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Original Article

# Minocycline containing local drug delivery system in the management of chronic periodontitis: A randomized controlled trial

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**Abstract:**

**Background:** The role of chemotherapeutic agents in periodontal therapy as adjuncts to mechanical debridement maybe justified by the inherent limitations of mechanical therapy. The aim of this study was to evaluate the long term efficacy of a locally delivered 2% minocycline gel as an adjunct to scaling and root planing in managing chronic periodontitis. **Materials and Methods:** This was a randomized controlled trial using a split-mouth study design. Twenty two pairs of sites with similar probing depths were randomly allocated to test and control groups. All sites received thorough scaling and root planing followed by minocycline gel application in the test sites. Probing depths, relative attachment levels, plaque index, and microbiological parameters were evaluated for both the groups over a 9-month period. **Results:** Overall parameters improved from baseline in both the test and control groups. For most parameters, the differences between test and control groups were not significant at different time intervals. The probing depth values in the test group at six (3.64±0.83 mm) and nine months (3.81±0.79 mm) were significantly less than control group(4.24±0.95 mm at six and 4.63±0.94 mm at nine months), these differences being significant at $P<0.05$ and $<0.01$, respectively. At the end of nine months, the number of non-motile bacilli in test group (21.65±3.74) were significantly less than control group (25.5±3.01), the difference being significant at $P<0.02$. **Conclusion:** The overall view of results in our investigation did not show any significant advantage of using 2% minocycline gel over scaling and root planning as an effective local drug delivery system and calls for further clinical trials to objectively evaluate its adjunctive in treatment of periodontitis.

**Key words:**

Antimicrobial, biofilm, minocycline, periodontitis

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## INTRODUCTION

Periodontal disease is primarily caused by specific groups of organisms which colonize the tooth surfaces in the form of a biofilm called plaque, which consists of colonies of bacteria embedded in a glycocalyx matrix. This matrix protects the microbes by inhibiting the penetration of harmful chemicals and antibiotics into the biofilm.[1] Thus, the only effective way to get rid of plaque is to mechanically disrupt it, a process which has become the mainstay of periodontal therapy.

But mechanical debridement may have certain limitations. These include difficult to reach areas like root concavities, narrow furcations,[2] and other extradental sites which may serve as reservoirs of bacteria leading to early recolonization of tooth surfaces after instrumentation. Thus, adjunctive use of chemotherapeutic agents like antibiotics has been advocated along with mechanical instrumentation.[3] Among the most widely used agents to treat periodontal disease are the tetracycline group of drugs. These are used both systemically and in the form of local drug delivery agents. Local drug delivery systems have the advantage of avoiding the harmful effects of systemic administration including development of resistant flora, suppression of normal flora, poor patient compliance etc.

Minocycline is a semisynthetic derivative of tetracycline. For local use, it is available in the form of two drug delivery systems: a gel form and a microencapsulated microsphere form.[4,5] Dentomycin is a bioabsorbable system which contains 2% minocycline HCl in a matrix of hydroxyl-ethyl cellulose, aminoalkyl methacrylate, triacetine and glycerine in the form of a gel. Magnesium chloride is added to modify the drug release properties. It is categorized as a sustained release system and the drug concentration decreases exponentially following a first order kinetics. The drug is delivered into the pocket with the help of a polypropylene applicator and provides high drug concentration, subgingivally, for 24 hrs. A meta-analysis published in 2005 showed improvement in clinical parameters including attachment level with adjunctive minocycline use along with mechanical therapy when compared to mechanical therapy alone.[6]

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The purpose of this study was to evaluate the long term efficacy of a 2% minocycline gel as an adjunct to scaling and root planing in managing moderate to severe chronic periodontitis.

Objectives of the study: To evaluate the efficacy of 2% minocycline gel in the treatment of chronic periodontitis by estimating the alterations in bleeding index, probing pocket depth, and clinical attachment level.

## MATERIALS AND METHODS

### Participants

The participants of this study were chosen from the patients attending the out-patient services of Dept. of Periodontia, M. R. Ambedkar Dental College, Bangalore. Patients suffering from moderate to severe chronic periodontitis, without any other medical or smoking history and not hypersensitive to minocycline were included in the study. Pregnant ladies, lactating mothers, patients on antibiotics, anti-inflammatory, and steroid therapy within last three months were excluded from the trial. Written informed consents were taken from patients after explaining the protocol of the study.

Moderate chronic periodontitis was defined as an attachment loss of 4mm on atleast two teeth and severe chronic periodontitis was defined as attachment loss of >5 mm on atleast two teeth. The study used a split mouth design, contralateral sites with deep pockets in similar teeth were chosen and randomly assigned to control or test groups using a coin-flip method.

### Interventions

In the first visit, patients received full mouth supragingival scaling and were recalled after a week when baseline parameters were recorded. This was followed by subgingival scaling and root planing and placement of minocycline gel in The test sites as seen in Figures 1 and 2. After root planning, the sites were thoroughly dried to get rid of blood and debris. The applicator tip was gently advanced to the deepest point of the pocket till resistance was felt and the gel was expelled by gently pressing the plunger till some material overflowed. The sites were then covered with a thin layer of cynoacrylate glue to restrict the effect of drug to the particular site. Control sites received only subgingival scaling and Root planning as seen in Figure 3. Patients were advised to postpone brushing for 12 hr period. Gel application was repeated at two and four weeks after scaling and root planing in test sites, according to the manufacturers' instructions (three to four applications, once in every 15 days).

### Outcomes

Clinical parameters evaluated were probing depth, relative attachment level, and bleeding index.[7] In addition, the overall plaque index[8] was also measured. Readings were taken at baseline, 3, 6, and 9 months. Probing depth and relative attachment level was measured with the help of an endodontic spreader, An acrylic stent as seen in Figures 4 and 5[9] and a vernier caliper to standardize measurements and take readings as precisely as possible. Apart from the clinical parameters, microbiological evaluation of subgingival plaque samples was done using a dark field microscope. At recall visits, only supragingival scaling was done, in orders to avoid contamination of subgingival plaque by the supragingival plaque. Subgingival plaque was collected using a sterile after-five curet. The sample was mixed with two to three drops of saline, and immediately taken to lab for assessment of different morphotypes of bacteria. The number of cocci, motile and non-motile rods, branching filaments, and small, medium and large spirochetes were assessed.

### Statistical analysis

The unit of measurement in this study was the site, rather than the subject. Student-t test was performed to compare parameters in test and control sites at each time interval. Overall improvement in plaque and bleeding indices was also evaluated from baseline to nine months.

## RESULTS

Twenty two pairs of contralateral sites in 15 patients were evaluated. Thirteen out of fifteen patients completed the study with 18 pairs of test and control sites. Two patients dropped out of the study after six months [Figure 6], so their data is considered till six months. All treated sites showed uneventful healing and no complications were reported for any site by any patient.

### Clinical parameters

#### *Bleeding index*

There was a significant reduction in overall mean bleeding scores in both groups from baseline (62.12%) to three months (45.97%), which was then maintained till the end of study as seen in Figure 7. Between the groups, the difference was not statistically significant at any time period.

#### *Plaque index*

Overall plaque scores showed significant improvement from baseline (0.722±0.363) to three months (0.594±0.225), but returned to baseline (0.715±0.283) by the end of six months.

#### *Probing depths*

Probing depth values reduced significantly from baseline to three months in both test (6.17±0.9 mm to 3.71±0.97 mm) and control (6.02±0.7mm to 4.22±0.94 mm) groups [Figure 8]. Between the groups, the difference reached statistical significance at six months (t-3.64±0.83 and c-4.24±0.95) at a $P$ value of <0.05 and nine months (t-3.81±0.79 and c-4.63±0.94) at a $P$ value of <0.01.

#### *Attachment level*

Both test and control groupS showed a significant improvement in relative attachment level from baseline (t-13.3±1.55 mm and c-12.91±1.55 mm) to three months (t-11.3±1.48 mm and c-11.4±1.37 mm), which was maintained till the end of nine months (t-11.16±1.27 mm and c-11.29±1.39 mm) but the difference between the groups was not statistically significant At any time [Table 1].

#### *Microbiological parameters*

There was a significant reduction in the total number of organisms from baseline (t-153.2±37.68 and c-144.7±28.79) to three months (t-66.98±25.16 and c-66.46±21.24) in both groups [Table 2]. This number gradually increased at six months (t-105.23±40.58 and c-117.46±31.41) and returned to baseline at the end of nine months. The difference between the test

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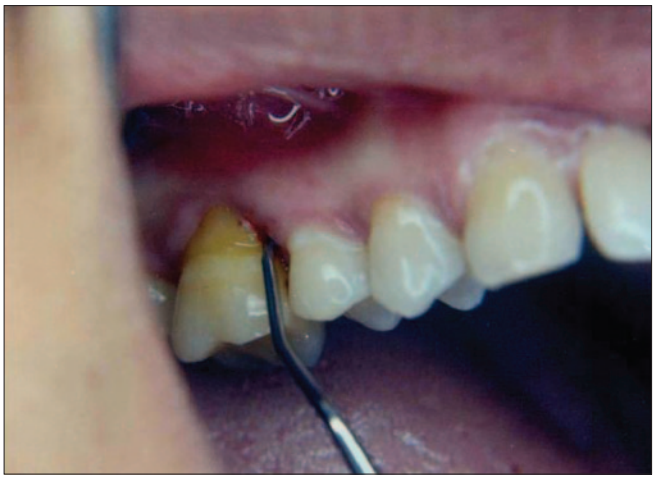


**Figure 1:** Root planing at test site



**Figure 2:** Placement of minocycline gel at the test site



**Figure 3:** Root planing at control site



**Figure 4:** Measuring the relative attachment level with plastic stent and endodontic spreader at test site

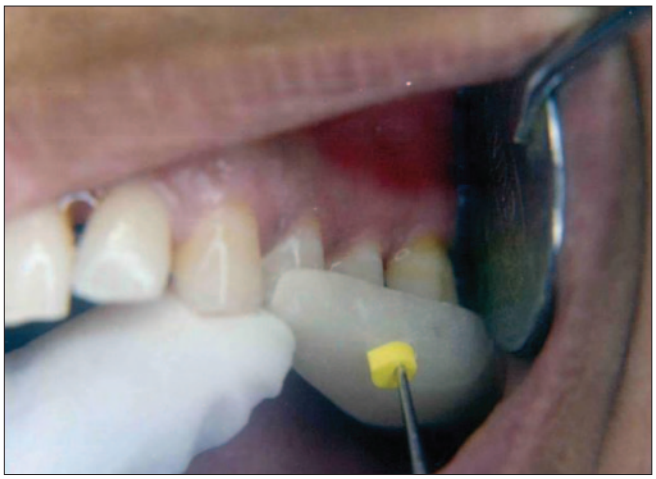


**Figure 5:** Measuring the relative attachment level at the control site

and control groups did not reach statistical significance at any time in the study except at nine months, when control group showed significantly higher number of non-motile organisms (25.5±3.01) than test group (21.65±3.74), this difference being significant at $P<0.02$.

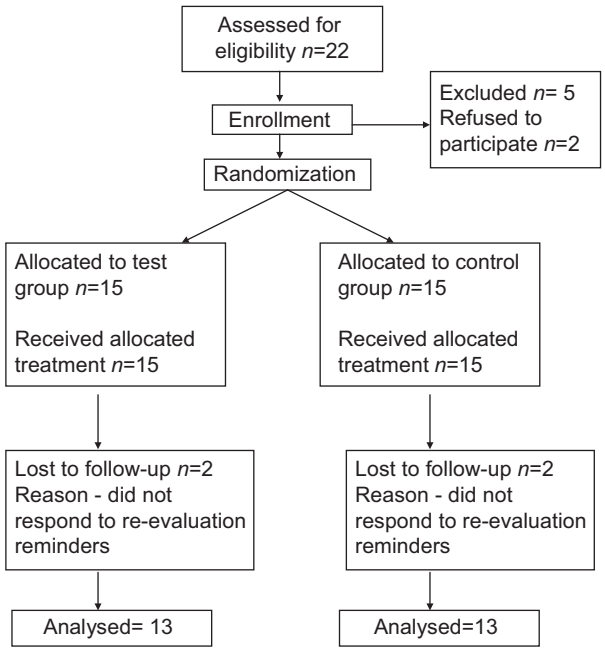



**Figure 6:** Depicting patients through various stages of the study

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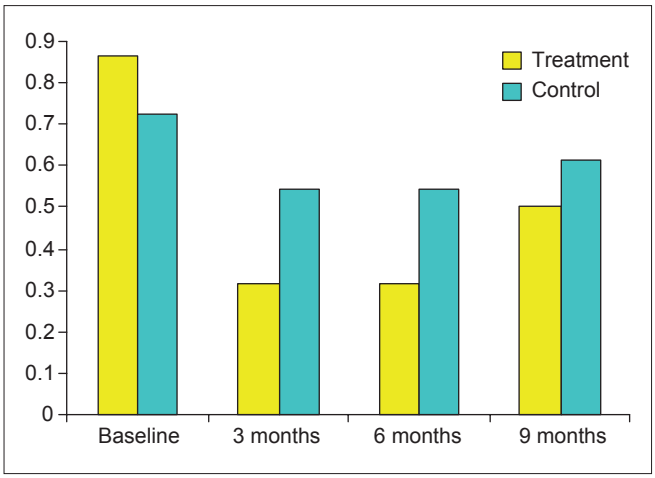



**Figure 7:** Depicting bleeding index values for test and control sites

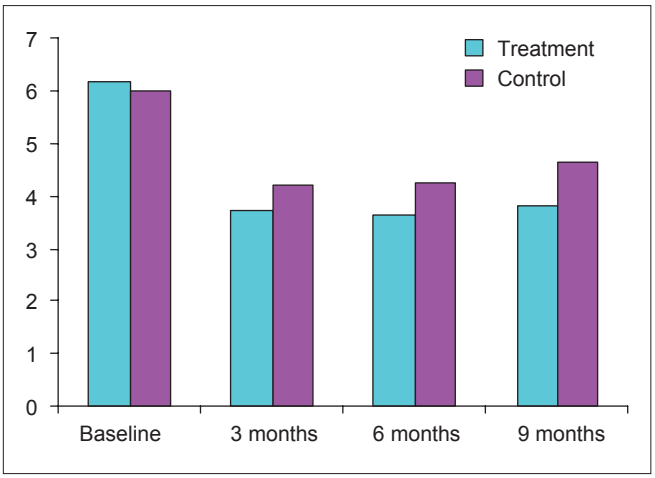



**Figure 8:** Depicting probing depth values for treatment and control groups

**Table 1: Clinical values for both treatment and control groups at various time intervals**

| | Bleeding index | | Probing depth | | Relative attachment level | | Total organisms | |
|---|---|---|---|---|---|---|---|---|
| | t | c | t | c | t | c | t | c |
| Baseline | 0.863 | 0.727 | 6.17 | 6.02 | 13.03 | 12.91 | 153.20 | 144.70 |
| 3 months | 0.318 | 0.545 | 3.71 | 4.22 | 11.30 | 11.40 | 66.98 | 66.46 |
| 6 months | 0.318 | 0.545 | 3.64* | 4.24 | 11.31 | 11.30 | 105.23 | 117.46 |
| 9 months | 0.500 | 0.611 | 3.81˘ | 4.63 | 11.16 | 11.29 | 147.17 | 166.27 |

*The difference being significant for $P<0.05$, ˘The difference being significant for $P<0.01$, t – Treatment; c – Control

**Table 2: Average number of organisms at treatment and control sites at various time intervals**

| | Spirochetes | | Cocci | | Motile bacilli | | Non-motile bacilli | |
|---|---|---|---|---|---|---|---|---|
| | t | c | t | c | t | c | t | c |
| Baseline | 50.34 | 45.45 | 33.71 | 32.00 | 28.63 | 28.25 | 28.68 | 28.32 |
| 3 months | 14.38 | 15.14 | 22.84 | 20.91 | 12.70 | 13.41 | 14.04 | 14.09 |
| 6 months | 31.66 | 34.57 | 31.96 | 31.11 | 18.25 | 21.71 | 17.04 | 19.45 |
| 9 months | 48.90 | 55.40 | 39.78 | 40.45 | 24.80 | 19.2 | 21.65 | 25.50* |

*The difference being significant for $P<0.02$; t – Treatment; c – Control

## DISCUSSION

It is well understood that most destructive types of periodontal diseases occur due to the presence of pathogenic micro-organisms colonizing the subgingival area and the suppression or eradication of these microbes result in improvement in periodontal health. Mechanical debridement is effective in both disturbing the biofilm and reducing the bacterial load. However, sometimes mechanical instrumentation may not be sufficient to control the disease due to tissue invasive pathogens, or other tooth related anatomic factors. In such conditions, adjunctive use of a chemotherapeutic agent provides an additional benefit in controlling the disease.

The systemic use of antibiotics along with mechanotherapy dramatically improves clinical results,[10] but at the same time is not free from its inherent adverse effects and disadvantages. To overcome these undesirable effects, several local drug delivery systems have been developed. Local delivery of antibiotics into the pocket achieves a greater concentration of the drug locally, proving bactericidal for most periopathogens, and at the same time, exhibits negligible impact on the microflora residing in other parts of the body.

Minocycline is a semisynthetic derivative of tetracycline which is more active and has a wider spectrum of action. Systemic administration of minocycline adjunctive to mechanical debridement in the management of chronic periodontitis has been reported.[11] Minocycline is also available as a local drug delivery system. Our study evaluated the efficacy of a 2% minocycline gel in a sustained release drug delivery system in the management of moderate to severe chronic periodontitis.

The results of this investigation demonstrated an overall improvement in all parameters at various time intervals both in test and control groups [Table 1]. The overall bleeding index score improved from baseline to three months and this improvement was maintained till the end of the study period. Our results are similar to another study by Graca *et al.* who also used minocycline gel, however, their observations were limited to 6 and 12 weeks, post-treatment.[12] Pocket depth is an important variable and has an impact on the type of subgingival flora and the treatment outcome. Our study demonstrated significant reductions in probing depths in both groups from baseline to three months. At the end of six and nine months, probing depth values in the test group were significantly lower than those in control group. Graca *et al.* also observed marked reductions in probing depth in both groups from baseline to 6 and 12 weeks, but unlike our study, their results did not show significant difference between the test and control groups.[12] The important point to be noticed in these observations is that their study lasted for 12 weeks, whereas ours lasted for 9 months. Relative attachment levels also showed significant improvement in both test and control groups from baseline to three and six months. But between groups, the values did not reach statistical significance at any time. This maybe because chronic periodontitis is a chronic disease which progresses in an episodic manner and the rate of progression of disease is very slow, so a 9-month period may not be sufficient to record noticeable differences in attachment loss. Our results are in accordance with a recent meta-analysis published in 2005, which found a marginal improvement in attachment level with

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adjunctive use of minocycline as compared to SRP alone which did not reach statistical significance.[6]

A new dimension was added to this investigation by microbiological examination of bacterial morphotypes using dark-field microscopy. It was thought appropriate to evaluate the effect of minocycline gel on subgingival microbial population, the primary etiological factor for periodontitis. Our results demonstrated a marked reduction in total number of organisms in both test and control groups from baseline to three months. A significant reduction was seen in the number of spirochetes, cocci, and motile bacilli at three months in both the groups. Between treatment groups, no significant differences were observed with respect to different morphotypes except at nine months when control group showed significantly higher number of non-motile bacilli as compared to test group. This maybe a chance finding, due to small sample size of our study or maybe attributed to the re-growth of plaque over time.

The overall view of results of our investigation cast a shadow of uncertainity on the efficacy and efficiency of 2% minocycline containing gel as an effective local drug delivery system, and it calls for further clinical trials to objectively evaluate the adjunctive use of locally delivered minocycline in periodontal therapy.

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