)	M+A (n=15)	C (n=15)	P
Age	29.27±6.76	29.80±6.45	31.86±5.22	NS
Gender(male/female)	3/12	6/9	4/11	NS
PD	3.43±0.59	3.65±1.46	3.67±0.69	NS
PI	1.05±0.73	0.71±0.57	1.11±0.44	NS
BOP	64.47±26.49	57.53±31.46	79.23±17.32	NS
GI	2.93±6.76	2.98±6.45	2.05±0.52	NS

AZT=SRP + azithromycin; M+A = SRP + metronidazole + amoxicillin; C=SRP only. PD=Probing depth; PI=Plaque index; BOP=Bleeding on probing; GI=Gingival index; SRP=Scaling and root planning; NS=Nonsignificant; AMX: Amoxicillin

There were clinical improvements in almost all parameters at 3 months for all groups. The PD, RAL, GI, and BOP were reduced significantly in all groups. The PI also showed a significant clinical improvement for the M + A and C groups (–0.71 ± 0.64, P <0.01 and –0.58 ± 0.44, P <0.001, respectively).

Table 2. The average changes in periodontal parameters for T1-T0

	GI	BOP	PI	PD
AZT	−1.56±1.74**	−0.99±0.76***	−38.18±28.78***	−0.19±0.61NS
M+A	−1.56±0.96***	−1.26±0.62***	−50.88±26.83***	−0.71±0.64**
C	−0.79±0.69**	−0.90±0.66***	−33.23±16.77***	−0.58±0.44***
P	NS	NS	NS	0.044

**P<0.01, ***P<0.001. Results of one-way ANOVA comparing the three groups. AZT=SRP+azithromycin; M+A=SRP + metronidazole + amoxicillin; C=SRP only; NS=Statistically nonsignificant.; ANOVA=Analysis of variance

Table 3. Multiple comparisons of clinical periodontal parameters amoung groups by Turkeys HSD test

Groups	PD	CAL	GI	BOP	P
AZT versus M+A	NS	NS	NS	NS	0.044
AZT versus C	NS	NS	NS	NS	NS
M+A versus C	NS	NS	NS	NS	NS

HSD=Honestly significant difference; NS=Nonsignificant;

However, PI did not change significantly at 3 months in the AZT group (–0.19 ± 0.61, P ≥ 0.05). All of the treatment protocols significantly reduced the PD in all groups. However, an additional reduction in PD was seen in the test groups compared with the control group (–1.29 ± 1.39, –1.27 ± 0.51, and –0.79 ± 0.55, for AZT, M + A, and C, respectively). The clinical periodontal parameters are shown in Table 3. There were no significant differences in the reductions in the clinical parameters in all cases, with the exception of the difference in the reduction in PI between groups AZT and M + A.

DISCUSSION

This study assessed the short-term clinical benefits of two treatment protocols for nonsurgical periodontal therapy of GAP. Many studies have compared antibiotic regimens as adjuncts to SRP (Casarin, 2012; Xajigeorgiou *et al*., 2006; Guerrero *et al*., 2005; Haas *et al*., 2008). We reviewed their findings to assess the use of antimicrobials administered after an initial period of oral hygiene motivation. Our study comprised a control and two test groups. There were no differences among groups in terms of age, gender, and initial periodontal parameters. All patients were nonsmokers. Our data indicate that all three therapies improved the PD, GI, and BOP at the 3-month follow-up. Scaling and root planning is an essential initial therapy to induce the resolution of inflammation via the removal of plaque, calculus, and endotoxins from the root surfaces. In our series, all clinical parameters improved in the control group. In most clinical studies, M + A combined with SRP leads to significantly greater reductions in clinical periodontal parameters (Casarin *et al*., 2012; Guerrero *et al*., 2005; Mestnik *et al*., 2010; Scharf *et al*., 2014). Guerrero *et al*. assessed the adjunctive benefits of M + A in the nonsurgical treatment of GAP and found that all clinical parameters were improved at 2 and 6 months in both the test and placebo groups (Guerrero *et al*., 2005). Regarding deep pockets, however, the M + A therapy resulted in an additional 1.4-mm PD and 1-mm CAL gain. Similarly, Casarin*et al*. treated GAP patients with full-mouth ultrasonic debridement with or without administering M + A. (Casarin *et al*., 2012). Their results showed the clinical and microbiological benefits of M + A administration 3 and 6 months posttherapy. The PD reductions were 3.99 ± 1.16 and

3.09 ± 0.78 in the test and control groups, respectively. In another study, aggressive periodontitis was treated similarly, using M + A in addition to nonsurgical treatment; the use of M + A resulted in additional clinical benefits (Scharf *et al*., 2014). In that study, the PD decreased from 3.5 ± 0.7 to 2.5 ± 0.5 mm at 12 weeks. In addition, the gingival bleeding index, plaque control record, and BOP all decreased significantly. Silva-Senem*et al*. also showed significant clinical improvements in most parameters at 1-year in the nonsurgical treatment of GAP patients with or without M + A, although the M + A group had shallower residual pockets than the placebo group (Silva-Senem *et al*., 2013). Another randomized, controlled, clinical trial evaluated the short-term effects of nonsurgical treatment of aggressive periodontitis with M + A and photodynamic therapy (PT); both treatments improved the clinical parameters after 3-month, although the systemic administration of antibiotics resulted in a greater reduction in PD compared to the PT group (Arweiler *et al*., 2013). Our results were similar to these reports in that the clinical periodontal parameters improved in both the M + A and control groups. The PD was reduced significantly ($P < 0.001$) by 1.27 ± 0.51 and 0.79 ± 0.55 for the respective groups. The reduction was greater in the M + A group. Similar healing tendencies were observed for the other parameters. Therefore, both treatment protocols helped to resolve the periodontal inflammation. The differences were greater in the M + A group, albeit not significantly so. Recently, AZT has been administered as an adjunctive antimicrobial in the treatment of periodontal disease. Several studies have evaluated the benefits of AZT,(7,20,22,26,31,32) although fewer have evaluated the clinical benefits of AZT in GAP. Haas *et al*. treated 24 subjects with SRP with or without the administration of 500-mg AZT once per day for 3 days (Haas, 2008).

They showed a reduction in PD and improvement in the CAL in both groups from baseline to 12 months. However, the test group showed a significantly greater reduction in PD and a higher percentage of attachment gain. Emingil*et al*. treated 32 GAP patients with nonsurgical therapy with or without AZT and found that all clinical parameters improved, and the microbiological parameters and gingival crevicular fluid matrix metalloproteinase-8 levels decreased significantly in both groups.(Emingil *et al*., 2012). They found that AZT exerts no beneficial effect compared to nonsurgical periodontal therapy in GAP patients. In 2010, Hirsch reported three cases of chronic or aggressive Periodontitis. who received AZT adjunctive to nonsurgical treatment; in all cases the periodontal inflammation resolved and pocket depth decreased (Hirsch, 2010) Han *et al*. examined the efficacy of AZT in combination with nonsurgical periodontal therapy for 6 months in generalized chronic periodontitis patients; AZT and placebo resulted in similar significant improvements in all clinical parameters (Han *et al*., 2012). In addition, in both groups, numbers of A. actinomycetomcomitans, P. gingivalis, T. forsythia, P. intermedia, and total bacteria were reduced at 6 months. The levels of F. nucleatumdecreased significantly at all visits in the test group. Therefore, adjunctive AZT provides no additional benefits over a placebo for GAP. In our study, the clinical periodontal parameters healed significantly in the AZT group. When we compared whole groups, the parameters improved similarly. However, the reduction in PD was higher in the AZT group than the controls, albeit not significantly so (–1.29 ± 1.39, –1.27 ± 0.51, and –0.79 ± 0.55 for the AZT, M + A, and control groups, respectively). The GI, and BOP showed similar tendencies to the PD. The PI also decreased compared to baseline, albeit not significantly so. AZT is active against the bacteria in dental plaque, (Tamura, 2008) which might be an advantage. Although clinicians attempt to motivate, patients to perform plaque control, maintaining a high level of oral hygiene can be difficult. Thus, AZT administration might be useful for the treatment of periodontitis. Mechanical treatment may not be effective on periodontal pathogens such as A. actinomycetomcomitansat inaccessible areas and periodontal soft tissues (Prakasam *et al*., 2012). Therefore, patients with aggressive periodontitis may provide benefits from the adjunctive use of antibiotics adjunct to treatment. There are various antibiotic regimes that recommended for the treatment of GAP. We compared two of them and in our knowledge; this is the first study that compared the AZT and M + A combination adjunct to SRP. Hence, the results may be a useful guide about the choice of antibiotics. In addition, the patient records were selected meticulously for this study. The GAP patients had been treated in the same clinic, by the same treatment protocol and by previously standardized, experienced clinicians. Hence, the differences between treatment protocols were eliminated and gave us the chance to obtain more homogenous data. However, there were several limitations to this study, including the short follow-up time and the fact that no immunological or microbiological parameters were evaluated. Further research is needed to identify the optimum adjunctive antibiotic therapy for the nonsurgical treatment of GAP.

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