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Effect of Subgingival Placement of 0.5% Azithromycin Gel on Clinical Parameters in Molars of Patients with Chronic Periodontitis

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Abstract

Background: Scaling and Root Planing (SRP) alone had been proved to be effective in treating mild to moderate cases of periodontitis. But in molars where complex anatomical features are present, SRP alone had been proven to be least effective. SRP won't eradicate tissue invading pathogens also. In such situations Local Drug Delivery (LDD) as an adjuvant to SRP seems to be effective, with minimal side effects when compared to systemic antimicrobial therapy. In our study we had evaluated the effect of 0.5% Azithromycin (AZM) gel in LDD form as an adjuvant to SRP in treatment of periodontal pockets of 1st and 2nd molars.

Materials and Methods: The outpatients who reported to the department of periodontics, Sri Ramakrishna dental college and hospital, Coimbatore were included in this study. Maxillary or Mandibular first or second molars were the teeth to be tested. Patients were allocated to two groups: control group (SRP only) and test group (SRP plus 0.5% AZM gel). On baseline and post-operative examination after 45 days, clinical parameters were recorded for the tooth to be tested.

Results: Probing Depth (PD) reduced significantly and significant Clinical Attachment Level (CAL) gain was achieved in both groups, with more gain in test group when compared to control group ($p<0.05$). The mean Gingival Index (mGI) and mean modified Sulcular Bleeding Index (mSBI) scores were found to be reduced in both test and control groups ($p<0.05$) with no significant differences between test and control groups.

Conclusion: PD reduction and CAL gain improved after SRP with 0.5% AZM gel as LDD in 1st and 2nd molars.

Keywords: Azithromycin • Local drug delivery • Root planing • Probing depth • Clinical attachment level

Introduction

Periodontitis is a microbial plaque induced inflammatory disease of periodontium [1]. The Scaling and Root Planing (SRP) reduces bacterial mass, but major pathogens may escape due to tissue invasion or poor host defence as well as due to complex anatomical factors [2]. Systemic antimicrobials are useful in above situation, but have many drawbacks. But, by using Local Drug Delivery (LDD), higher concentration of therapeutic agent can be achieved and maintained for long period without any systemic effects [3,4]. Azithromycin(AZM) is effective against tissue invading pathogens and has immunomodulatory properties [5-7]. It has longer half-life and good tissue penetration [8,9]. Systemic AZM as an adjuvant to SRP proved to be effective [10-17]. 0.5% AZM as a LDD showed promising results [18-20]. This is the first study to find the effectiveness of AZM as LDD in molars which has complex anatomical features. The aim of the study was to evaluate the effect of 0.5% AZM gel as an adjuvant to SRP on clinical parameters in 1st and 2nd molars.

Materials and Methods

This clinical study followed the principles in the Declaration of Helsinki. The study was approved by Institutional Review Board and Ethical Committee. Informed consent was obtained from each patient before enrolling them in the study. The outpatients who reported to the department of periodontics, Sri Ramakrishna dental college and hospital, Coimbatore were included in this study. In both test and control groups, systemically healthy patients with probing depth ≥ 5 mm and no antibiotic therapy or periodontal therapy in the preceding six months were included. Radiographic bone loss was recorded to select subjects with chronic periodontitis. Exclusion criteria: In test group, patients with known or suspected allergy to the macrolide group were excluded. The smokers, alcoholics, and pregnant or lactating females were excluded in both the groups. Maxillary or Mandibular first or second molars were the teeth to be tested. Patient's consent was obtained before including them in the study. Patients were allocated to two groups: control group (SRP only) and test group (SRP plus sub gingival AZM). Patients were recalled after 45 days post treatment for review. On baseline and post-operative examination, clinical parameters such as Gingival Index (GI), Conventional Probing Depth (PD), Clinical Attachment Level (CAL) and modified Sulcular Bleeding index (mSBI) were recorded for the tooth to be tested.

Method for preparation of Azithromycin gel

0.5% AZM gel was prepared in Sri Ramakrishna college of Pharmacy, Coimbatore. Weighed amount of Poly Lactic-co-Glycolic Acid (PLGA- 7502A Purac Biomaterials, PURASORBR, Gorinchem, the Netherlands) was placed in a glass vial, and solvent (N-Methyl-2-pyrrolidone) of required amount was added to it. The vial was heated to 60ºC and agitated using a magnetic stirrer on an electromagnetic heater to obtain a clear solution. Azithromycin of required amount was added to the above polymer solution and dissolved completely to obtain a homogeneous phase of polymer, solvent and drug. The formulation constituents were N-methyl-2-pyrrolidinone as the biocompatible solvent and

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PLGA copolymer in a ratio of 75:25, with a molecular weight of 72000 Dalton (72 kilo Dalton) and a microenvironment pH of 7.4.

Local drug delivery

0.2 ml prepared AZM gel was injected into the periodontal pockets using a blunt cannula. Periodontal dressing wasn't applied after delivery of the drug as the prepared formulation decreases in viscosity, which causes swelling and occlusion of the periodontal pocket. After gel placement, patients were instructed to avoid chewing hard or sticky foods, brushing near the treated areas, or using any interdental aids for 1 week. Adverse effects were noted at recall visits, and any supragingival deposits if accumulated were removed.

Statistical analysis

The sample size was calculated with 95% confidence level using Slovin's formula. The data were transferred to Microsoft excel sheet and statistical analysis were done using SPSS software (version 24.0). Mean values and standard errors for PD, CAL, GI, and mSBI were calculated for each subject at each time point. Differences between intragroup was done using paired t test and intergroup was done using independent sample t test. Differences with a P value <0.05 at a confidence level of 95% were considered significant.

Results

Eighty patients were enrolled in this study. 40 patients were in the test group and their average age was 42.75 years. 40 patients were in the control group and their average age was 42.65years. There were no statistically significant baseline differences between the groups for any demographic or clinical parameters (Table 1). No adverse drug reactions were reported. Intra-group comparison and inter-group comparison had been done. The mean GI (mGI) scores were found to be reduced in both test and control groups ($p<0.05$) with no difference between test and control groups (Table 2). The mSBI scores were also found to be reduced in both test and control group ($p<0.05$) with no difference between test and control group. PD reduced in test-group significantly from 6.33 to 3.93 ($p<0.05$) and in control group from 7.38 to 5.55 ($p<0.05$). Reduction in PD was more in test group when compared to control group ($p<0.05$) (Table 2). CAL gain was achieved in both test group as well as control group ($p<0.05$), with more gain in test group when compared to control group ($p<0.05$).

Table 1. Age and clinical parameters at baseline and six weeks after SRP, SRP with AZM gel placement in test and control groups.

	Groups	N	Mean	Std. Deviation	Std. Error Mean
Age	Test Group	40	42.75	9.12801	1.44326
	Control Group	40	42.65	9.28895	1.46871
Probing Depth Baseline	Test Group	40	6.325	0.97106	0.15354
	Control Group	40	7.375	1.40854	0.22271
CAL Baseline	Test Group	40	6.875	1.22344	0.19344
	Control Group	40	7.75	1.85016	0.29254
Gingival Index Baseline	Test Group	40	1.7188	0.67981	0.10749
	Control Group	40	1.9562	0.61729	0.0976
mSBI Baseline	Test Group	40	1.925	0.72986	0.1154
	Control Group	40	2.1	0.63246	0.1
Probing Depth 6weeks	Test Group	40	3.925	0.72986	0.1154
	Control Group	40	5.15	1.73279	0.27398
CAL 6weeks	Test Group	40	5.4	0.81019	0.1281
	Control Group	40	6.525	1.69445	0.26792
Gingival Index 6weeks	Test Group	40	0.675	0.47434	0.075
	Control Group	40	0.625	0.54006	0.08539
mSBI 6weeks	Test Group	40	0.65	0.48305	0.07638
	Control Group	40	0.625	0.54006	0.08539

Table 2. Differences in clinical Parameters at baseline and 6 weeks in Test and Control groups.

	Probing Depth			CAL			mGI			mSBI		
	Baseline	6 Weeks	P	Baseline	6 Weeks	P	Baseline	6 Weeks	P	Baseline	6 Weeks	P
Test Group	6.33	3.93	<0.05	6.88	5.40	<0.05	1.72	0.68	<0.05	1.93	0.65	<0.05
Control Group	7.38	5.15	<0.05	7.75	6.53	<0.05	1.96	0.63	<0.05	2.10	0.63	<0.05
P	<0.05	<0.05		0.015	<0.05		0.106	0.661		0.255	0.828	

Discussion

SRP helps in the removal of plaque and contributing factors. Even though studies had justified the efficacy of SRP in improving the periodontal and systemic parameters, it has few limitations in case of complex anatomic factors. In such cases LDD plays a role. In our study, we evaluated the effect of 0.5% AZM gel as an adjuvant to scaling and root planing in treating maxillary and mandibular molars. In our study, all the clinical parameters such as mGI, mSBI, PD and CAL were significantly improved post operatively in test group and control group, with test group recording great improvement in PD and CAL when compared to control group.

In test group, PD significantly reduced by 2.4mm ($p<0.05$) and in control group, PD reduced by 1.83 mm ($p<0.05$). Also, reduction in PD was more in test group when compared to control group ($p<0.05$).

In test group, CAL gain achieved was 1.48 mm ($p<0.05$) whereas in control group, CAL gain achieved was 1.22 mm ($p<0.05$). CAL gain achieved was also more in test group when compared to control group ($p<0.05$).

In test group, mGI significantly reduced by 1.04 ($p<0.05$) and in control group, mGI reduced by 1.33 ($p<0.05$). The reduction in mGI was more in control group when compared to test group but not significant ($p>0.05$). But previous studies showed a marked reduction in mGI.

In test group, mSBI significantly reduced by 1.28 ($p<0.05$) and in control group mSBI reduced by 1.47 ($p<0.05$). The reduction in mSBI was slightly more in control group when compared to test group but not significant ($p>0.05$). There was reduction in bleeding in both test and control groups.

AZM could have a triple role in the treatment and resolution of periodontal diseases: Suppressing periodontal pathogens, anti-inflammatory activity, and healing through persistence at low levels in macrophages and fibroblasts in periodontal tissues. First, AZM, when given as a single course of three, 500 mg tablets, its effectiveness against Gram-negative bacteria, and the ability to penetrate biofilm and a long antibacterial half-life and short course make it an attractive antibiotic option as an adjunct to the management of advanced inflammatory periodontitis. Second, the uptake of AZM by neutrophils and macrophages allows it to target and be concentrated at sites of periodontal inflammation and exert its anti-inflammatory properties. As hyper responsive macrophages are considered to be determinants of susceptibility to periodontitis by producing large quantities of pro inflammatory cytokines in response to LPS and bacterial products, a possible beneficial role of AZM is to down regulate pro inflammatory cytokine production. Third, AZM appears to exert a long-term healing influence on the periodontal tissues. This property may be related to its effect on changing the macrophage phenotype, thus increasing the production of anti-inflammatory cytokines and favoring healing. The resolution of cyclosporine-induced gingival overgrowth over time is a pointer to the drug's long-term host modulatory/healing properties.

Conclusion

The results of our study supports the results of the previous studies with significant reduction in PD and CAL gain in test group when compared to control group. Here in our study all the clinical parameters had been checked which was not done in previous studies. This is the only and first study which had been done exclusively in molars.

The limitations of our study are it was not a split mouth design, patient selection was not randomised and also not blinded and radiographic comparisons was not done in both groups. Within the limitations of our study we can conclude that PD reduction and CAL gain improved with 0.5% AZM local drug delivery in 1st and 2nd molars. Further studies with much more samples and long term post-operative assessment are needed to substantiate our results.

Further studies are needed to evaluate the long-term clinical advantage of adjunctive therapy with 2 mg tetracycline hydrochloride fibers and 0.5% AZM gel in the treatment of chronic periodontitis. It might be interesting to explore the possible surplus value of sub-gingival administration of 0.5% AZM gel for other forms of periodontal diseases such as aggressive periodontitis, refractory periodontitis, and peri-implantitis. However, long-term studies, using different vehicles and concentrations of AZM and tetracycline, should be carried out to affirm the observations of our study. It may be possible to develop a sub-antimicrobial AZM dosing regimen that avoids potential bacterial resistance. Of interest, the development of a non-antibiotic macrolide derived from AZM has recently been reported; it had immunomodulatory effects in animal models of inflammatory bowel diseases and arthritis.

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