

ORIGINAL RESEARCH

A Comparative Study to Evaluate the Effectiveness of Subgingivally Delivered Antimicrobial Bio-absorbable Controlled Release 0.5% Azithromycin Gel and 2 mg Tetracycline Hydrochloride Fibres as an Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis

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ABSTRACT

Introduction: Local delivery of antimicrobials in sustained or controlled delivery systems is used to enhance the effect of non-surgical periodontal therapy; it might be possible to achieve gingival health without the need for invasive techniques with the use of local drug delivery systems.

Objectives: Thus, the aim of the present study was to investigate and compare the effectiveness of subgingivally delivered antimicrobial bioabsorbable controlled release 0.5% azithromycin (AZM) gel and 2 mg tetracycline hydrochloride fibers as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis.

Methods: A 6-month randomized controlled clinical trial was carried out in 15 patients suffering from chronic periodontitis. A total of 60 sites were divided into experimental sites A and experimental sites B. The experimental sites A were treated with SRP in combination with subgingival application of bio-degradable 0.5% AZM gel. The experimental sites B received SRP and subgingival application of 2 mg tetracycline hydrochloride fibers. Plaque index (PI), gingival index (GI), probing pocket depth (PPD), clinical attachment level (CAL), and gingival margin position were recorded at baseline, 3 and 6 months.

Results: All the treatments showed significant reductions in PI, GI, PPD, and clinical attachment level (CAL) at 3 and 6 months when compared to baseline values ($P < 0.05$). At 6 months, experimental Group A showed significantly greater improvement in all clinical parameters than experimental Group B.

Interpretation and Conclusion: The adjunctive use of 0.5% AZM gel showed greater PPD reductions and CAL gains compared to the combination of SRP and tetracycline hydrochloride.

Keywords: Azithromycin, Drug delivery systems, Periodontitis, SRP, Tetracycline hydrochloride.

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INTRODUCTION

Periodontitis is an infection of the periodontium caused by bacterial etiology evoking an immune response. Once destruction of tissue occurs, the condition is referred to as a disease. Usually, the host response can contain subgingival bacterial challenges and subclinical infections are resolved without any clinical manifestation of pathosis. However, if the host-parasite equilibrium becomes unbalanced, an exuberant host response can result in destruction of the periodontium.^[1]

Traditional periodontal therapies have focused on the mechanical debridement of the root surfaces to maintain a healthy sulcus or produce an environment suitable for new attachment. The inability of mechanical treatment to produce a desirable root surface in all cases coupled with the nature and complexity of the subgingival biofilm has fueled the search for adjunctive treatment regimens that increase the likelihood to successfully manage periodontal diseases.^[2]

Adjunctive administration of systemic antimicrobials has been useful in treating recurrent periodontal pockets after seemingly adequate conventional therapy or patients with aggressive periodontitis or associated with predisposing medical conditions. However, the doses necessary to

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achieve sufficient local concentrations of antimicrobials in the periodontal environment are associated with undesirable side effects; therefore, the local administration can be considered as an alternative to overcome these problems.

Goodson *et al.*, in 1985, first proposed the concept of controlled delivery in the treatment of periodontitis. The effectiveness of this form of therapy is that it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur.^[3]

Antimicrobial agents are administered directly into the periodontal pocket aiming at inhibition of the growth of periodontal pathogenic bacteria or modulate the inflammatory response, thereby limiting periodontal tissue destruction. Local application of antimicrobials could reduce the risk of adverse events associated with systemic antimicrobials, including the development of bacterial resistance.^[4] Various antimicrobials have been used by researchers, which include tetracycline, metronidazole, doxycycline, minocycline, chlorhexidine, azithromycin, and ornidazole and drugs such as simvastatin and hyaluronic acid have also been investigated as local drug delivery agents.^[5]

Sulcular administration of an antibiotic through a controlled-release delivery system has the advantage of directly reaching the target area at the base of the periodontal pocket in low doses at concentrations high enough to achieve a possible reduction in the emergence of resistant bacteria.^[6] Tetracycline fibers are able to maintain a mean gingival crevicular fluid concentration of 1300 µg/mL over 10 days, compared with 4–8 µg/mL when administered systemically.^[7] This concentration, though substantially greater than the minimum inhibitory concentration for periodontal pathogens, has not been reported to cause toxicity.^[8,9]

Azithromycin (AZM) is a semi-synthetic and acid stable antibiotic and represents the prototype of a novel class of macrolides named azalides. It has a long half-life and good tissue penetration.^[10,11] These properties make AZM a potential candidate for further investigation of its effects as a local antimicrobial agent that can be a valuable addition to the field of periodontics.

The present study is designed to investigate and compare the effectiveness of subgingivally delivered antimicrobial bioabsorbable controlled release 0.5% AZM gel and 2 mg tetracycline hydrochloride fibers as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis.

MATERIALS AND METHODS

A single-center randomized double-blind controlled split-mouth clinical trial study was conducted at the

Department of Periodontics, M.S. Ramaiah Dental College and Hospital, Bengaluru, Karnataka, including 40 patients with chronic periodontitis.

Inclusion Criteria

The following criteria were included in the study:

1. Patients with age group between 35 and 60 years.
2. Patients having at least four periodontal pockets with probing depth ranging between 5 and 7 mm.
3. Patients who have not undergone any periodontal therapy 6 months before the initial examination.
4. Patients without any antibiotic treatment in the past 6 months.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients who are medically compromised.
2. Patients with smoking habit.
3. Pregnant or lactating women.
4. Sites with overhanging restoration.
5. Patients with known or suspected allergy to the macrolide group or tetracyclines which is prescribed in this study.
6. Patients having periodontal pockets <5 mm after initial prophylaxis.

Study Design

A total of 40 patients were enrolled in the study. Following baseline evaluation and subject to lack of follow-up, only a total of 30 patients were analyzed for the study. 60 sites were selected after the completion of initial screening phase in all the patients. These selected sites were divided into experimental site A ($n = 30$) and experimental site B ($n = 30$) randomly with the use of equal number of opaque sealed envelopes and were treated according to split-mouth technique as follows:

Experimental sites A

These sites were treated with SRP and subgingivally delivered 0.5% AZM gel into periodontal pockets.

The formulation constituents for AZM 0.5% *in situ* gel were N-methyl-2-pyrrolidinone as the biocompatible solvent and polylactic and polyglycolic acid (PLGA) copolymer in a ratio of 75:25, with a molecular weight of 72,000 (72 kilodaltons) and a microenvironment pH of 7.4.

Experimental sites B

These sites were treated with SRP and subgingivally delivered 2 mg tetracycline hydrochloride fibers placed into periodontal pockets. Periodontal plus AB

is a biodegradable, controlled release local drug delivery system. 2 mg tetracycline hydrochloride is evenly dispersed in 25 mg of collagen fibers. Periodontal plus AB fibers provide continuous release of tetracycline for minimum 10 days.

Clinical Parameters

The clinical parameters were recorded at baseline, 3 and 6 months post-treatment during the period of 18 months. All clinical measurements were performed by single examiner who was unaware of treatment carried out for each subject using customized acrylic stents with grooves, which were prepared on the study model of the patients. The recordings were made using a University of North Carolina 15 probe (Hu-Friedy's). 1 week before baseline measurements, all patients received supragingival prophylaxis and oral hygiene instructions. Experimental sites A and B were randomly assigned on the day of subgingival application of drugs. All the subjects were examined based on the following clinical parameters at baseline, 3 and 6 months, respectively, after subgingival application of drugs.

1. Gingival index (GI) (Loe and Silness, 1967)
2. Plaque index (PI) (Silness and Loe, 1967)
3. Probing pocket depth (PPD) (fixed reference point [FRP] to base of the pocket [BoP] - FRP to gingival margin [GM])
4. Clinical attachment level (CAL) (FRP to BoP - FRP to cemento-enamel junction [CEJ])
5. Gingival margin position (FRP to CEJ - FRP to GM).

Treatment Procedure

Patients were educated about the disease and the subject of the study and informed consent was taken. After 1 week of initial therapy in the patients, baseline clinical parameters (PPD, CAL, PI, GI, and GM) were recorded. Subjects received standard periodontal therapy, meaning SRP using ultrasonic scaler and standard periodontal curette. The treatment was performed by applying subgingivally drug A (0.5% AZM gel) and drug B (2 mg tetracycline hydrochloride fibers) directly

into the deepest part of their respective pocket sites followed by periodontal dressing. The post-operative instructions included a gentle approach to oral hygiene and to avoid any interdental hygiene for 1 week in the treated areas [Figures 1-11].

Method of Statistical Analysis

The results were averaged (mean \pm standard deviation) for each continuous parameter and numbers and percentages are presented for categorical data in tables and figures. Proportions were compared using Chi-square test of significance. Data were analyzed for treatment effect on each parameter using repeated measures mixed effects model. The serial measurement of the parameters on baseline, month 3 and month 6 was analyzed separately. Treatment, period, and baseline value were fitted as fixed effect; subject was fitted as random effect. In the above tests, $P < 0.05$ was accepted as indicating statistical significance. Data analysis was carried out using Statistical Package for the Social Sciences package.

RESULTS

The purpose of this clinical trial was to evaluate the clinical effects of subgingivally delivered antimicrobial bioabsorbable controlled release 0.5% AZM gel as an adjunct to SRP and also to compare the clinical parameters of subgingivally delivered antimicrobial bioabsorbable controlled release 0.5% AZM gel and 2 mg tetracycline hydrochloride fibers as an adjunctive to initial periodontal therapy. At 6-month PI and GI score, reduction was significant in between the two experimental groups ($P < 0.05$).

The mean probing depth reduction (in mm) from baseline to 3 and 6 months was 2.50 ± 0.62 and 3.04 ± 0.42 for experimental Group A, respectively ($P < 0.0001$); 1.76 ± 0.22 and 2.16 ± 0.32 for experimental Group B, respectively ($P < 0.0001$) [Table 1]. When a comparison was made between experimental Groups A and B, the experimental Group A scored significantly better at each reexamination visit ($P < 0.0001$). The mean CAL (in mm) gain was 2.50 ± 0.64 at 3 months ($P < 0.0001$) and 3.04 ± 0.65 at 6 months ($P < 0.0001$) for experimental Group A, respectively; while it

Table 1: Comparison of PD at different observation periods in different groups

| Group | Visit (months) | Group | Visit | t value | P value |
|-----------|----------------|-----------|----------|---------|---------------------|
| SRP+Exp A | Baseline | SRP+Exp B | Baseline | -0.44 | 0.6575 [▼] |
| SRP+Exp A | 3 | SRP+Exp B | 3 months | -5.33 | <.0001* |
| SRP+Exp A | 6 | SRP+Exp B | 6 months | -6.22 | <.0001* |
| SRP+Exp A | 3 | SRP+Exp A | Baseline | -18.00 | <.0001* |
| SRP+Exp A | 6 | SRP+Exp A | Baseline | -21.84 | <.0001* |
| SRP+Exp B | 3 | SRP+Exp B | Baseline | -12.72 | <.0001* |
| SRP+Exp B | 6 | SRP+Exp B | Baseline | -15.60 | <.0001* |

[▼]Non-significant- $P > 0.05$. *Significant- $P < 0.05$. PPD: Probing pocket depth

Table 2: Comparison of CAL at different observation periods in different groups

| Group | Visit | Group | Visit | t value | P value |
|-----------|-------------------|-----------|----------|---------|---------------------|
| SRP+Exp A | Baseline (months) | SRP+Exp B | Baseline | 0.72 | 0.4705 [▼] |
| SRP+Exp A | 3 | SRP+Exp B | 3 Months | -2.46 | 0.0155* |
| SRP+Exp A | 6 | SRP+Exp B | 6 Months | -2.61 | 0.0106* |
| SRP+Exp A | 3 | SRP+Exp A | Baseline | -18.00 | <.0001* |
| SRP+Exp A | 6 | SRP+Exp A | Baseline | -21.84 | <.0001* |
| SRP+Exp B | 3 | SRP+Exp B | Baseline | -12.72 | <.0001* |
| SRP+Exp B | 6 | SRP+Exp B | Baseline | -16.32 | <.0001* |

[▼]Non-significant- $P > 0.05$. *Significant- $P < 0.05$. CAL: Clinical attachment level



Figure 1: Polyglycolic acid based 0.5% azithromycin gel



Figure 2: Sterile container of tetracycline hydrochloride fibers (2 mg)

was 1.77 ± 1.12 at 3 months ($P < 0.0001$) and 2.27 ± 0.36 at 6 months ($P < 0.0001$) for experimental Group B, respectively [Table 2]. When a comparison was made between the experimental groups, the experimental group A scored significantly better at 3 months ($P < 0.05$) and 6 months ($P < 0.05$) reexamination visit.

DISCUSSION

The ultimate goal of any periodontal therapy is to preserve as many teeth as possible by slowing down, arresting, or reversing the periodontal destruction.^[12] Even though the outcome of mechanical debridement usually satisfies in terms of reduction in periodontal disease, difficulties reaching the bottom of pocket can lead to its failure. As a consequence, supplementary treatment becomes inevitable.^[13]

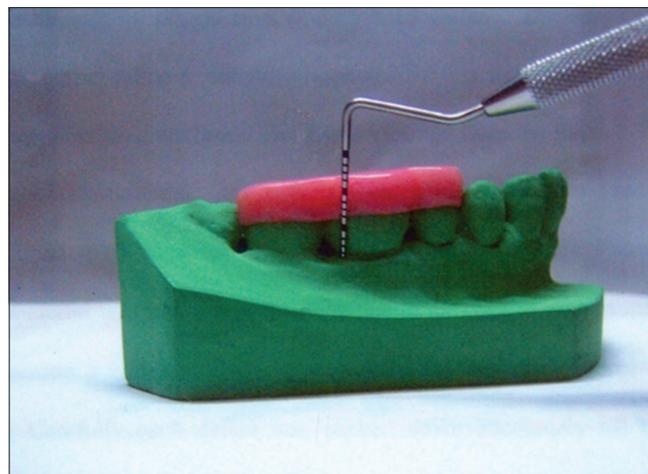


Figure 3: Grooved stent with Pcp Unc-15 probe in place



Figure 4: Experimental site A Baseline measurements ("0" day) Fixed reference point to base of pocket

A local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent in sub-gingival sites compared with a systemic drug regimen. It is possible that chemical antimicrobial agents locally applied into periodontal pockets may further suppress periodontal pathogens and thereby augment the effects of conventional mechanical periodontal therapy.^[4]

Local and systemic drug therapies provide different benefits. For example, local drug delivery provides a high drug concentration, it is efficacious, there are



Figure 5: Subgingival application of polyglycolic acid-based 0.5% azithromycin gel into the pocket



Figure 8: Experimental site A Post-operative measurements at 3 months Fixed reference point to base of pocket



Figure 6: Experimental site B Baseline measurements ("0" day) Fixed reference point to base of pocket



Figure 9: Post-operative measurements at 6 months Fixed reference point to base of pocket



Figure 7: Subgingival application of tetracycline fiber 2 mg into the pocket



Figure 10: Experimental site B Post-operative measurements at 3 months Fixed reference point to base of pocket

limited side effects, and it does not need to be administered daily for a defined time period. On the other hand, systemic administration of antibiotics facilitates treatment of bacterial reservoirs of reinfection such as the tonsil, saliva, and tissue invasive bacteria. It also is more

time efficient for the clinician, costs less, and multiple drugs can be used simultaneously.^[3]

The decision to use local drug delivery during active treatment or maintenance should be based on clinical findings, responses to therapy recorded in the literature,



Figure 11: Post-operative measurements at 6 months: Fixed reference point to base of pocket

desired clinical outcomes, and the patient's dental and medical history.^[14]

The strategic use of AZM may become useful in primary periodontal therapy of patients with a poor treatment response, with respect to both its antibacterial and immunomodulating action. Macrolides, including AZM, are, therefore, used to treat diseases not associated with bacteria such as severe asthma, chronic obstructive pulmonary diseases, and, more recently, cystic fibrosis.^[15]

AZM could have a triple role in the treatment and resolution of periodontal diseases: Suppressing periodontopathogens, 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, 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 hyperresponsive macrophages are considered to be determinants of susceptibility to periodontitis by producing large quantities of proinflammatory cytokines in response to LPS and bacterial products, a possible beneficial role of AZM is to downregulate proinflammatory 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 (to M2), 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.^[16]

Robert *et al.*, in 1993, tested the bioabsorbability and biocompatibility of a polylactic membrane and showed

excellent tissue tolerance with minimal inflammatory reaction. PLGA used in the present study has been widely investigated and has regulatory approval as a carrier for the delivery of drugs including antibiotics.^[17]

Tetracyclines are bacteriostatic inhibitors of protein synthesis. They accumulate intracellularly by way of energy-dependent transport systems present in bacterial membranes.^[14] Once inside the cell, the drug may be transported out again, bind to cellular constituents, or chemically modified so that efflux does not occur.^[18]

Tetracycline fibers are available in both non-resorbable and bioresorbable devices. These fibers release tetracycline in an exponential fashion with 95% of the drug released in first 2 h; they are primarily local delivery devices with minimal control of drug release. Tetracycline fiber application shows significant (± 0.5 mm) additional probing depth reduction and/or attachment gain when used along with SRP.^[19]

In the current study, reduction in PI and GI scores at the 6-month interval in experimental Group A was statistically significant ($P < 0.05$) when compared to experimental Group B. This may have been due to the better efficacy of AZM compared to the local delivery of tetracycline.

On comparison, experimental Group A showed significantly greater reduction in PPD than that of experimental Group B at 3 and 6 months, respectively. This result might be due to the sufficiently high concentration of AZM locally for a long duration as estimated by HPLC >2 $\mu\text{g}/\text{ml}$ from baseline to 28 days by Pradeep *et al.*^[20] when compared to tetracycline which has concentration of 1.6 $\mu\text{g}/\text{ml}$ from baseline to 10 days as shown by Kinane and Radvar.^[21]

Clinical studies investigating the effectiveness of adjunctive AZM in the management of chronic periodontitis and generalized aggressive periodontitis suggest benefits.^[22]

On the contrary, Han *et al.* conducted a randomized, double-blind, placebo-controlled, parallel group study of 6 months' duration and concluded that adjunctive AZM provides no additional benefit over non-surgical periodontal treatment on parameters investigated in severe generalized chronic periodontitis.^[23]

Inferring from the current study, 0.5% AZM gel was better than 2 mg tetracycline hydrochloride fibers in terms of reduction in probing depth and gain in CAL. Thus, the results favor the adjunctive use of 0.5% AZM gel with SRP.

CONCLUSION

The findings of the study suggest that the outcome of the initial periodontal therapy may benefit from the

adjunctive subgingival administration of 0.5% AZM gel and 2 mg tetracycline hydrochloride fibers. However, 0.5% AZM gel was found better when compared to 2 mg tetracycline hydrochloride fibers in terms of improvement in clinical parameters. It is also significant to emphasize that meticulous SRP bears primordial importance in the treatment of chronic periodontitis.

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 subgingival 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 subantimicrobial 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.^[24]

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