Original Research Paper

University J Dent Scie 2022; Vol. 8, Issue 2

Subgingival Application of 0.5% Azithromycin Gel as a Local Drug Delivery System as an Adjunct to Scaling and Root Planing in Controlled Diabetic Patients- An in vivo study :

Abstract:

A recent trend involving the use of local delivery systems to deliver chemotherapeutic agents implies improved periodontal health. As part of this study, a locally delivered 0.5% azithromycin gel was evaluated for its clinical and microbiological efficacy in treating chronic periodontitis patients with controlled diabetes.

Material and Methods: The split-mouth study design was used in this randomized control trial. The study included 50 sites from 25 patients who had pocket depths greater than 5 mm and were diagnosed with chronic periodontitis. Two treatment groups were randomly assigned: scaling and root planing only (control group) or scaling and root planing with 0.5% azithromycin gel (test group). At selected sites, gingival index, probing pocket depth, and clinical attachment level were analyzed for both groups at baseline, 6 weeks, and 12 weeks.

Result & observations: Both the test and control groups had improved parameters when compared to baseline.The depth of the probing pocket was 6.64±1.07 mm and 7.36±1.15 mm at baseline, which decreased to 4.84±0.59 mm and 4.32±0.98mm respectively at 12 weeks. The difference was statistically significant at $p<0.001$. Statistically significant difference in clinical attachment levels between baseline and 12 weeks, at $p<0.001$. The results of all microbiological categories improved significantly in both groups, while the test group showed a greater improvement.

Conclusion: It was concluded that locally delivered azithromycin could be beneficial in treating chronic periodontitis patients with diabetes when used in conjunction with scaling and root planing.

Keywords: Local drug delivery, Periodontal disease, Diabetes, Azithromycin gel

Introduction:

Periodontal disease is considered an infection of the periodontium due to bacterial infection, inflammation, and a breakdown of periodontal structures.1 This causes clinical attachment loss, increased pocket depth, and alveolar bone loss. Even though periodontitis is caused by an infection and mediated by biofilm, it is a difficult condition to treat.[1]

Diabetes is a metabolic disease characterized by abnormal fat, sugar, and protein metabolism, as well as hyperglycemia, which can eventually lead to a variety of multiple system pathologies. The link between periodontitis and diabetes is widely acknowledged.1Diabetes patients had a higher frequency and severity of periodontitis, according to epidemiologic studies.1When a chronic presence of plaque causes an immune response in the gingival and periodontal tissues, periodontal structural components are destroyed, resulting in the clinical signs of chronic periodontitis (CP).1Hyper-inflammatory traits, a type of abnormal inflammatory response, are linked to diabetes and can increase the risk of infections, such as periodontal disease.[2]

The treatment of periodontal disease has evolved over the past couple of decades. Non-surgical approaches to periodontal treatment have gained a lot of attention. Non-surgical therapy

Access this article online

Website: www.ujds.in

Quick Response Code

DOI: https://doi.org/10.21276/ujds.2022.8.2.8

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Received : 14 March, 2022, **Published :** 30 June, 2022

How to cite this article: Gupta, M., Kapoor, A., Vijay, S., Sharma, V., Sharma, P., & Jain, S. (2022). Subgingival application of 0.5% Azithromycin gel as a local drug delivery system as an adjunct to scaling and root planing in controlled diabetic patients- An in vivo study . UNIVERSITY JOURNAL OF DENTAL SCIENCES, 8(2). 42-50

involves removing the subgingival gram-negative flora and controlling the bacterial plaque to stop the repopulation of pathogenic microorganisms. The goal of this treatment is to restore the tissues to a healthy state, so that the patient can maintain whenever necessary with periodontal debridement procedures. The use of an adjunctive antimicrobial agent is needed to suppress the bacterial load in inflammatory periodontal disease, due to the fact that mechanical debridement is insufficient to eradicate the putative pathogenic organism.[3] A wide variety of antibiotics are effective against pathogens associated with periodontal disease.[4,5]

A wide range of topical and systemic agents have been used to halt the progression of periodontal disease[4]. Systemic antibiotics may allow for the drug to be administered to multiple sites of disease activity simply and easily. They may also eliminate or reduce pathogens that colonize the oral mucosa and other extra-dental sites such as the tongue and tonsils. Systemic antibiotic therapy, however, has some drawbacks, such as the inability to achieve high GCF concentrations, the increased risk of adverse drug reactions, the presence of multiple antibiotic-resistant microorganisms, and uncertainty regarding the compliance of the patient[6]. A local drug delivery system was developed to address the shortcomings of antibiotic therapy. We must deal with microorganisms not just in the periodontal pocket, but also in soft tissue walls and exposed dentine or cementum while treating periodontal disease[7].A local drug delivery system allows for the use of concentrations that are approximately 100 times higher than systemic administration. Site-specific, controlled-release delivery systems have made it possible for us to maintain therapeutic levels of the drug at the site of infection for an extended period of time8. Local agent delivery can be achieved through supra or subgingival irrigations, as well as sustained or controlled released products[8]. Antimicrobials such as chlorhexidine, tetracycline, metronidazole, clindamycin, and ofloxacin have been used in the development of local delivery systems for the treatment of periodontitis[9]. However, because repeated administration of the same class of agents can lead to resistance or side effects, efforts have been made to screen other classes of antibacterial agents for efficacy against periodontitis[10]. Studies have shown that macrolides are effective against periodontitis, since they appear to act as anti-inflammatory as well as anti-microbial agents[10]. Azithromycin belongs to the first subclass of macrolides known as azalides. It has good bacteriostatic activity in vitro against a wide range of organisms found in the mouth.[11] Azithromycin, like erythromycin, is a macrolide antibiotic. Azithromycin is a fascinating drug with a similar spectrum of activity to erythromycin but greater potency against gram-negative organisms.[12] Azithromycin has a long half-life and superior tissue penetration[11]. The study compared Azithromycin gel with scaling and root planing to scaling and root planing alone in the treatment of chronic periodontitis in patients with controlled diabetes, and assessed the effect of Azithromycin gel on clinical parameters such as gingival index, probing pocket depth, and clinical attachment level.

Material and Methods:

The patients were selected from the Department of Periodontology at the RUHS College of Dental Sciences in Jaipur. A total of 25 patients were selected, including both males and females between the ages of 25 and 55 years (Table 1). Patients diagnosed with chronic periodontitis with controlled diabetes and probing pocket depth of 5mm or more, aged 25-55 years, and free of any other systemic disease were included in the study, whereas patients who had received any topical or systemic antimicrobial treatment for the previous 6 months, including the use of mouthwash, periodontal treatment in the previous 6 months, allergic to macrolide antibiotics, pregnant, and lactating were excluded.

Clinical study participants were explained the concept and nature of the study and oral hygiene instructions were provided for the control of supragingival plaque. The study employed a split-mouth design, with two sites chosen in the contralateral quadrants that required periodontal treatment and had a probing pocket depth of at least 5mm at baseline. For this study, 50 sites were chosen from a total of 25 patients. To measure the pocket depth, a UNC-15 graduated periodontal probe was used.

Azithromycin Dihydrate (3.50 %), Chlorbutol BP (0.50 %), Carbopol® 934P (2.50 %), NaOH (6.50 %), and Water (87%)

were used to make 0.5 percent Azithromycin gel under strict aseptic conditions. Azithromycin dihydrate was dispersed in sterile unneutralized Carbopol in water solution containing chlorbutol BP. Following that, a sterile 4% w/v sodium hydroxide solution was added with constant mixing to achieve a final pH of 7-8.

Clinical Procedure:

The sites were categorized into two groups: experimental and control. On experimental sites, scaling and root planing were performed in combination with 0.5% Azithromycin gel, while on control sites scaling and root planing alone were performed (Fig. 1,2). To reduce errors, the maxillary first molar was chosen for local drug delivery only for standardization, and 0.2 ml prepared gel was injected into the periodontal pockets with a blunt cannula (Fig. 3). After the drug was placed, no periodontal dressing was applied, taking advantage of the drug formulation's filling, swelling, and occlusion of the pocket. Patients were given post-operative instructions. During the observation period, patients were advised not to floss the treated site, not to probe the area with their tongue, finger, or toothpick, and not to use chlorhexidine or any other anti-plaque formulations.

Periodontal status assessment: These clinical parameters were used to evaluate the periodontal status: gingival index, probing pocket depth, and clinical attachment level. Clinical parameters were recorded at the baseline, six weeks, and twelve weeks (Fig. 1,2,4,5).

Gingival Index: The tissues were divided into four gingival scoring units: Mesiofacial papilla, Facial margin, Distofacial papilla, and Lingual gingival margin. Each of the four gingival units was evaluated using the following criteria: The '0' value denoted Normal Gingiva, while the '1' value denoted Mild inflammation, a slight change in color, slight edema, no bleeding on probing, the '2' value denoted Moderate inflammation, redness, edema, glazing, bleeding on probing, and the '3' value denoted Severe inflammation, marked redness and edema, ulceration, and a tendency to spontaneous bleeding. The gingival index score for the area was computed by adding the scores around each tooth. The gingival index score for a tooth was calculated by adding the scores around each tooth and dividing them by four. Gingival Score '0' was rated as Excellent, while '0.1-1.0' was rated as Good, '1.1-2.0' was rated as Fair, and '2.1-3.0' was rated as Poor.

Probing Pocket Depth:With a UNC-15 graduated periodontal probe, the pocket depth was measured from the crest of the marginal gingiva to the base of the pocket.

Clinical Attachment level:The distance between the bottom of the pocket and the CEJ is denoted by CAL. This will be used to determine clinical attachment gain or loss later on.

Microbiological procedure:

Plaque samples were collected from the specified sites at baseline for bacteriological examination. To avoid contaminating the flora, the supragingival plaque was removed. The area was then isolated, and subgingival plaque was collected via a sterile universal curette that was inserted subgingivally into the deepest portion of the periodontal pocket parallel to the root axis and scraped coronally (Fig. 6). The samples were then placed on a transport swab and placed in a bottle containing thioglycolate transport media (Fig 7). After six weeks, the procedure was repeated. The collected samples were taken to the Microbiology lab for culture. The samples were emulsified before being inoculated onto blood agar plates. The Dynaxanaeroble jar was filled with the plates. To maintain the anaerobic environment, a 3.5 L Anaerogas pack (Himedia) containing 60% Kieselguhr, 30% Iron Powder, 20% Citric Acid, and 10% Sodium Carbonate was added to the anaerobic jar. Anaerobic jars were kept at 37 degrees Celsius for 48 hours, and then opened afterward for examination of microbial colonies on blood agar plates (Fig. 8). Colony morphology was used to identify the colonies. The growth of microorganisms was quantified in CFU/ml.

Statistical Analysis: The data was collected and organized on a spreadsheet (MS Office Excel 2010; Microsoft Corp.). The data was evaluated using statistical tools (IBM SPSS Statistics, v20.0; IBM Corp.). For numerical data, mean and standard deviation were used to represent the statistical data. For quantitative variables, the paired sample t test was used.

Results:

The difference in gingival index score between the two groups was not significant, while the difference in probing pocket depth and clinical attachment level was significant at baseline (Table 2). Between baseline and 12 weeks, there was a highly significant improvement in the gingival index and probing pocket depth scores in both groups. However, the experimental group improved more than the control group (Table 3,4). From baseline to 12 weeks, there was a highly significant improvement in clinical attachment level in both groups. However, the experimental group outperformed the control group (Table 5). Between baseline and 6 weeks, there was a highly significant difference in cocci and bacilli counts in both the experimental and control groups (Table 6).

Discussion:

There is growing evidence that organisms found in microbial plaque are the primary, and possibly the only, extrinsic etiologic agent involved in the development of inflammatory periodontal disease.[13] Given the bacterial etiology of periodontal disease, which is the leading cause of tooth loss in adults, the microbial contents of the gingival sulcus or pocket may reflect not only the state of health or disease but also the presence or absence of acute disease. Though scaling and root planing are commonly used to treat chronic inflammatory periodontal disease, antimicrobial therapy has also been directed at specific bacteria associated with clinically diseased sites to help augment mechanical treatment aimed at removing subgingival calculus and toxins. According to Goodson JM et al.14, for the treatment of chronic inflammatory periodontitis, three methods of drug delivery were typically used: systemic administration of antibiotics, topical administrations of antibacterial agents (such as oral rinses), and pocket irrigation. Each of these methods has merits and disadvantages. Furthermore, agents in mouth rinses and those used during supragingival irrigation do not reach beyond 5mm into the periodontal pocket predictably. Systemic administration necessitates frequent dosing, which increases the risk of resistant organisms and superinfection, as well as the risk of adverse effects such as gastrointestinal disorders.

To address these issues, local drug delivery systems are developed. A local delivery device is made up of a drug reservoir and a limiting element that regulates the rate of drug release. Local delivery devices are classified into two types based on the duration of medication release. Sustained release delivery devices and controlled release delivery devices are the two types of devices. Sustained-release formulations are intended to deliver drugs for less than 24 hours. Controlled delivery systems, on the other hand, should have drug release times that exceed one day. The controlled release local delivery systems that are currently being investigated can be classified as reservoirs with or without a rate-controlling system.

Tetracycline is the most commonly used drug delivery system reported in periodontal literature.[13] According to Goodson J.M.15, the GCF concentration achieved by Tetracycline fibers was 1300g/ml, but the main disadvantage of this system was that it was not resorbable and had to be removed. Furthermore, the time required for placement was 10 minutes per tooth. These concerns fueled the development of absorbable antibiotic delivery systems. Actisite was the first local antibiotic therapy for periodontal disease, but it is no longer commercially available.[16] According to Knoll-Kohler E[17], the limitation of 25% Metronidazole was that its spectrum of activity was restricted to anaerobes only, and the GCF concentration achieved was 120mg/ml for the first few hours but quickly decreased, necessitating multiple applications of this system. Stelzel[18] conducted a 6-month study with 30 patients in which treatment consisted of applying 25 percent Metronidazole gel at weekly intervals. The results were comparable to scaling and root planing without any additional benefits. Krayer et al.[16] reported a 14-day therapeutic drug level of 2% Minocycline microspheres. Williams RC et al.[19] discovered that scaling and root planing combined with minocycline microspheres was more effective than scaling and root planing alone in reducing probing in 748 patients over 9 months.

According to Krayer et al.[16], a major disadvantage of 10 percent Doxycycline (Atridox) was the need to mix the powder and liquid components, and it was frequently pulled out while removing the syringe. At 4 weeks after treatment,

Jorgensen MG[20] found that controlled-release Doxycycline placed in 6-7 mm pockets caused no significant additional reduction in subgingival pathogenic microbiota compared to thorough scaling and root planing alone. Since controlled release Doxycycline does not appear to have a distinct advantage in suppressing several subgingival pathogenic microorganisms, the rationale for its use in periodontal therapy is unclear. Jorgensen MG et al.[20] compared the subgingival microbiota of periodontitis sites treated with the Chlorhexidine chip plus scaling and root planing to scaling and root planing alone. According to the findings, there was no statistically significant difference in total colony counts between subgingival locations treated with a Chlorhexidine chip plus scaling and root planing and those treated with only scaling and root planing. Furthermore, there was no significant difference in the percentages of major periodontal pathogens and total periodontal pathogens between the Chlorhexidine plus scaling and root planing and scaling and root planing alone groups. According to the findings of this study, chlorhexidine chip treatment provides little or no additional benefits in adults with periodontitis.

Azithromycin gel was utilized in this study due to its advantages over other medications. Azithromycin is a semisynthetic, acid-stable antibiotic that serves as the prototype for the azalides, a new class of macrolides. Furthermore, the GCF concentration achieved by locally delivered Azithromycin gel is 2041g/ml, which can be retained on the site for up to 28 days.[16,21] Because of its increased acid stability, increased tissue distribution, decreased binding to plasma proteins, and rapid absorption, azithromycin is useful in the treatment of periodontal infections. Another important feature of this drug is its increased concentration in cells such as neutrophils, macrophages, fibroblasts, monocytes, and epithelial cells, which may explain the high level of Azithromycin found in infected tissue. Furthermore, Azithromycin is the most effective macrolide against gram-negative anaerobes, such as Fusobacterium species, Bacteroid species, A.actinomycetem-comitans, and Selemonoas species.[11] As an adjunct to non-surgical therapy, azithromycin has been used systemically in the treatment of periodontal disease.

In this study, an indigenously prepared formulation containing 0.5 percent Azithromycin gel was used. Azithromycin dihydrate was incorporated into Carbopol® 934P, and the Azithromycin concentration was adjusted to 0.5 percent. The concentration was determined based on an in-vitro study in which it was reported that the MIC90 or the concentration required to inhibit the growth of 90% of the bacteria, for Azithromycin is 0.5g-2.0g. Carbopol® 934P, which is used in the formulation, is low in toxicity, has high compatibility with other chemicals, and can solubilize drugs with varying physicochemical properties.

The gingival index was used to assess the severity and quantity of gingival inflammation. The gingival index changed significantly in both the control and experimental groups. The gingival index was 2.51±0.38 mm and 2.53±0.17 mm at baseline for control and experimental sites, and at 12 weeks mean score was 1.02±.057 mm and 1.02±.048 mm respectively(Table 3). These findings were consistent with the findings of Eickholz P[22], who discovered a significant reduction in the gingival index for both control and experimental sites, which were 1.81± 0.55 and 1.1±1.0 respectively. Similar findings were found in Nikolaosetet al.'s [23] studies of locally applied Doxycycline. Reduction in the gingival index was found to be statistically significant for control and experimental groups ($P<0.05$) at the end of 3 months and 6 months. Dr. N Priyanka et al.[24] discovered comparable results when they investigated locally administered Satranidazole in the treatment of Type 2 Diabetes Subjects with Chronic Periodontitis. The reduction in gingival index was found to be statistically significant ($P<0.05$) at the end of three months for both the control and experimental groups.

The main clinical outcome used to determine the success of a treatment is a reduction in probing depth. When compared to baseline, both groups showed a highly significant reduction in probing depth at all time intervals. Probing pocket depth for control and experimental sites were 6.64±1.07 mm and 7.36±1.15 mm at baseline, which reduced to 4.84±0.59 mm and 4.32±0.98 mm respectively at 12 weeks (Table 4). Pradeep et al.[21] investigated the effect of subgingivally

delivered 0.5% Azithromycin as an adjunct to scaling and root planing in the treatment of chronic periodontitis and found a significant reduction in probing pocket depth of 4.40±1.12 mm and 4.00±0.76 mm for control and experimental sites, respectively, with p-value ($p<0.05$). These findings were consistent with current study's findings, which show a greater reduction in pocket depth in experimental sites versus control sites. The findings from this study were consistent with those of Esha Agarwal.[25], who evaluated locally delivered 0.5% Azithromycin as an adjunct to non-surgical treatment in chronic periodontitis with Type 2 Diabetes. SRP plus placebo gel was given to Group 1, while SRP plus 0.5 percent AZM was given to Group 2. Probing depth (PD) was measured at baseline, 3, 6, and 9 months. Both therapies resulted in significant improvements in periodontal disease. Over 9 months, patients in Group 2 treated with SRP + 0.5 percent AZM had greater reductions in PD ($p<0.05$) than patients in Group 1. When Dr. N Priyanka et al.[24] evaluated locally applied Satranidazole in the Treatment of Type 2 Diabetes Subjects with Chronic Periodontitis, they found similar results. The experimental group had a greater mean reduction in PD than the control group at 6 months ($p<0.05$). Similarly, Gomi et al.[26] discovered that systemic Azithromycin administration in conjunction with scaling and root planing resulted in a 1.77 mm reduction in probing depth after 13 weeks.

When the present study's findings were compared to those of other local antibiotic therapies, better results were observed. Similarly, in studies using locally applied tetracycline, Jegon et al.[27] and Yalsin et al.[28] found that mean probing depth reductions were 0.93 mm at 12 weeks ($P<0.05$) and 0.41 mm at 7 weeks ($P<0.047$), respectively, while Van Steenberghe D.[29] found 1 mm reduction in probing depth at 12 weeks after Minocycline application.

The gain in clinical attachment level is the primary clinical outcome used to determine treatment success. At all-time intervals, both groups showed a highly significant increase in clinical attachment level when compared to baseline. The present study found that the clinical attachment levels for the control and experimental groups at baseline were 6.72±1.02 mm and 7.44±1.12 mm, respectively, and 5.04±0.45 mm and 4.40±1.04 mm at 12 weeks. These findings were consistent with the findings of Pradeep et al.[20], who found that the clinical attachment levels for the control and experimental groups at baseline were 5.53±1.06 mm and 5.33±1.11 mm, respectively, and 4.93±0.96 mm and 4.27±0.96 mm at 12 weeks. Gomi et al.[26] discovered that systemic Azithromycin administration in combination with scaling and root planing contributed in a clinical attachment level gain of 2.76 mm after 13 weeks.

Esha Agarwal.[25] studied the use of locally delivered 0.5% azithromycin as an adjunct to non-surgical treatment of chronic periodontitis in type 2 diabetes patients. SRP plus placebo gel was used in Group 1, and SRP plus 0.5 % AZM was used in Group 2. Both therapies resulted in significant reductions in CAL. Over 9 months, patients in Group 2 treated with SRP + 0.5 % AZM gained more CAL ($p<0.05$) than patients in Group 1. These findings were consistent with the current study's findings, which show a greater gain in CAL in experimental sites compared to control sites. Dr. N Priyanka et al.[24] found similar results when they evaluated locally applied Satranidazole in the Treatment of Type 2 Diabetes Subjects with Chronic Periodontitis. At 6 months, the experimental group had a higher mean CAL gain than the control group ($p<0.05$). In a study by Mascarenhas et al.[30] comparing full-mouth scaling and root planing plus Azithromycin to scaling and root planing alone, mean clinical attachment level gains of 1.01 and 1.52 mm in moderate pockets (4 to 6 mm) were seen at 6 months, respectively, whereas a study by Watts et al.[31] using Minocycline gel locally applied showed a slight gain of 0.46 mm in clinical attachment level after 12 weeks.

Microbial parameters were measured at the baseline and end of the 6-week study. The control group's mean values for cocci at baseline and 6 weeks were 39640±12640 and 46000±16140 ($P<0.001$), respectively, and the experimental group's mean values were 41040±13150 and 55360±16340 ($P<0.001$), respectively, indicating a highly significant improvement in the number of coccoid cells at 6 weeks. Mean values for bacilli at baseline and 6 weeks in the control group were 66560±43500 and 46160±26880 respectively and for the experimental group 75880±52770 and 42840±27700

(P<0.001) respectively. Both the experimental and control groups had statistically significant microbiological results. These findings were consistent with the findings of Pradeep et al.[21], who discovered coccoid cells and (straight rods and filaments) in the experimental group, which showed a highly significant difference after azithromycin gel application (P<0.001) at the end of 6 weeks. Sander et al.[23] observed an increase in cocci 4 weeks after 0.2 percent chlorhexidine irrigation and a decrease in motile rods and spirochetes after 4 weeks. Okuda et al. 32 and Hejil L.[33] obtained comparable results for Minocycline gel and locally applied Tetracycline fibers. Similarly, Gomi et al.[26] discovered a reduction in the total number of bacteria and black pigmented rods after using systemic Azithromycin in conjunction with a full mouth rinse. Root planing and scaling in terms of microbial parameters, all bacteriologic categories in both groups demonstrated a shift toward health. This was consistent with the findings of Greenwell and Bissada[34], who discovered that coccoid and other (straight rods, filaments, and fusiform) groupings were regarded health markers.

Within the scope of this study, it was discovered that using 0.5 percent Azithromycin gel in combination with scaling and root planing enhanced the outcome of non-surgical treatment of chronic periodontitis patients with controlled diabetes.

Conclusion:

The study investigated the therapeutic effect of 0.5% Azithromycin gel as a local drug delivery system as an adjuvant to scaling and root planing in diabetic patients. The findings of this study led to the following conclusions.

- Clinical parameters such as gingival index, probing pocket depth, and clinical attachment level decreased statistically significantly in both groups.
- When the groups were compared, the experimental group outperformed the control group statistically significantly in all clinical parameters.
- The experimental group had a statistically significant reduction in bacilli and an improvement in coccoid cells when compared to the control group.
- This study discovered that when combined with scaling and root planing, 0.5% Azithromycin gel is well tolerated by patients, is safe and easy to administer, and is effective in patients with chronic periodontitis.

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