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Periodontics

# Efficacy of Locally Delivered 0.5%Azithromycin Gel as an Adjunct to Nonsurgical Periodontal Therapy in Patients with Chronic Periodontitis -A Clinical Trial

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**Original Research Article**

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**Abstract:** Azithromycin is an azalide antibiotic, effective against a wide range of oral bacteria including periodontopathic bacteria. Adjunctive use of systemically administered Azithromycin (AZM) along with conventional mechanical therapy has proven to show improvement in periodontal health in many studies. The present study is designed to evaluate the clinical effects of subgingivally delivered 0.5% AZM gel as an adjunct to scaling and root planning (SRP) in chronic periodontitis patients. A randomized clinical trial was conducted where 40 subject were categorized into 2 groups: group A (SRP + subgingivally delivered 0.5% Azithromycin gel) and group B (SRP + placebo gel) and the clinical parameters were recorded at baseline, 1st, 3rd and 6th month which included gingival index (Loe and sillness, 1963), plaque index (Silness and Loe, 1964), probing pocket depth, clinical attachment level. Both the therapies resulted in significant improvement. The gingival index and plaque index showed no difference between groups ($p>0.05$) whereas the mean probing pocket depth reduction (group A=2.85, group B=2.25) and mean clinical attachment level gain (group A= 2.75, group B=2.20) was statistically significant ($p<0.05$) from baseline to 6th month in both the groups. The combination of SRP and 0.5% Azithromycin gel was more effective than SRP alone in reducing probing depths and improving the clinical attachment levels.

**Keywords:** Azithromycin, Local drug delivery, SRP, chronic periodontitis.

## INTRODUCTION

Periodontal disease is one of the most common inflammatory diseases of microbial origin seen in adults who affects the tooth-supporting tissues.

Even though the etiology of Periodontitis is considered to be multifactorial, the primary etiological factor in the development of periodontal disease is the bacterial plaque that coats the teeth [1, 2]. More than 500 microbial species have been identified in the subgingival plaque. It consists of microorganisms involved in periodontal health and disease. Elevated proportions of some subgingival microbial species have been associated with destructive periodontal disease activity. The bacterial profile of chronic periodontitis has been explored in cross sectional and longitudinal studies. These putative periodontal pathogens include *Porphyromonas gingivalis (P.gingivalis), Tannerella forsythia (T.forsythia), P. intermedia, Campylobacter rectus (C.rectus), Eikenella corrodens, F. nucleatum, Aggregatibacter actinomycetemcomitans (Actinobacillus actinomycetemcomitans* previously) (A. *actinomycetemcomitans*), *P. micros and Treponema spp*. But *P. gingivalis, T. forsythia, P. intermedia, C. rectus* and *F. nucleatum* have been reported at higher levels in sites with active disease or with progressing disease [2, 3, 4].

Elimination or adequate suppression of putative periodontopathic microorganisms in the sub gingival microbiota is essential for periodontal healing. The periodontal healing can be achieved by nonsurgical and surgical therapies. The nonsurgical periodontal therapy is the gold standard for periodontal therapy. The nonsurgical periodontal therapy includes scaling and root planing which involves removal of subgingival plaque and calculus, that reduces bacterial load, shrink swollen and inflamed gingiva and recondition the subgingival ecology, making it biologically compatible with optimal healing and allow reattachment of epithelium to root surface. Various longitudinal studies [8, 9] have demonstrated the effectiveness of this approach, which is based on scaling and root planing, reinforcement of the patient oral hygiene practices and regular follow-up to eliminate new deposits. Inspite of meticulous scaling and root planing procedures, the

reduction in probing depth and gain in clinical attachment level is not happening in moderate to deep periodontal pockets (pocket depth ≥5 mm) because of the invasive potential of the putative periodontal pathogens into gingival epithelial cells and sub epithelial connective tissues and their high affinity for crevicular epithelium and dentinal tubules [1, 3, 4].

A microbiological approach to periodontal therapy aiming primarily at suppressing specific pathogenic bacteria and permitting a subsequent recolonization of a microbiota compatible with health is effective. The antimicrobials can be given systemically and locally. Systemic route pose a risk of adverse effects such as drug toxicity, acquired bacterial resistance, drug interaction and patient's compliance which limits the use of systemic antimicrobials. To overcome these shortcomings, local delivery of antimicrobial agents is extensively studied. It was Dr. Max Goodson [5] in 1979 that championed and developed local delivery of therapeutic agents into a viable concept. Local antimicrobial therapy in Periodontitis involves direct placement of an antimicrobial agent into sub gingival sites, minimizing the impact of the agent on non oral body sites, limiting the drug to its target sites and hence achieving a much higher concentration. For local delivery in subgingival areas various antimicrobials have been used such as Tetracyclines, Chlorhexidine, Metronidazole etc. and clinical studies [6, 7, 8] have shown that these agents are effective when used as an adjunctive to mechanical debridement [4].

In the past few years the macrolide group of antibiotics is being extensively investigated. The macrolides are a group of antibiotics that have in common macrocyclic lactone rings linked with amino sugars. Azithromycin is a semi synthetic acid stable antibiotic and represent the protype of a novel class of macrolides called azalides. Azithromycin has a wide antimicrobial spectrum of action towards anaerobic bacteria as well as gram negative bacilli. It is effective against periodontal pathogens like *A. actinomycetemcomitans* and *P. gingivalis* and this antimicrobial activity supports its use in periodontal infections. Azithromycin has significantly less bacterial resistance development, long half–life and good tissue penetration. It gets concentrated in fibroblast and phagocytes and is transported to the areas of inflammation as a result of chemotactic effects exerted on the phagocytes, thus delivering the drug at those target sites [9, 10]. Various studies [11, 12] have found that scaling and root planing with adjunctive use of systemic azithromycin demonstrated improvement in clinical parameters.

The present study is designed to investigate the efficacy of subgingivally delivered 0.5% controlled release azithromycin gel on clinical status of patients with chronic periodontitis as an adjunct to scaling and root planing.

## AIM AND OBJECTIVES

The aims and objectives of the present study were:

- To evaluate the role of subgingivally delivered antimicrobial bio-absorbable controlled release 0.5% azithromycin gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis.
- To evaluate the clinical effects by assessing clinical parameters such as probing depth, clinical attachment level, plaque index and gingival index.

## PATIENTS AND METHODS

### Materials

### Formulation of Azithromycin gel

The azithromycin gel was prepared as described by the shah *et al*., [13]. N-methyl 2-pyrrolidone (NMP) was taken in a beaker and heated on a magnetic stirrer till a temperature of $60^0$C was attained. Poly lactic-co-glycolic acid (PLGA 75:25) (molecular weight 66,000-1, 07,000) is added to the hot solvent and stirred on the magnetic stirrer till a clear solution was observed indicating the complete solubilization of PLGA. Azithromycin was added to the polymer solution, which rapidly dissolved to give a homogeneous phase of the drug, polymer and the solvent. The resultant solution was transferred to a glass vial and stored under cold condition which was further subjected to sterilization using 25kGy gamma irradiation. In-Vitro Drug release studies of sustained release azithromycin gel formulation was done in artificial saliva using high pressure liquid chromatography (HPLC).

### Methodology

A total of forty subjects who visited the Department of Periodontics, Meghna Institute of Dental Sciences, Nizamabad were recruited for this study. Written and verbal consent was taken from the subjects All the subjects enrolled in the study fulfilled the inclusion and exclusion criteria.

### Inclusion criteria

- Subjects with age group between 25-50yrs
- Systemically healthy subjects with probing pocket depth ≥ 5mm.
- Periodontal disease of all the subjects be confirmed by taking radiograph (IOPA)
- Subjects who have not undergone any type of periodontal therapy in the past 6 months.
- Subjects without any antibiotic treatment in last 6 months.

### Exclusion criteria

- Subjects with known or suspected allergy to the macrolide group which is prescribed in this study.
- Subjects having periodontal pockets <5mm.

- Subjects who are medically compromised.
- Pregnant or lactating women.
- Subjects with smoking habit.
- Subjects who are not co-operative to the study.

The subjects were categorized into two groups. Randomization was done by alternatively allotting the subjects into the following two groups.

- Group A: (scaling and root planing [SRP] + subgingivally delivered 0.5% azithromycin gel into periodontal pockets).
- Group B: (scaling and root planing [SRP] + subgingivally delivered placebo gel into periodontal pockets).

In this study a double blinding technique was used where the operator and the patient were blinded for the agent placed in periodontal pocket. The agents i.e the azithromycin gel and placebo gel were taken in two separate vials that were named as 1 and 2. The operator and the patient were not informed about the actual agent present in these vials.

**Method of collection of Data**

After the inclusion of subjects into study the periodontal status of the subjects was recorded using Gingival index according to Loe and Silness [24], Plaque Index according to Silness and Loe [25], Probing Pocket Depth (UNC-15 (University of North Carolina 15 probe, Hu - Friedy) periodontal probe), Clinical Attachment Level (The level of attachment was measured from the base of the pocket to the CEJ). Standardization was done with the preparation of occlusal stent with groove for recording PPD and CAL.

After all the clinical parameters were recorded for all subjects at baseline, full mouth scaling and root planing was done. After SRP was performed, for the subjects in group A the gel from vial 1 was delivered subgingivally where as for the subjects in group B the gel from vial 2 was delivered subgingivally. All the measurements were recorded by a single evaluator at baseline, 1st month, 3rd month and 6th month.

**STATISTICAL ANALYSIS**

The collected data was subjected to statistical analysis using package for social sciences (SPSS version 20.0). The quantitative data was summarized using mean and standard deviation.

Tukey's HSD test is a pair wise multiple comparison test. It is used to compare the changes in the clinical parameters throughout the study period within the group. The comparison between the groups was done using unpaired t test.

**RESULTS**

All patients showed good compliance and the healing period was uneventful for both the treated groups without any signs of inflammation and swelling indicating the biocompatibility of the materials used.

The age of the subjects ranged between 25-50 years with a mean age in the group A was 33.95±7.32 and that of group B was 37.90±8.56 with an overall mean age of 35.93.

Clinical parameters such as plaque index, gingival index, probing pocket depth, loss in clinical attachment level were recorded for all forty subjects in both the groups at baseline, 1st month, 3rd month and 6th month. All the data collected were analyzed statistically (Table-1, 2 and Fig-1, 2).

**Gingival index**

The mean gingival index scores at baseline, 1st month, 3rd month and 6th month are 1.81±0.16, 1.29±0.08, 1.35±0.07 and 1.36±0.11 respectively in group A and 1.83±0.18, 1.31±0.17, 1.36±0.10 and 1.40±0.05 respectively in group B . There was a change in mean gingival index scores when compared to baseline at 1st month, 3rd month and 6th month which were statistically significant in both the groups.

The gingival index scores of the group A and the group B were compared at baseline, 1st month, 3rd month and 6th month. No statistically significant difference was observed between the groups (i.e) P>0.05 at baseline, 1st month, 3rd month and 6th month.

**Plaque index**

The mean plaque index scores at baseline, 1st month, 3rd month and 6th month are 1.37±0.22, 1.19±0.13, 1.18±0.08 and 1.17±0.06 respectively in group A and 1.50±0.24, 1.30±0.19, 1.19±0.18 and 1.22±0.09 respectively in group B. There was a change in mean plaque index scores when compared to baseline at 1st month, 3rd month and 6th month which were statistically significant.

The plaque index scores of the group A and the group B were compared at baseline, 1st month, 3rd month and 6th month. No statistically significant difference was observed between the groups (i.e) P>0.05 at baseline, 1st month, 3rd month and 6th month.

*Probing pocket depth*

The mean probing depth scores (in mm) at baseline, 1st month, 3rd month and 6th month are 5.90±0.16, 4.70±1.03, 3.60±0.68 and 3.05±0.76 respectively in group A and 5.75±0.64, 4.80±0.70, 4.25±0.85 and 3.50±0.76 respectively in group B. There was a decrease in mean probing depth scores when compared to baseline at 1st month, 3rd month and 6th month which were statistically significant (P=0.00). The mean probing depth reduction (in mm) from baseline to 6th months was 2.85 in group A and 2.25 in group B.

**Clinical attachment level**

The mean scores of loss in clinical attachment level at baseline, 1st month, 3rd month and 6th month are 4.70±0.92, 3.60±0.94, 2.50±0.76 and 1.95±0.89 respectively in group A and 4.70±1.03, 3.75±1.02, 3.20±1.06 and 2.50±1.05 respectively in group B . At each follow up visit, CAL gain was statistically significant in comparison to baseline levels (P=0.00). The mean clinical attachment level (in mm) gain was 2.75 in group A & 2.20 in group B at 6th months when compared to baseline with more gain in CAL observed in group A.

**Comparison between group A and group B of PPD and CAL**

The mean PPD scores and CAL scores of the group A and the group B was compared at baseline, 1st month, 3rd month and 6th month. No statistically significant difference was observed between the groups (i.e) P>0.05 at baseline and 1st month but at 3rd and 6th month there was a statistically significant difference between group A and group B (i. e) P<0.05 (Fig. 3 &4).

**Table-1: Comparison of mean scores of clinical parameters to baseline at 1st month, 3rd month and 6th month in group A**

| GROUP A | Baseline | 1st month | 3rd month | 6th month |
|---|---|---|---|---|
| Gingival index | 1.81±0.16 | 1.29±0.08 | 1.35±0.07 | 1.36±0.11 |
| Plaque index | 1.37±0.22 | 1.19±0.13 | 1.18±0.08 | 1.17±0.06 |
| PPD | 5.90±0.97 | 4.70±1.03 | 3.60±0.68 | 3.05±0.76 |
| CAL | 4.70±0.92 | 3.60±0.94 | 2.50±0.76 | 1.95±0.89 |

**Table-2: Comparison of mean scores of clinical parameters to baseline at 1st month, 3rd month and 6th month in group B**

| GROUP B | Baseline | 1st month | 3rd month | 6th month |
|---|---|---|---|---|
| Gingival index | 1.83±0.18 | 1.31±0.17 | 1.36±0.10 | 1.40±0.05 |
| Plaque index | 1.50±0.24 | 1.30±0.19 | 1.19±0.18 | 1.22±0.09 |
| PPD | 5.75±0.64 | 4.80±0.70 | 4.25±0.85 | 3.50±0.76 |
| CAL | 4.70±1.03 | 3.75±1.02 | 3.20±1.06 | 2.50±1.05 |

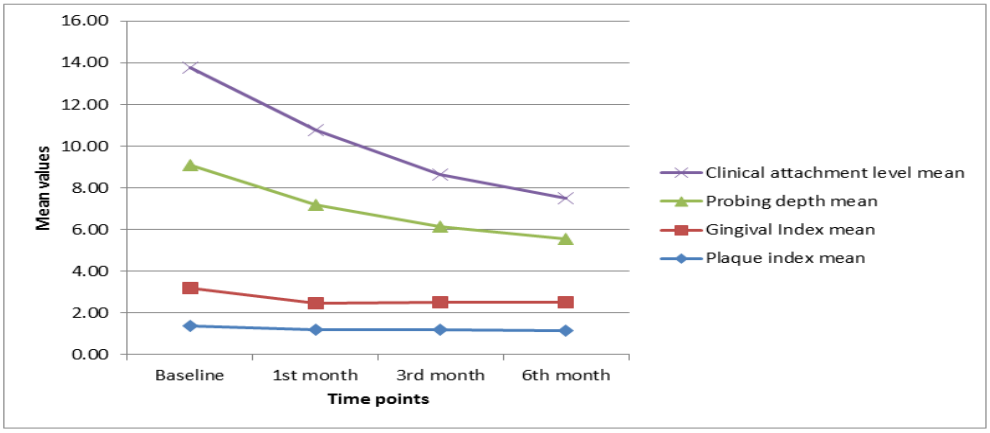


**Fig-1: Profile plot for four parameters studied (Within GROUP A)**

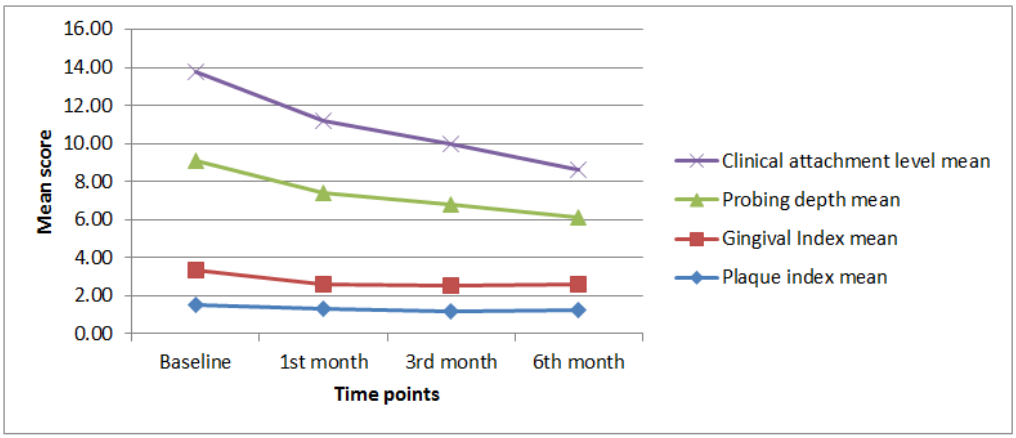


**Fig-2: Profile plot for four parameters studied (Within GROUP B)**

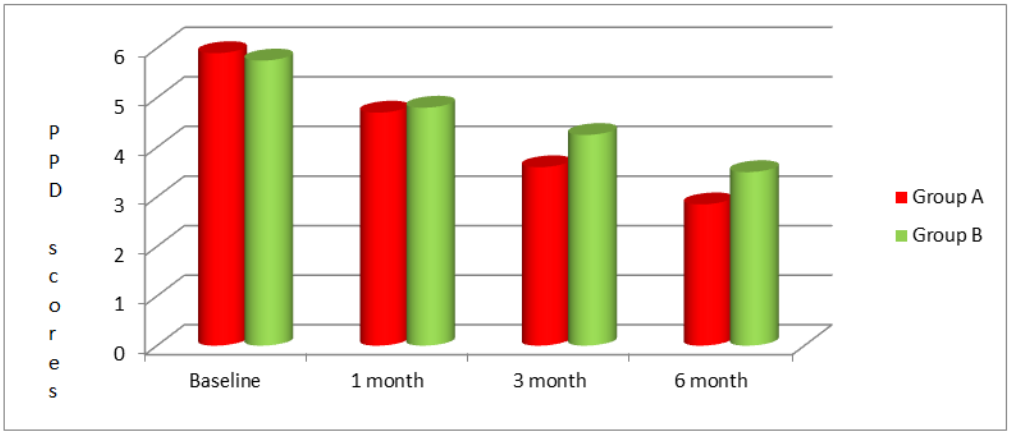


**Fig-3: Comparison of mean PPD scores (in mm) between group A and group B**

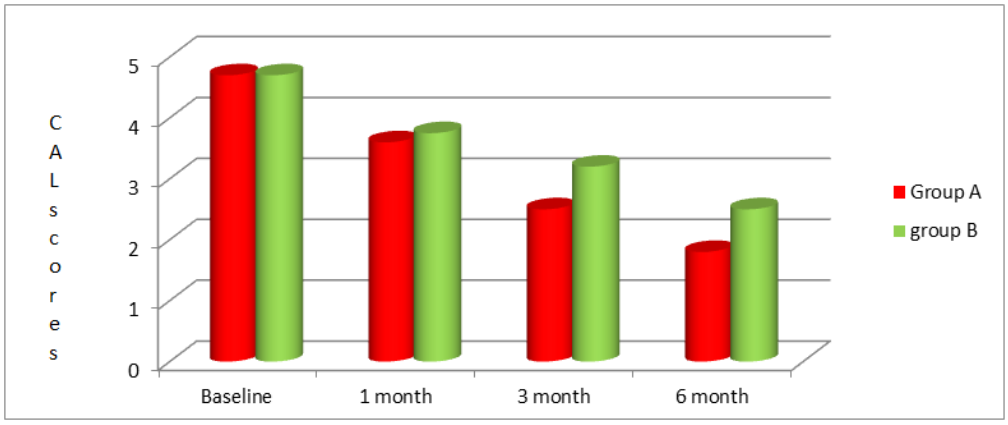


**Fig-4: Comparison of mean CAL scores (in mm) between group A and group B**

## DISCUSSION

Azithromycin (9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin) is a macrolide antibiotic belonging to sub class azalides discovered in 1980. It is a semi synthetic analogue of erythromycin in which an additional nitrogen atom has been inserted into the macrocyclic lactone ring. This extra nitrogen atom provides a higher degree of structural stability for azithromycin compared to erythromycin, resulting in excellent tissue penetration, low toxicity and a long half-life of 68 hours [14].

Azithromycin is also found to be effective in the management of odontogenic infections. The pharmacological properties of azithromycin that makes it a desirable agent in the management of dental infections includes stable in acid pH, absorption not affected by food, sustained high tissue concentrations, rapid uptake by phagocytes, delivery in high concentration to infection sites, good patient compliance due to short course of administration and low incidence of side effects [15].

Pajukanta in 1993 investigated the invitro antimicrobial susceptibility of *P. gingivalis* to azithromycin and found that azithromycin was highly effective against *P.gingivalis and a*ll strains were inhibited at 1.0ug/ml of azithromycin or less. It was also found that the minimal inhibitory concentration was 0.25ug/ml for 50% of strains and 0.5ug/ml for 90% of strains. As *P. gingivalis* have been reported at higher levels in sites with active disease or with progressing disease and azithromycin was found to be effective against *P. gingivalis* and other gram negative anaerobic microorganism use of azithromycin is supported in the management of chronic periodontitis [16].

Azithromycin has a good tissue penetration. In a study conducted by Tecla Malizia et al., it was found that the highest concentrations of azithromycin were observed 12 hours after the last dose in plasma, saliva, gingiva and bone and then declined gradually. But consistent levels of the drug in saliva and periodontal tissues were detected upto 6.5 days, indicating that azithromycin was retained in target tissues and fluids for a long time after the end of treatment [17].

Corrado Blandizzi *et al*., found in their study that the azithromycin levels in both normal gingiva and pathological tissues exceeded the MIC of most pathogens involved in pathophysiology of chronic inflammatory periodontal disease, supporting its use as an adjunctive or prophylactic agent in the treatment of chronic inflammatory periodontal diseases [18].

The important characteristic of azithromycin is that it gets concentrated in fibroblast, especially appears to be localized in lysosomes, phagocytes, macrophages and is transported to the areas of inflammation as a result of chemotactic effects exerted on the phagocytic cells [10]. This is proved by the in-vitro study conducted by R. P. Gladue *et al*., [19]

Antibiotic uptake by host cells provides several potential benefits in the treatment of periodontitis. Elevated macrolide concentration inside oral epithelial cells could facilitate the killing of invasive pathogens. As fibroblasts are a relatively large cellular compartment of the gingiva, these cells function as drug reservoirs that enhance and sustain therapeutic concentrations at that site [20].

Various studies [11, 21] have been conducted using systemically administered azithromycin to treat various periodontal conditions like chronic periodontitis, aggressive periodontits. To avoid effect on non target tissues, the concept of local drug delivery was used and the present study was designed to evaluate the role of subgingivally delivered bioabsorbable controlled release 0.5% azithromycin gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis

In the present study the formulation of azithromycin gel was done using 75:25 PLGA as the delivery system. PLGA is synthetic biodegradable FDA approved polymer which is highly biocompatible and extensively studied as delivery vehicles for drugs, proteins and various other macromolecules such as DNA, RNA and peptides. PLGA was also successfully used in the field of periodontics with good results. Kurtis *et al.*, [22] conducted a study using PLGA loaded with and without metronidazole for guided tissue regeneration in dogs and observed successful regeneration without toxicity and adverse reaction. The advantages of using PLGA as vehicle is easy placement, bioabsorable, do not require a periodontal dressing for retention.

The MIC of azithromycin against standard and clinically isolated strains of bacteria associated with periodontal diseases such as *P. gingivalis, P. intermedia, A. actinomycetemcomitans, Eikenella corrodens* and *F. nucleatum* is between 0.025 and 2.0µg/ml [10] The invitro analysis showed that the concentration of the azithromycin released from the formulation was above the MIC of common periodontal pathogens which was maintained for about 7 days showing that sufficient subgingival drug-microbial contact time could be expected.

The ages of the subjects selected were within the range of 25-50 years with the overall mean age of the study population being 35.93±8.11. As chronic periodontitis occurs in response to chronic plaque and calculus formation at any age, the age range can be justified.

The oral hygiene maintenance of subjects was evaluated using plaque index and the severity of gingival inflammation was assessed using gingival index. The mean GI and PI scores showed statistically significant reduction from baseline to 6 months. Similar reduction in mean GI scores and PI scores were reported by Vidya Dodwad *et al*., [1] and Mahesh chavda *et al*., [23]. The GI and PI scores in the group A and the group B were compared at baseline. There was no statistical significant difference between the groups. When the GI and PI score at 1, 3 and 6 month were compared between the group A and group B, there was no statistically significant difference between the groups. This may have been due to the ability of the subjects to maintain proper oral hygiene.

Reduction in the probing depth is one of the major clinical outcomes measured to determine the success of a treatment. A statistically significant reduction in probing depth was found in both groups when compared to baseline at all time intervals. There was a change in the mean PPD score from 5.90± 0.97mm at baseline to 3.05±0.76mm at the end of 6 months in group A and from 5.75±0.64mm at baseline to 3.50±0.76mm at the end of 6 months in the group B. The mean probing depth reduction from baseline to 6 months was 2.85mm in group A and 2.25mm in group B. When group A and group B were compared, the reduction in PPD was statistically significant at 3$^{rd}$ and 6$^{th}$ month. Similar results were confirmed by A R Pradeep *et al*., [10], Vidya Dodwad *et al*., [1] and Mahesh chavda *et al*., [23].

In the present study a statistically significant gain in the CAL was found in both groups when compared to baseline at all time intervals. There was a change in the mean CAL score from 4.70± 0.92mm at baseline to 1.95±0.89mm at the end of 6 months in group A and from 4.70±1.03mm at baseline to 2.50±1.05mm at the end of 6 months in the group B. The mean clinical attachment level (in mm) gain was 2.75 in group A & 2.20 in group B at 6 months when compared to baseline with more gain in CAL observed in group A. When group A and group B were compared, the gain in the CAL was statistically significant at 3$^{rd}$ and 6$^{th}$ month. Similar results were confirmed by A R Pradeep *et al*., [10], Vidya Dodwad et al., [1] and Mahesh chavda *et al*., [23]

Because group A showed significant improvement in clinical parameters (reduction in PPD, gain in CAL) compared to group B and on unblinding the group A was found to be receiving 0.5% azithromycin gel along with scaling and root planing. Hence, 0.5% azithromycin along with SRP was found

to be more effective in the treatment of chronic periodontitis patients when compared with SRP alone.

## CONCLUSION

The results of the present study showed that both the therapeutic approaches led to significantly greater gain in clinical attachment level and reduction in probing depths compared to baseline. The combination of SRP and 0.5% azithromycin gel was more effective than SRP alone in reducing probing depths and showed greater gain in clinical attachment level. However, long-term studies, using different vehicles and concentrations of azithromycin should be carried out to confirm the observations of our study.

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