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Antimicrobial effect of systemic and local delivery of Azithromycin against Porphyromonas gingivalis : A Randomized clinical trial

[1]Dr.Shruthi.K.R, Postgraduate Student, Department of Periodontology, M.S. Ramaiah University of applied sciences, faculty of dental sciences, Bengaluru-560054, Karnataka, India.

[2]Dr.Bhavya.B, Associate Professor, Department of Periodontology, M.S. Ramaiah University of applied sciences, faculty of dental sciences, Bengaluru-560054, Karnataka, India.

Corresponding Author: Dr. Shruthi K R, Post graduate student, Department of Periodontology, M. S. Ramaiah University of Applied Sciences, Faculty of Dental Sciences, Gnanagangothri campus, New BEL Road, MSR Nagar, Bengaluru-560054, Karnataka, India.

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Abstract

Our goal was to examine the differences in clinical and microbiological effects after non-surgical periodontal therapy in patients with chronic periodontitis. Hence, the aim of the present study was to assess the antimicrobial effect of systemic and local delivery of Azithromycin against Porphyromonas gingivalis in chronic periodontitis before and after non-surgical periodontal therapy.

A total of 40 patients were randomized into two groups: Group 1 included 20 subjects who received scaling and root planing(SRP)+ systemic Azithromycin (AZM) and Group 2 included 20 subjects who received SRP+2% locally delivered Azithromycin gel. Clinical parameters: Bleeding on probing(BOP), Probing pocket depth (PPD),Clinical attachment level(CAL) were recorded and the colony forming units of Porphyromonas gingivalis were assessed at baseline and 6 months after non-surgical periodontal therapy(NSPT).

A 2% locally delivered Azithromycin gel has shown statistically significant reduction in bleeding on probing, probing pocket depth, colony forming units of Porphyromonas gingivalis, and improvement in clinical attachment level when compared to systemic administration of Azithromycin after 6 months of non-surgical periodontal therapy.

A Study concluded that the adjunctive use of 2% locally delivered Azithromycin gel showed better results in both clinical and microbiological parameter after 6 months follow-up of non-surgical periodontal therapy.

Keywords: Chronic periodontitis, Digital colony counter, 2% locally delivered Azithromycin gel, Porphyromonas gingivalis, Systemic Azithromycin, Sheep's blood agar culture media.

Introduction

Periodontal diseases are chronic, predominantly gram-negative infections of the oral cavity that are initiated in the gingiva and if untreated leads to alveolar bone destruction and eventual tooth loss. It occurs as a result of local infection by pathogenic micro-organisms within the periodontal pocket[1]

Azithromycin is a semi- synthetic, acid-stable macrolide belongs to Azalides group, which has better oral absorption because of its higher resistance to gastric acids. It has wide antimicrobial action towards anaerobic bacteria as well as gram-negative enteric bacilli and periodontal pathogens like A.a and Porphyromonas gingivalis.[2]

Systemic antibiotics were mainly used as an adjunct to scaling and root planing. Use of systemic antibiotics provides enhanced clinical outcomes in terms of pocket depth reduction and clinical attachment level gain than SRP alone in treating chronic form of periodontitis.

Very few patients maintain periodontal health over lifetime without benefits of regular dental care consisting of oral hygiene instructions and non-surgical periodontal therapy. A novel approach is local biodegradable sustained or controlled release of antimicrobial agents that are effective against periodontopathogens can also reduce pocket depth.

Benefits of using local delivery of antimicrobial agents are:

- Better patient compliance
- Enhanced pharmacokinetic response
- Greater access and ability to position the drug adjacent to tissue
- Better ability to deliver a total lower dosage of drug at more controlled concentration.

Local drug delivery of AZM can provide 100 fold higher therapeutic doses of the agent in sub gingival areas than systemic therapy.

The strength of anaerobic culture is the ability to detect all species present in a cultured sample. Although it is, time consuming and labour intensive, that limits the number of subjects that can be analysed.[3]Anaerobic culture media is considered as “Gold standard” because of its ability to detect new bacterial species and its susceptibility to antibiotics.[4] No study has assessed the use of Azithromycin (Systemic & LDD) in treating periodontitis in India.

Hence, study was required to check the antimicrobial efficacy of both systemic and local delivery of AZM in reducing colony-forming units of Porphyromonas gingivalis in chronic periodontitis patients before and after non-surgical periodontal therapy.

Materials and Methods

The present study was a Single blinded, Randomized clinical trial, an Interventional in nature. Patients who were reported to Department of Periodontology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bengaluru were selected for the study. The duration of study was planned for 6 months from May-October 2017.

Inclusion criteria

- Patients between the age group of 25 - 65 years both males and females were enrolled in the study.
- Patients with chronic periodontitis with bleeding on probing; pocket depth≥ 5mm; clinical attachment loss ≥ 3mm
- Patients who were diagnosed with chronic periodontitis

Exclusion Criteria

- Patient with a history of any systemic diseases
- Patients who were allergic to Azithromycin
- Patients who smoke
- Patients with history of periodontal treatment in previous 6 months.
- Patients who were pregnant or lactating
- Patients who were on antibiotic or other drugs that affect periodontal status in the past 6 months
- Patients regularly using chlorhexidine mouthwash

Sample size Determination

The ideal sample size of 19 subjects for each group were necessary to provide an 80% power with an alpha value of 1.96 and alpha error of 5% by considering an attrition of about 5%, 20 participants were included in each group.

The protocol of this study was reviewed and approved by the Institutional Review Board.

Methodology for objectives

Objective 1: To assess and compare the effectiveness of both systemic and local delivery of Azithromycin in reducing colony forming units of *Porphyromonas gingivalis* in chronic periodontitis patients.

Objective 2: To assess the clinical parameters: BOP, PD, CAL in chronic periodontitis before and after non-surgical periodontal therapy.

Microbial sampling and isolation of *Porphyromonas gingivalis* by culture

Microbial sampling on periodontitis patients were performed with pocket depths of ≥5 mm. The deepest periodontal pockets were selected for sampling by the first blinded examiner. After removing supra-gingival plaque the area was isolated with cotton pellets and the absorbent paper points were inserted into each periodontal pocket for about 20 seconds. The paper points were transferred into an aliquot with Reduced Transport Fluid (RTF) medium. All samples were coded and sent to laboratory for processing within 72 hours after sample collection. These samples were further analyzed using microbial culture techniques to detect the presence of periodontopathogens that were processed at room temperature (25°C) and incubated in CO2 for anaerobic culture system. The Sheep's blood agar medium was incubated in 10% CO2 at 37°C for four days and then colonies were observed on culture plates which were later appreciated as black pigmented colonies after gram staining. The species found on blood agar media were enumerated and their percentage of TVC was calculated. After obtaining the reports of Total viable counts from laboratory, the patients were randomly allocated into 2 groups by a toss of coin method by second examiner, who prescribed Tab. Azithral 500mg once daily 1 hour before food or 2 hours after food for 5 days for Group 1 (systemic) patients and also delivered commercially available 2% Azifast gel as LDD into periodontal pocket where subgingival plaque samples were collected for Group 2 (LDD) patients. After 6 months of follow up, the first examiner repeated sub-gingival sample collection and Total viable counts were measured. BOP was measured by first examiner using modified sulcus bleeding index (Mombelli, 1987). Customized acrylic occlusal stents and UNC-15 probe was used to record PD and CAL at baseline and after 6months of NSPT.

Planned statistical analysis

- The Statistical Analysis was done using SPSS version 22 software IBM. Corp. with normality of all the variables at baseline and 6 months in 2 study groups were analysed by using Kolmogorov Smirnov test, clinical parameters were expressed in terms of Mean and Standard deviation, mean difference between two study groups were analysed by using Mann-Whitney U test and Wilcoxon matched pair test and level of significance was set at $P<0.05$.

Results

A total of 50 patients were recruited in the present study from May to November 2017. After microbiological screening for *Porphyromonas gingivalis*, 40 patients were assessed for clinical parameters and followed by SRP to both the groups by first examiner (blinded) to avoid bias, then Group 1 (20 patients) were provided with systemic AZM and Group 2 (20 patients) with 2% locally delivered AZM gel by second examiner and both the groups were re-evaluated after 6months to assess the efficacy of AZM. Based on Per Protocol method we included study patients who reported to the department throughout the study duration at baseline and at six months. So at the end of 6 months, 19 patients were subjected towards statistical analysis in each group.

Bleeding on probing (BOP)

Mean BOP showed significant differences of 0.42 in systemic group, 0.47 in LDD group at baseline and with standard deviation of 0.58 in both Group 1 and 2 at baseline. Significant percentage change of 18.18% in systemic,20.45% in LDD group were seen after treatment with BOP reduction from 2.32 to 1.89 in systemic group and 2.32 to 1.84 in LDD group. A statistically significant reduction was observed in both groups on intra group comparison of BOP scores from baseline and 6 months by Wilcoxon matched paired test. (Table 5.1).Mean BOP was about 2.32% in both groups at baseline .But after 6 months, no statistically significant differences were noticed on intergroup comparison between both systemic and LDD groups at baseline and 6months by Mann-Whitney U test.(Graph 5. 2).

Probing pocket depth (PPD)

Mean PPD showed significant differences of 5.21 in systemic group, 4.63 in LDD group at baseline and with standard deviation difference of 0.61 in both Group 1 and 2 at baseline. Significant percentage change of 11.11% in systemic,27.27% in LDD group were seen after treatment with BOP reduction from 5.21 to 4.63 in systemic group and 5.21 to 3.79 in LDD group. A statistically significant reduction was observed in both groups on intra group comparison of PPD scores from baseline and 6 months by Wilcoxon matched paired test. (Table 5.3). A statistically significant difference in PPD scores were noticed on inter group comparison in LDD group when compared with systemic group after 6 months.(Graph 5.4).

Clinical attachment level (CAL)

Mean CAL showed significant differences of 3.95 in systemic group, 4.42 in LDD group at baseline and with standard deviation difference of 1.39 in both Group 1 and 2 at baseline. After treatment, increase in CAL score from 3.95 to 4.42 in systemic group and 4.42 to 4.95 in LDD group was noticed. A statistically significant increase in CAL scores were observed in both groups on intra group comparison from baseline and 6 months by Wilcoxon matched paired test. (Table 5.5).A statistically significant increase in CAL scores were noticed on intergroup comparison between systemic and LDD groups at baseline to 6 months. (Graph 5.6).

Colony Forming Units (CFU)

Mean CFU counts showed significant differences of 93.68 in systemic group, 105.26 in LDD group at baseline. A statistically significant decrease in CFU counts were observed in both groups on intra group comparison from baseline to 6 months by Wilcoxon matched paired test. (Table 5.7).A statistically significant decrease in difference of CFU counts were noticed on inter group comparison from baseline to 6 months. (Graph 5.8).Not all variables of baseline and 6 month in two study groups (Systemic and LDD) followed a normal distribution. Therefore, the non-parametric tests were applied, which showed a statistically significant difference in all groups from baseline to 6months. (Table 5.9)

Discussion

The efficacy of scaling and root planing as a part of the non-surgical periodontal treatment of chronic periodontitis has been established through longitudinal studies of periodontal therapy. However, several anatomic factors such as furcation and deep pockets have been suggested to limit the effectiveness of non-surgical periodontal therapy. Hence, antibiotic therapy can be used as an adjunct to specific periodontal treatment. The present randomized clinical trial compared the effect of scaling and root planing with an adjunct use of AZM both systemic and local delivery, revealed statistically significant differences among clinical parameters and microbiological effects after 6 months of re-evaluation.To the best of our knowledge, this is the first study where Azithromycin was used in both systemic and local delivery with an adjunct to non-surgical periodontal therapy in patients with specific microbiological profile.

According to reviewed literature, authors have followed selection of patients with specific microorganism in order to prescribe an adequate drug strategy.Studies conducted by Loesche et al.,Flemming et al.,Saxen and Asikainen et al.,[1] has shown that if targeted pathogens were identified previously and treated with adjunctive systemic antibiotics showed better results after appropriate therapy. The selection of Azithromycin dosage may be controversial, because the approved dosages were different in the United States (5-day regime, first dose of 500 mg and then 250 mg daily) and in Europe (3- day regime of 500 mg daily). As per review of literature done by (Smith et al.[5], Mascarenhas et al,[6] Dastoor et al[7], Gomi et al.[8], Haffajee et al.[9], Haas et al.,[10] Yashima et al.,[11]) 500 mg of systemic Azithromycin once daily before 1 hour of food or 2 hours after food for 5 days was beneficial in reducing CFU of microflora. Therefore, in the present study Group 1 patients received same regime after non-surgical periodontal therapy.

To be effective, antibiotic dosing should achieve drug levels in infected tissues equal to or exceeding minimal inhibitory concentration of the target organism. MIC is the lowest concentration of the antibiotic that prevents visible growth of bacterium determined in culture plates using serial dilutions of the antibiotic. The MIC of AZM against standard and clinically isolated strains of bacteria associated with periodontal diseases such as *Porphyromonas gingivalis, A.a, Fn* is between 0.025 and 2 µgm/ml. In a study carried out by (Pradeep et al.,2008) using High pressure liquid chromatography analysis, they confirmed that 0.5% AZM gel delivered subgingivally sustained concentration above 2 µgm/ml in GCF at the end of 28days. To maintain the concentration of 4 µgm/ml in GCF for 6 months in the present study we used 2% AZM gel for Group 2 subjects.

A hypothesis on local drug delivery of AZM by A.R Pradeep et al.,[12]resulted in high concentration of drug in the periodontal pocket, which might have penetrated into the periodontal tissues as well. This dual effect on pocket microflora as well as on pathogens invading the tissue might have resulted in enhanced clinical results without any systemic side effects and bacterial resistance. Therefore, they used 0.5% AZM gel to check efficacy in adjunct to SRP for the treatment of periodontal pocket in patients with chronic periodontitis and showed significant improvement in clinical parameters when compared to placebo gel. In the present study, we used 2% of AZM as local delivery to check the efficacy with an adjunct to SRP in chronic periodontitis patients, which showed a statistically significant improvement in both clinical and microbiological parameters after 6-months of non-surgical periodontal therapy.

A study conducted by Yashima et al., showed that no significant differences in BOP scores were noticed after 12-months of non-surgical periodontal therapy between FM-SRP, PM-SRP, and control groups. In another study conducted by Oteo et al.,[13] where significant reduction of BOP was observed ranging from 35-39% in AZM group and 19-24% in placebo group after treatment. The present study was in accordance to above mentioned two studies. However, the mean BOP in the present study showed significant differences of 0.42% in systemic group and 0.47% in LDD group at baseline with a. significant percentage changes of 18.18% in systemic and 20.45% in LDD group were seen after treatment, with a BOP reduction from 2.32 to 1.89 in systemic group and 2.32 to 1.84 in LDD group.

A study done by A R Pradeep et al.,[14] evaluated the effect of subgingivally delivered 0.5% AZM in the treatment of chronic periodontitis as an adjunct to SRP showed significant reduction of probing pocket depth. In harmony to the above mentioned study, the present study showed significant mean PPD differences of 5.21mm in systemic group and 4.63mm in LDD group at baseline and with significant change of 11.11% in systemic is 27.27% and in LDD group were seen after 6-months. A statistically significant reduction in PPD score was observed in both groups on both intra-group and inter group comparison from baseline to 6-months.

A study conducted by Esha Agarwal et al.,[15] has shown gain in mean CAL from 1.03mm to 2.04mm in SRP+AZM group after 9-months of periodontal therapy and also a study done by AR Pradeep et al., 2013 revealed a mean gain in CAL of 2.44mm with 0.5% gel Azithromycin after 9-months after non-surgical periodontal therapy. In solidarity to these studies, the present study showed mean CAL of 3.95mm in systemic and 4.42mm in LDD group at baseline. There was an increase in CAL score from 3.95 to 4.42mm in systemic group and 4.42 to 4.95mm in LDD group after 6-months follow up of NSPT.

The present study was in conflict to a study conducted by Gomi et al., where mean CAL at baseline was 8.3 mm, after SRP it has reduced to 7.3mm and no statistically significant difference in clinical parameters were observed at baseline, 1, 5, 13, 25 weeks. The present study was also in conflict to a study conducted by Emingil et al.,[16] where the mean CAL of 3 ± 0.9 mm showed significant reduction at 3-months post SRP, but not diminished further.

In a study conducted by Swierkot et al., [17] showed a positive correlation between clinical and microbiological parameters from baseline to 1,2,4,8 months after NSPT in Q-SRP, FMD, FM-SRP groups. They remarked that Porphyromonas gingivalis counts were significantly reduced after 8 months of non-surgical periodontal therapy. As stated by Sampaio et al.,[18] and Buket Han et al., Porphyromonas gingivalis, counts were significantly decreased after 6-months in AZM group.

In another study done by Hans et al., Porphyromonas gingivalis reduction of 32% in 3 months, 70% in 12 months were noticed. Based on published literature by Mascarenhas et al., Gomi et al., Yashima et al., also found significant reduction in Porphyromonas gingivalis counts after 1 and 3 months of NSPT with an adjunct to systemic AZM. In harmony to above mentioned studies, the present study showed significant differences in Porphyromonas gingivalis CFU counts of about 93.68 in systemic group and 105.26 in LDD group at baseline. After 6-months of NSPT, decrease in CFU counts from 93.68 to 82.11 in systemic group and 105.26 to 85.79 in LDD group were noticed.

Studies done by Yashima et al., Haffajee et al., showed no significant differences in Porphromonas gingivalis counts

after 9-months of non-surgical periodontal therapy which were contradictory to the present study that showed a statistically significant reduction in Porphyromonas gingivalis counts after 6-months of non-surgical periodontal therapy.

Conclusions

- It is clear that systemic or local delivery of Azithromycin has a role in treating periodontitis. However, due to the problems related to systemic side effects, microbiological adverse effects and bacterial resistances systemic Azithromycin is not commonly used.
- Although, both treatment strategies seemed to benefit the patients, In the present study with adjunctive use of locally delivered 2% Azithromycin gel showed better results in both clinical and microbiological parameters after 6months following non-surgical periodontal therapy.
- Moreover, when a decision has to be made in prescribing the drug, it should be used under most optimal conditions in order to achieve best results.

Future direction

- There is presence of limited evidences for the comparison of systemic and local delivery of Azithromycin after non-surgical periodontal therapy.
- Further multicentre research with larger sample size, different concentrations of Azithromycin gel should be carried out on patients whose host tissue defences are compromised to confirm the results of the present study.

Acknowledgements

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Legend Figure

Figure 1: Subgingival plaque sample collection

Figure 2: Inserting absorbent paper point into aliquot

Figure 3: Coded aliquot

Figure 4: Streaking of culture plates with loops

Figure 5: Anaerobic jar

Figure 6: Incubator

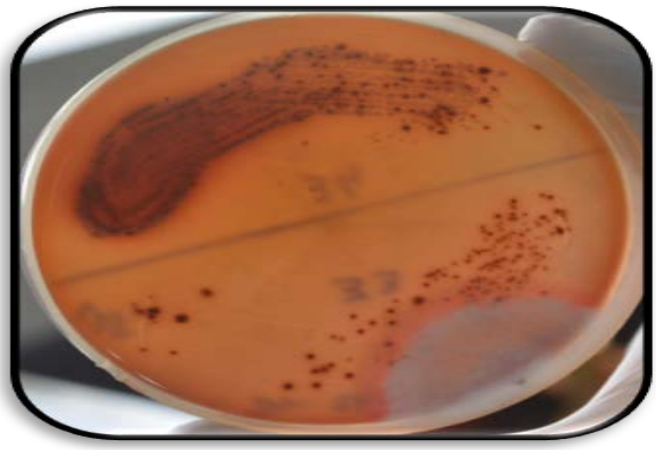

Figure 7: *Pg* detected on culture plates

Figure 8: Digital colony counter

Figure 10:Systemic AZM

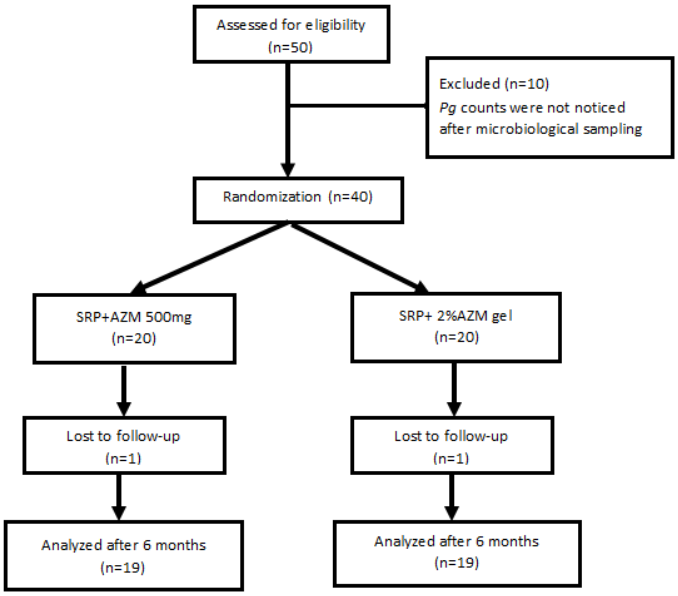

Figure 9: Study flow chart

Figure 11: 2% AZM gel

Figure 12: Locally delivered 2% AZM gel

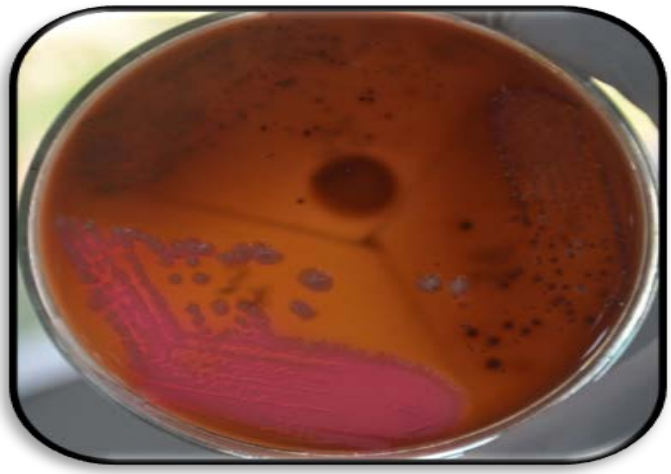

Figure 13: *Pg* counts on culture plate Pre-op (systemic AZM group)

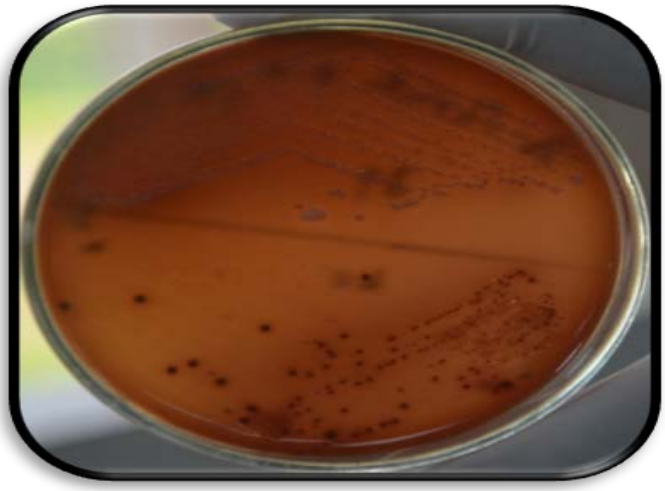

Figure 14: *Pg* counts on culture plate Post-op (systemic AZM group)

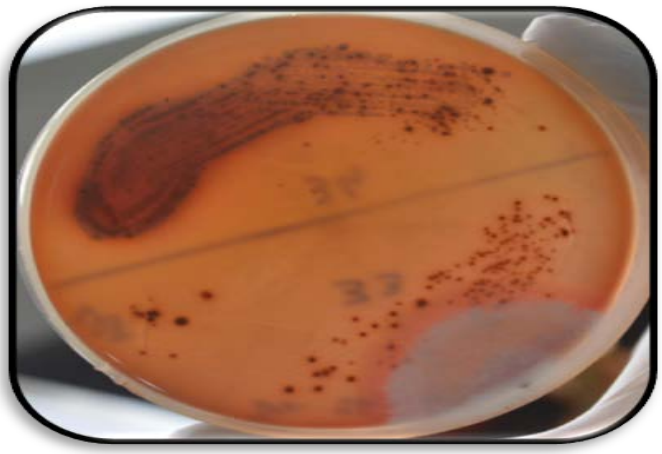

Figure 15: *Pg* counts on culture plate Pre-op (LDD AZM group)

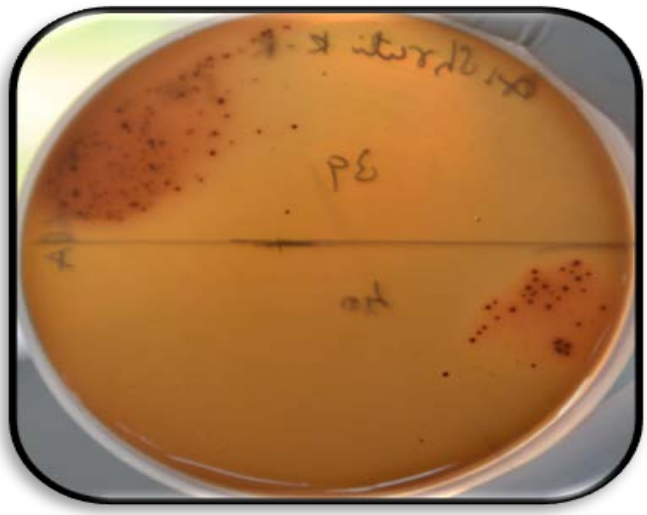

Figure 16: *Pg* counts on culture plate Post-op (LDD AZM group)

Figure 17: Pre-op (systemic AZM group)

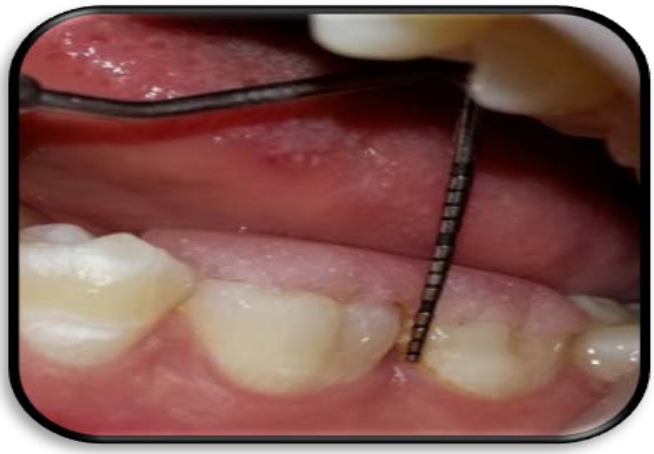

Figure 18: Post-op (systemic AZM group)

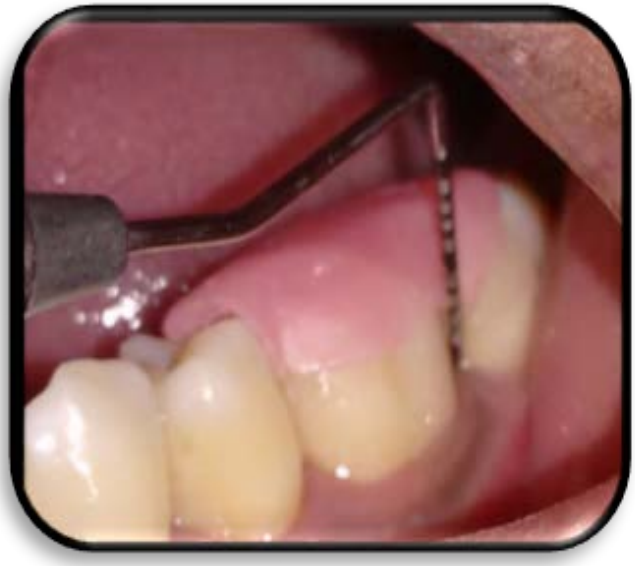

Figure 19: Pre-op (LDD AZM group)

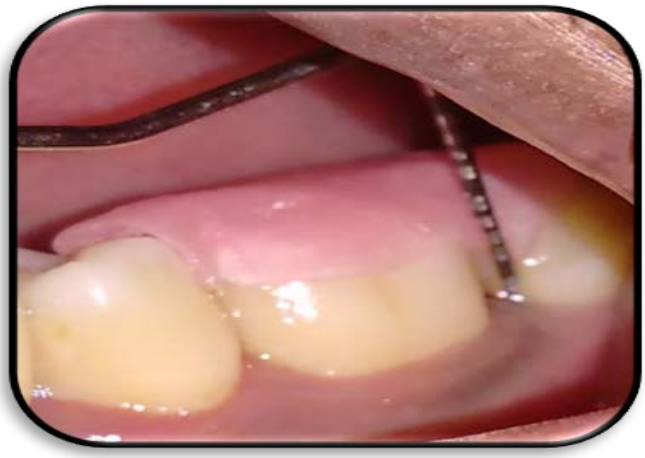

Figure 20: Post-op (LDD AZM group)