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Clinical efficacy of subgingivally delivered 0.5% controlled release clarithromycin gel in the management of chronic periodontitis



Ambika Arora [a,*], *Vidya Dodwad* [a], *Shubhra Vaish* [a], *Anshul Arora* [b]

[a] *Dept. of Periodontology, ITS Dental College, Muradnagar, Ghaziabad, India*
[b] *Dept of Conservative Dentistry & Endodontics, ITS Dental College, Muradnagar, Ghaziabad, India*

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ABSTRACT

Background: Main indication of adjunctive use of local antimicrobials lie around situations where the outcome of non-surgical mechanical treatment results in limited number of residual pockets. Purpose of this investigation was to evaluate clinical effect of subgingival application of 0.5% clarithromycin gel adjunctive to scaling and root planing (SRP) in management of localized chronic periodontitis.

Materials and method: Thirty sites in patients with chronic periodontitis were categorized randomly into two treatment groups: Scaling and Root Planing (SRP) plus 0.5% clarithromycin gel and SRP only. Clinical evaluation was undertaken using gingival index of Loe and Silness and plaque was assessed using the Turesky et al modification of Quigley Hein Index at baseline, 15 days and 1 month. Pocket probing depth and clinical attachment level were also measured using customized acrylic stents.

Result: Both therapies resulted in significant clinical improvements. Gingival index, probing depth and relative attachment level showed significantly better reduction in CLM group than in the control group. Plaque index also reduced in both the groups but the difference was not statistically significant between the groups.

Conclusion: Although both treatment strategies seem to benefit patients, the adjunctive use of 0.5% clarithromycin showed significant results with respect to clinical parameters.

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1. Introduction

Periodontal disease is a general term which encompasses several pathological conditions affecting the tooth supporting structures. It includes conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis.[1] It has been well-established that periodontal disease is the result of a local bacterial infection with a pathogenic microflora within the periodontal pocket. The microflora found in periodontitis is complex and composed mainly of gram negative anaerobic bacteria.[2] Moreover; studies have shown that the various clinical forms of periodontitis are associated with different microbiota.[3]

Traditional therapies for periodontal disease have included mechanical debridement to disrupt the subgingival flora and provide clean, smooth and biologically compatible root

* *Corresponding author*. NS-10 Mianwali Nagar, First Floor, Paschim Vihar, New Delhi 110087, India.
E-mail address: ambymahe@gmail.com (A. Arora).

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surfaces. Unfortunately, in some instances, the complex anatomy of the root and the contours of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load to make the tooth surface biologically acceptable. In addition, control of supragingival plaque is essential in order to prevent recolonization of the subgingival area by periodontal pathogens.[4] Poor supragingival and subgingival debridement and inadequate home care regimen leads to reestablishment of a pathogenic subgingival microflora and an associated rebound in the disease may occur in local sites.[5]

Anti-infective therapy, which combines both mechanical therapy and chemotherapeutic approaches to minimize bacteria, may be more effective in these cases.[6] Chemotherapeutic agents include systemic antibiotics, topical application of antiseptics and sustained release local drug delivery systems. However, systemic antimicrobials pose more side effects when compared to local chemotherapeutic approaches.[7]

Goodson, Haffajee and Socransky, in 1979,[8] first proposed the concept of controlled local drug delivery in the treatment of periodontitis. Local delivery of chemotherapeutic agents into the pockets, via syringe or irrigating device aims at targeting an anti-infective agent at the infection site and sustaining its localized concentration at the effective levels for a sufficient time, while concurrently evoking minimal or no side effects.

Controlled drug delivery is one which delivers the drug at a predetermined rate, for a predetermined period of time.[9] Many antimicrobials can be used in local drug delivery forms as Tetracycline fibers, Metronidazole, Minocycline ointment and chlorhexidine chip and doxycycline hyclate in bioabsorbable polymer. Penicillin and tetracycline derivatives have good efficacy, but the growing phenomenon of bacterial resistance and the induction of hypersensitivity reactions represent a serious limit to the use of these drugs.[10]

Another antibiotic that can be used as an adjunct to periodontal therapy is clarithromycin. Clarithromycin (CLM) is a macrolide antibiotic that inhibits protein synthesis by binding to the 23S ribosomal RNA in the 50S subunit of the bacterial ribosome. It possesses a broad antimicrobial spectrum, favorable tissue distribution, and a low incidence of adverse side effects.[11] Unlike many antibiotics, CLM readily penetrates cells to gain access to intracellular pathogens. It is highly effective against *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* and exhibits good activity against *Eikenella corrodens*, Prevotella sp., Fusobacteria, and other anaerobic and facultative pathogens.[12]

Recently, Pradeep et al (2011)[13] demonstrated that systemic utilization of CLM in combination with Scaling and Root planing (SRP) improved the efficacy of non-surgical periodontal therapy in reducing probing depth, improving clinical attachment level and in lessening microbial loads.

Thus, the present study was designed to investigate the clinical efficacy of subgingivally delivered 0.5% controlled release clarithromycin gel in the management of chronic periodontitis.

2. Materials and method

This double masked, randomized clinical trial was conducted in Department of Periodontology and Oral Implantology, I.T.S Dental College, Muradnagar, Ghaziabad. Ethical committee approval was obtained. All subjects were verbally informed and written informed consent was taken for participation in the study. One examiner recorded all indices.

2.1. Selection of subjects

Patients (15 in each group) in the age group of 25–40 years were selected from the Out-patient Department of Periodontology and Oral Implantology, I.T.S. Centre for Dental Studies and Research, Muradnagar, Ghaziabad, UP. A total of 30 patients suffering from chronic periodontitis were recruited and were allocated randomly into two groups.

Test group included the patients in which 0.5% CLM gel was placed along with SRP. In the control group, only SRP was done.

2.2. Inclusion criteria

- Patients were over the age of 25 years.
- Patients with at least one site with pocket probing depth (PD) 4–6 mm in posterior teeth were selected.

2.3. Exclusion criteria

- Allergy to macrolide antibiotics.
- Patients who were suffering from any known systemic diseases or immunocompromised.
- Patients who had received any surgical or non-surgical therapy 6 months prior to the start of the study.
- Patients who had received any antibiotic therapy in the last 6 months.
- Tobacco users and alcoholics were excluded.
- Pregnant and lactating females were also not included in the study.

2.4. Preparation of clarithromycin gel

The CLM gel was prepared as described by Shah et al.[14] The gel was prepared at Guru Nanak Institute of Pharmacy, Ibrahimpatnam, Hyderabad. Accurately weighed amount of poly lactic-co-glycolic acid (PLGA) was placed in glass vial and the required amounts of biocompatible solvents were added. The vial was heated to 60° and agitated using a mechanical shaker to obtain a clear solution. Weighed amount of CLM was added to the above polymer solution and dissolved completely to obtain homogeneous phase of polymer, solvent, and drug.

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

The study subjects were randomly assigned to either CLM or control group. Clinical parameters, i.e., Plaque Index (PI)[15] (Turesky-Gilmore-Glickman modification of Quigley Hein PI, 1970) and Gingival Index (GI)[16] (Loe and Silness, 1963) were recorded for all patients. Pocket PD and clinical attachment level (CAL) were assessed in the selected sites using a custom made stent and University of North Carolina-15 periodontal probe (UNC-15, Hu-Friedy, Chicago, IL) probe to standardize all measurements.

All patients received thorough SRP with Ultrasonic Scaler and Gracey Curettes. 0.2 ml of CLM gel was injected into the test sites using a blunt cannula. No periodontal dressing was applied and the patients were instructed to refrain from brushing in the vicinity of the sites. All measurements were recorded in both the groups at baseline, 15 days and 1 month.

2.5. *Statistical analysis*

Results were expressed as mean ± standard deviation and proportions as percentages. SPSS (statistical package for social sciences) version 16.0 was used for Statistical Analysis. "Independent samples" t-test was used for comparison of 2 mean values. ANOVA (Analysis of Variance) test was used for calculating difference between more than 2 mean values. The p-value was taken significant when less than 0.05 ($p < 0.05$).

3. Results

This study was designed to evaluate and compare the effects of 0.5% CLM gel plus SRP and SRP alone on the clinical parameters (GI, PI, PD, and CAL) in patients with chronic periodontitis. Thirty patients within the age group of 25–40 years (31 ± 42 years) were enrolled in the study and were distributed equally in both the groups.

Thirty treatment sites, 15 in each group, were evaluated for all the clinical parameters at baseline 15 days and 1 month. No adverse reactions were observed in any of the patients. No statistically significant difference in baseline values was observed between the groups ($p > 0.05$).

In the control group, mean plaque index reduced from 2.67 ± 0.82 at baseline to 1.93 ± 0.59 at 15 days and remained stable at 1 month. However, in the test group, PI reduced from 2.87 ± 0.52 at baseline to 1.67 ± 0.62 at 15 days and 2.13 + 0.92 at 1 month. Though this reduction was significant in both groups but not between the groups ($p > 0.05$) (Tables 1 and 2, Graph 1).

Mean reduction in gingival index in control group from baseline to 15 days was also significant i.e. from 2 ± 0.38 to 1.6 ± 0.51 but marginally increased to 1.73 ± 0.46 at 1 month. However, in the test group, the mean reduction in inflammation was more pronounced at all time intervals i.e. from 2 ± 0.0 at baseline to 0.87 ± 0.64 at 15 days and 1.13 ± 0.83 at 1 month (Tables 1 and 2, Graph 2).

Both probing depth and attachment level also showed significant reduction in both the groups from baseline to 15 days and slight increase at 1 month. However, the mean reduction was statistically significant in the test group only (Tables 1 and 2, Graphs 3 and 4).

Table 1 – Evaluation of change in clinical parameters between different time intervals in the control group (Anova test).

Parameter	Baseline	15 days	1 month	p value
GI	2.0 ± 0.38	1.6 ± 0.51	1.73 ± 0.46	0.05
PI	2.67 ± 0.82	1.93 ± 0.59	1.93 ± 0.7	0.01
PD	6.13 ± 0.99	5.33 ± 0.82	5.4 ± 0.99	0.04
CAL	9.6 ± 0.91	8.80 ± 1.01	8.87 ± 1.06	0.06

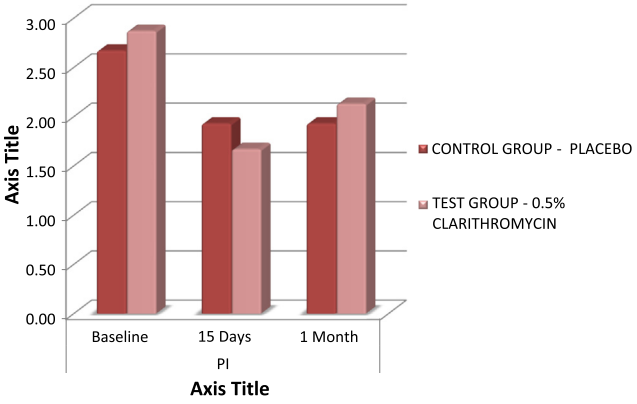
Table 2 – Evaluation of change in clinical parameters between different time intervals in the test group (Anova test).

Parameter	Baseline	15 days	1 month	p value
GI	2.0 ± 0.00	0.87 ± 0.64	1.13 ± 0.86	<0.001
PI	2.87 ± 0.52	1.67 ± 0.62	2.13 ± 0.92	<0.001
PD	5.93 ± 1.16	4.0 ± 0.93	4.13 ± 0.83	<0.001
CAL	10.6 ± 1.06	8.67 ± 1.01	8.80 ± 1.32	<0.001

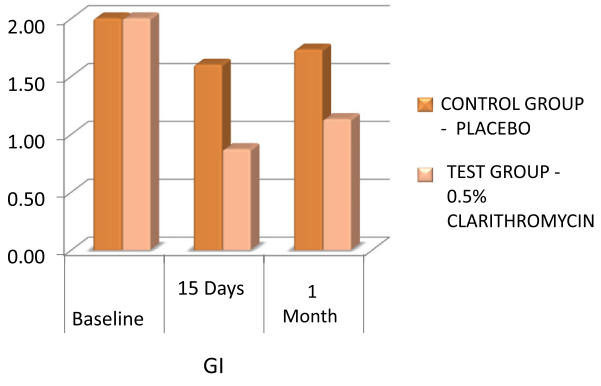
4. Discussion

This study was designed with the aim of assessing the efficacy of local drug delivery of 0.5% CLM gel as an adjunct to non-surgical periodontal therapy in the treatment of chronic periodontitis compared with a control group. The results of this study indicated that both therapies (SRP + 0.5% CLM and SRP) resulted in significant improvements with respect to all the clinical parameters evaluated.

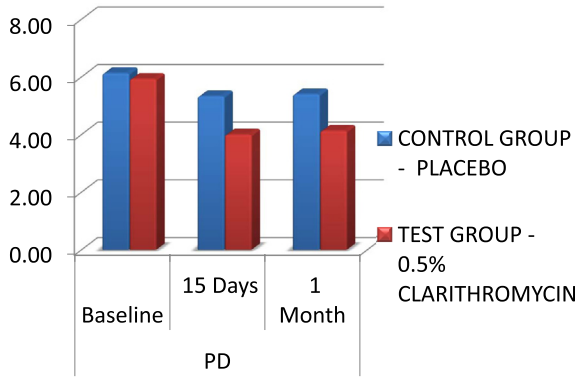
Agarwal et al (2012) reported that after application clarithromycin concentration in GCF reaches a peak value of 3678.20 mg/ml in 1 h after which the drug concentration



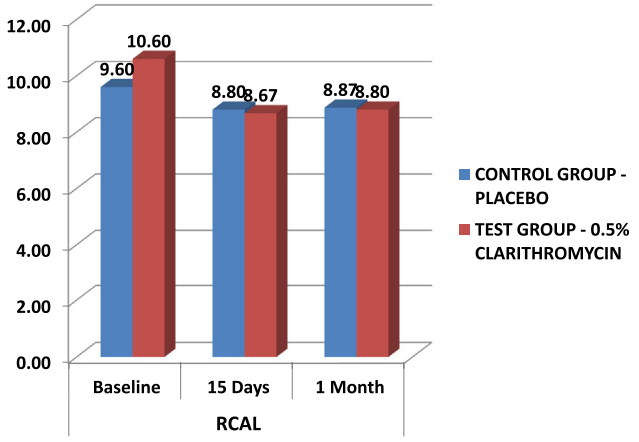
Graph 1 – Reduction in plaque index from baseline to 1 month.



Graph 2 – Reduction in gingival index from baseline to 1 month.



Graph 3 – Reduction in probing depth from baseline to 1 month.



Graph 4 – Improvement in clinical attachment level from baseline to 1 month.

steadily reduces.[17] However, the drug concentration is maintained well above the MIC 90 of *A. actinomycetemcomitans* which is 2.0 μg/ml upto a period of 7 weeks.[18]

Gingival fibroblasts and oral epithelial cells are also capable of accumulating intracellular clarithromycin levels that are higher than extracellular levels by 38- and 3.3-fold, respectively.[18] This suggests that fibroblasts could serve as reservoirs for clarithromycin in gingival connective tissue. Clarithromycin is also accumulated by phagocytes, monocytes, polymorphonuclear cells, macrophages, and lymphocytes. Recently, Burrell and Walters[19] concluded that CLM can attain higher levels in gingiva than in serum and reaches even higher levels in inflamed gingiva than in healthy gingiva. The CLM concentration obtained in inflamed gingiva in their study was 25% higher than that found in healthy controls. Thus, the authors reported that the distribution profile of CLM appears to be suitable for treatment of periodontitis.[19]

In our study, patients treated with SRP + 0.5% CLM showed enhanced reductions in PD and gains in CAL ($p < 0.001$) over a period of 30 days. Though the parameters slightly increased at the end of 1 month, the improvement in the test group was significantly better than the control group. There was also a significant reduction in gingival inflammation which was maintained during the study period.

Previous studies by Bajaj et al[20] and Agarwal et al[17] (2012) have also demonstrated significant improvement in probing depth and relative attachment level in smokers and Type II Diabetes Mellitus patients with adjunctive use of 0.5% clarithromycin gel.

Our results are also similar to that of Kathariya et al (2014)[21] who also reported improved gingival index, sulcus bleeding index, probing depth and attachment level after months of local application of 0.5% CLM gel.

The enhanced clinical results obtained in our study might be due to the high concentration of drug in the pocket and its dual effect, on pocket microflora as well as on pathogens invading the tissue.

However, long term efficacy of CLM with different concentration and preparations coupled with microbiological analysis are warranted to confirm its beneficial effects.

5. Conclusion

The use of local delivery systems with antimicrobial agents does not replace the need for thorough SRP, which remains the most important and the primary treatment modality.

Local drug delivery with the use of 0.5% CLM along with SRP is a simple and non-invasive technique that provides the drug at adequate therapeutic level, as a beneficial adjunctive treatment modality to enhance periodontal health. This clinical trial thus demonstrates that local delivery of 0.5% CLM gel as an adjunct to SRP into periodontal pockets of chronic periodontitis patients stimulated a significant improvement in clinical parameters as compared to SRP.

Conflicts of interest

All authors have none to declare.

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PIERRE FAUCHARD ACADEMY – INDIA SECTION.

28th ANNUAL CONVOCATION AND AWARDS CEREMONY

DECEMBER 14, 2014 – NEW DELHI.

The 28th Annual Convocation and Awards Ceremony of the Pierre Fauchard Academy, India section will be held at 9.00 am on Sunday December 14, 2014 at Maulana Azad Institute of Dental Sciences, New Delhi.

There will be one CDE Programme, First Maj. Gen. Kartar Singh Oration, in honour of (late) Maj. Gen. Kartar Singh. Lt. Gen. Vimal Arora, Director General of Dental Services and Colonel Commandant of Army Dental Corps, New Delhi has kindly consented to deliver the Oration on December 14, 2014 before the Convocation.

Further details regarding the Convocation and the Oration shall be intimated later.

The PFA India Section has started Maj. Gen. Dr. Kartar Singh Fund. Fellows are requested to contribute generously by sending their contribution as a cheque / DD, drawn in favour of Pierre Fauchard Academy to the Secretary" - Dr. T. Samraj, Secretary & Treasurer of Pierre Fauchard Academy on address given below.

Prof. T. Samraj,
24/12 C-1, Lakshmipuram,
Gandhi Road, Salem - 636 007
Mobile: +91-93456 93230
Website: www.pfaindia.org