

# Evaluation of a Novel Local Drug Delivery System Containing Tetracycline Hydrochloride Microparticles as an Adjunct to Mechanotherapy in the Management of Chronic Periodontitis

## Abstract

**Background:** Tetracycline hydrochloride is a primarily used antimicrobial for periodontitis. Due to its limitations when used systemically, local application in the subgingival zone is encouraged. The local concentration of the drug can be maximized further by optimizing its delivery vehicle. **Aim and Objectives:** The aim was to compare and assess the efficacy of novel drug formulation containing tetracycline microparticles with commercially available tetracycline fibers as local drug delivery agents in patients with chronic periodontitis. **Materials and Methods:** A total of 10 patients in the age group of 23–53 years with chronic periodontitis were selected. Patients having isolated periodontal pockets with probing pocket depth (PPD) >5 mm were selected. They were randomized into Group A (scaling and root planning [SRP] + tetracycline microparticles) and Group B (SRP + tetracycline fibers). Clinical parameters such as plaque index, gingival index, probing pocket depth (PPD), and clinical attachment level (CAL) were recorded at 0 and 90 days. The data obtained were consolidated and subjected to statistical analysis. **Results:** Both the groups confirmed statistically significant improvement in all the clinical parameters. Results of the study showed enhanced CAL gain in Group A compared to Group B. **Conclusion:** The novel drug formulation is equally efficacious to the commercially available formulation, with decreased manufacturing cost and greater drug availability. Nevertheless, more clinical trials are necessary to study the long-term results.

**Keywords:** Chronic periodontitis, local drug delivery, tetracycline microparticles

## Introduction

Since 1979, the usage of locally administered antimicrobial agents in periodontal pockets has been studied comprehensively.<sup>[1]</sup> The greatest benefit of such a mode of drug delivery, apart from restricting the drug to its intended destination, is obtaining a relatively greater concentration locally than its systemic counterpart. It also reduces the risk of developing resistant microflora and potential side effects.<sup>[2]</sup>

Owing to higher drug concentration in the sulcular fluid (gingival crevicular fluid), the tetracycline group of antibiotics is generally considered suitable for periodontal applications. A study conducted by Golub *et al.* confirms the anticollagenolytic property of the tetracycline class of drugs in addition to its antimicrobial and anti-inflammatory

properties.<sup>[3]</sup> The other properties of tetracycline group of drugs are inhibition of osteoclasts and promotion of fibroblastic attachment to the root surfaces, thus acting as a valuable adjunct to nonsurgical therapy.<sup>[4]</sup> Various local drug delivery vehicles for the placement of tetracyclines into periodontal pockets have been developed in the form of different fibers hollow,<sup>[5]</sup> ethylene vinyl acetate copolymer,<sup>[6]</sup> ethyl cellulose,<sup>[7]</sup> strips acrylic,<sup>[8]</sup> collagen preparations,<sup>[9]</sup> and films hydroxypropyl cellulose.<sup>[10]</sup>

The ideal drug delivery system should be designed such that it transports the antimicrobial agents to the bottom of the periodontal pocket at a bacteriostatic or bactericidal concentration.<sup>[11]</sup> This current study was designed to assess a novel drug formulation of tetracycline hydrochloride (TH) in the form of microparticles as a local drug delivery agent for the treatment of chronic periodontitis.

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## Materials and Methods

A pilot study with 10 participants was planned, after clearance from the ethical committee. Informed written consent was acquired from the study participants. Patients diagnosed with chronic periodontitis (probing pocket depths [PPD]  $\geq 5$  mm) and individuals who maintained satisfactory oral hygiene after the initial treatment were included, whereas patients with a history of periodontal/antibiotic therapy, systemic disorders, or smoking in the past 6 months were not included in the study.

A thorough scaling and root planning (SRP) was performed in both the groups, followed by the application of one of the two local drug delivery agents in the two groups as follows:

1. Group A (test): Five patients who were treated by a subgingival application of novel drug formulation containing tetracycline microparticles (TH)
2. Group B (control): Five patients who were treated by a subgingival application of tetracycline fibers (Periodontal Plus AB).

Followed by a thorough supragingival scaling, appropriate oral hygiene instructions were demonstrated to the individuals. The following clinical parameters such as plaque index (PI),<sup>[12]</sup> gingival index (GI),<sup>[13]</sup> PPD, and clinical attachment level (CAL) were assessed at baseline before SRP [Figure 1] and reassessed at 3 months after the treatment [Figure 2].

### Need for novel drug formulation

The requisite for drug formulation is the development of a novel concept of long-acting microparticles with TH which effectively has a greater surface area for action, with a biocompatible delivery agent dispersing into the instrumented periodontal pocket. The more compact structure ensures a more enhanced packing of the formulation, hence a greater drug concentration at the base of the pocket.

### Novel drug formulation

The novel drug formulation containing tetracycline microspheres was formulated by K. M. Kundnani College of Pharmacy, Mumbai, India. This novel solvent-free process to formulate long-acting, sustained-release microparticles of TH using a granulation process involving hot-melt extrusion with a reduction in size using Comil was investigated using hydrogenated castor oil which was used as a hydrophobic matrix former. Xanthan gum gel was used as delivery vehicles to ensure the smooth administration of microparticles inside periodontal pockets. The microparticles so obtained were subjected to series of analytical tests to assess their particle size, morphology, syringeability, stability, safety, and drug diffusion.<sup>[14]</sup> Samples with 3 mg of the novel formulation (to compensate

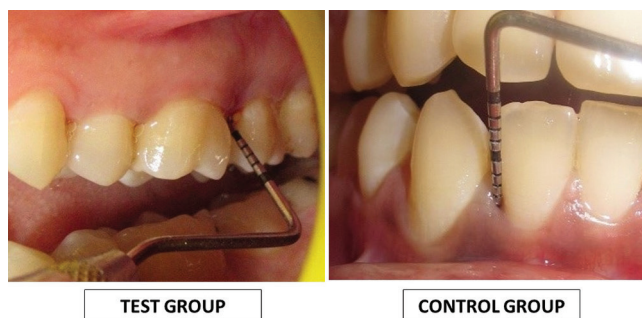


Figure 1: Baseline PPD in the test and control groups. PPD: Probing pocket depth

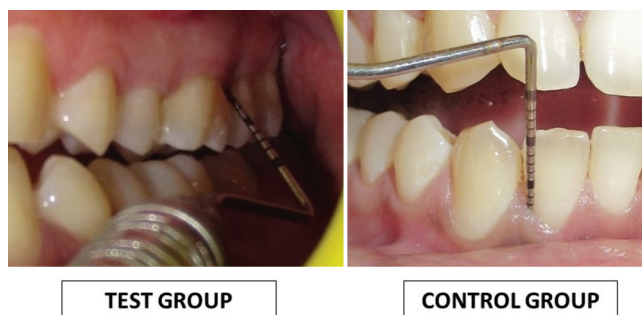


Figure 2: PPD 3 months postoperative in the test and control groups. PPD: Probing pocket depth

for wastage) were packed inside the glass vials with rubber closure, followed by an aluminum cap seal. The samples were irradiated to a dose of 25 kGy in a gamma irradiation chamber with a dose rate of 10 kGy/h.

### Comparison drug release of Group A (tetracycline hydrochloride) and Group B (periodontal plus AB)

Drug release was carried out using a dialysis membrane, hydrated for 30 min before use. This dialysis membrane sac was then submerged inside a beaker with phosphate buffer at pH 6.8 and a magnetic stirrer. The assembly was kept on a magnetic plate with heating provision to maintain the temperature at 36–38°C. The sampling was done from the beaker at the a specified interval, and drug release is analyzed using a ultraviolet spectrophotometer, which was found comparable to tetracycline fibers [Graph 1].

### Local drug delivery

Following SRP, subgingival curettage was done at the respective sites under 2% lignocaine (with 1:200,000 adrenaline). The sites were irrigated with a normal saline, and respective agents were delivered to the base of the periodontal pockets; in Group A with the aid of a blunt cannula of the syringe and in Group B with a tweezer and a curette [Figure 3].

A noneugenol-based periodontal dressing was applied to the site [Figure 4]. Patients were advised to avoid chewing on hard and sticky foods. Mechanical plaque control methods like brushing or use of interdental aids were also avoided at the surgical site for 1 week.

### Follow-up

No serious complications were observed during the study. The novel drug formulation was well accepted by all the patients with minimum postoperative discomfort.

### Statistical analysis

The level of significance was determined at  $P = 0.05$  and any value  $\leq 0.05$  was considered statistically significant.

### Results

The present study incorporated 10 patients (seven males and three females) having a mean age of 35 years (23–55 years).

### Intragroup and intergroup analysis

At baseline, all the clinical parameters were observed to be matched in all the three groups with intergroup difference being statistically insignificant ( $P > 0.05$ ) [Tables 1-4]. At the end of 3 months, all the parameters showed statistically significant differences within the groups when compared to their respective baselines ( $P < 0.05$ ) [Tables 1-4]. Intergroup analysis for PI, GI, and PPD was comparable at the end of 90 days with a statistically higher gain in CAL in Group A ( $P < 0.05$ ) [Table 4].

### Discussion

Periodontal disease is a multifactorial immunoinflammatory disorder, distinguished by reduction in the attachment apparatus and bone.<sup>[15,16]</sup> Various tissue destruction

mechanisms have been suggested in the pathogenesis of the periodontal disease. Among those, of utmost importance is the action of the protein-destructive enzymes (released by periodontal pathogens and from host defenses) such as matrix metalloproteinases, which cause collagen destruction.<sup>[17]</sup>

The nonsurgical periodontal therapy, while demonstrating significant long-term benefit in most of the patients, does present with some constraints. These include difficulty to reach deeper sites or complex pockets, or furca, and the difficulty in eliminating bacteria from the dentinal tubules, root hollows, lacunae, and soft tissues. Therefore, antimicrobial therapy may be considered a valuable additive when used as an adjunct to mechanotherapy.

Given the disadvantages of systemic therapy, local applications of subgingival antimicrobials provide significant reductions in pocket depth and CAL, thus proving to be a better alternative. The benefit in the reduction of the pocket depth is most conspicuous with the use of antibiotics of the tetracycline group.<sup>[18]</sup> The tetracycline groups of drugs are delivered subgingivally using various drug delivery systems – all aimed at achieving maximum drug concentration locally.<sup>[5]</sup> An ideal drug delivery agent should be such that it provides optimal drug concentration with minimal loss of drug at the depth of the pocket, for an adequate duration, thus maximizing the drug benefits at the diseased sites.<sup>[11]</sup>

The restorative potential of microparticles rests in the properties such as larger surface area, site-specific sustained

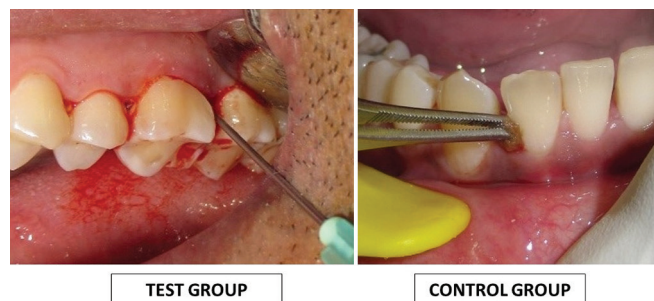


Figure 3: Administration of LDD agent in the test and control groups. LDD: Local drug delivery

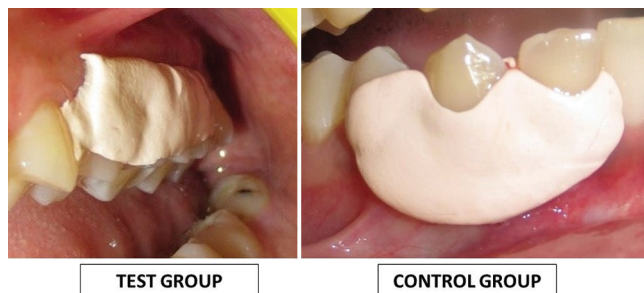


Figure 4: Placement of noneugenol-based periodontal dressing (Coe-Pak™) in the test and control groups

**Table 1: Comparison of the values of plaque index in terms of mean (standard deviation) at different time intervals among the groups using ANOVA test**

Group	n	Mean		SD		P
		Baseline	1 month postoperative	Baseline	1 month postoperative	
Group A	5	1.9270	0.3220	0.38761	0.14047	<0.001**
Group B	5	1.9455	0.3805	0.43375	0.22988	<0.001**
<b>Tukey's post hoc analysis</b>						
		Group A		Group B		
Group A		-		0.806		
Group B		0.806		-		

\*\* $P < 0.001$  highly significant. PI shows statistically significant intragroup improvements with no intergroup difference. PI: Plaque index, SD: Standard deviation

**Table 2: Comparison of the values of gingival index in terms of mean (standard deviation) at different time intervals among the groups using ANOVA test**

Group	n	Mean		SD		P
		Baseline	1 month postoperative	Baseline	1 month postoperative	
Group A	5	1.8870	0.2960	0.34339	0.10007	<0.001**
Group B	5	2.0555	0.5700	0.51639	0.26428	<0.001**

Tukey's <i>post hoc</i> analysis		
	Group A	Group B
Group A	-	0.014
Group B	0.442	-

\*\*P<0.001 highly significant. GI shows statistically significant intragroup improvements with no intergroup difference. GI: Gingival index, SD: Standard deviation

**Table 3: Comparison of the values of probing pocket depth in terms of mean (standard deviation) at different time intervals among the groups using unpaired t-test**

PPD	n	Mean	SD	t	P
Baseline					
Group A	5	5.30	1.105	0.8033	>0.05
Group B	5	6.1	1.252		
3 months					
Group A	5	3.9	1.119	0.9324	>0.05
Group B	5	4.25	1.251		

PPD shows statistically significant intragroup improvements with no intergroup difference. PPD: Probing pocket depth, SD: Standard deviation

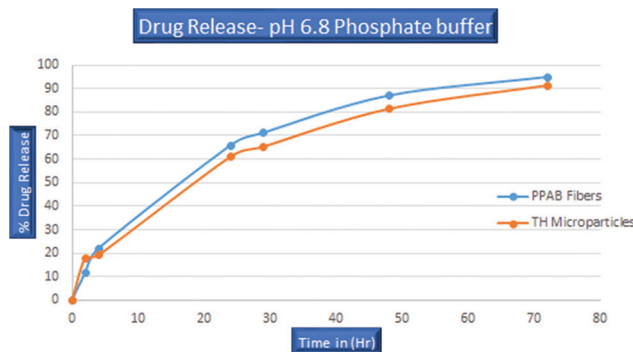
**Table 4: Comparison of values of clinical attachment levels in terms of mean (standard deviation) at different time intervals among both the groups using unpaired t-test**

Clinical attachment level	n	Mean	SD	t	P
Baseline					
Group A	5	8.90	1.071	0.477	0.636
Group B	5	8.75	0.910		
3 months					
Group A	5	4.65	0.745	4.210	<0.001**
Group B	5	5.60	0.681		

\*\*P<0.001 highly significant. CAL shows statistically significant intragroup and intergroup improvements. CAL: Clinical attachment level, SD: Standard deviation

drug delivery, the wide diversity of biocompatible polymers that can be employed, and the ease of implantation at the target.<sup>[19,20]</sup> More so, these criteria can be manipulated as per demands to formulate microparticulate systems adapted to suit the requirements of the clinical condition.

The present pilot study was designed to assess the efficacy of the novel drug formulation against commercially available formulation as a local drug delivery agent in isolated periodontal pockets. To the best of our knowledge, the present study is one of the kinds that compares the effectiveness of tetracycline microparticles as a local drug delivery agent for the management of chronic periodontitis.



**Graph 1: Comparison drug release of Group A (TH) and Group B (PPAB). TH: tetracycline hydrochloride, PPAB: Periodontal plus AB**

A sample population comprising 10 adult patients with no comorbidities (five in each group), having isolated periodontal pockets, were treated with subgingival curettage and placement of novel drug formulation of tetracycline microparticles and tetracycline fibers, respectively. At the conclusion of 90 days, a reduction in clinical parameters was noted in both groups. PI and GI showed a comparable reduction in the groups indicating improvement in oral hygiene and gingival status. CAL gain was greater in Group A, whereas PPD reduction was comparable in both the groups.

The results of this study are in compliance with the findings of similar studies published by Dang *et al.*<sup>[21]</sup> and Boyeena *et al.*<sup>[22]</sup>

The major advantage of microparticles over fiber is less wastage of drug owing to its compact size, a simple manufacturing process with low production costs, and reduced risk of human error.<sup>[23]</sup>

### Conclusion

The study reveals that the subgingival delivery of tetracycline microparticles after mechanotherapy is equally efficacious and favorable to patients with chronic periodontitis as tetracycline fibers.

### Limitations

This study being a pilot study, the results cannot be extrapolated to a larger population. Nevertheless, additional

studies with a longer duration of follow-up will help establish these results.

### Ethical statement

The study was approved by the institutional Ethics Committee of Nair Hospital Dental College. (EC-122a/PERIO-22ND/2019-2020).

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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