

## Original Research

### Comparing the Effect of Combination of 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel with 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel in the Treatment of Chronic Periodontitis: A Randomized, Single-Blind, Split-Mouth Study

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#### ABSTRACT:

**Introduction:** Periodontitis is very common occurrence with a multifactorial etiology, dental plaque being the primary etiologic agent. The removal of such etiologic factor through scaling and root planing builds the foundation of treatment. In addition, the use of an antimicrobial adjunct augments elimination of microbes leading to subsequent control of the disease. Chlorhexidine and Metronidazole have been found to be active against several periodontopathogens. In this study, the use of these antimicrobial gels has been made to evaluate and compare the clinical efficacy of subgingival application of two different concentrations of Metronidazole and Chlorhexidine combination gel. **Materials and Methods:** 100 sites of mild to moderate periodontitis in 50 patients were randomly divided into two groups – group I and Group II in a split mouth study design. In Group I sites, 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel was delivered inside pocket every week and in group II sites, 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate gel was delivered as in group I for 4 weeks. Baseline and 4 weeks measurements were done and compared for plaque index, gingival index, bleeding index, pocket probing depth and clinical attachment levels. **Results:** Results showed that both the combinations of Metronidazole and Chlorhexidine were significantly effective in reduction of plaque index score, gingival index score, bleeding index score, pocket probing depth and clinical attachment level at 4 weeks with no significant difference between two concentrations. **Conclusion:** Local drug delivery of a combination of Metronidazole and Chlorhexidine is an effective treatment modality for the management of periodontitis as an adjunct to scaling and root planning in mild to moderate periodontitis cases.

**Key Words:** Periodontitis, Local Drug Delivery, Metronidazole, Chlorhexidine

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#### INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus. Periodontitis is a major public health problem due to its high prevalence, as well as because it may lead to tooth loss and disability, negatively affect chewing function and aesthetics, be a source of social inequality and impair quality of life.<sup>1</sup> To combat periodontal disease, nonsurgical periodontal therapy (NSPT) is one of the gold standards besides a broad range of treatment modalities advocated to eliminate periodontal disease.<sup>2</sup>

Systemic antibiotics are recommended by many authors but the additional use of antibiotics systemically in the treatment of periodontitis is limited, due to the need for high doses to achieve the appropriate concentration of the drug in the gingival fluid, rapidly growing resistance of the bacteria, and side effects of the drugs. Also, due to the advanced organization of the structure and function of the subgingival biofilm, antibiotics may not be effective or can be inactivated.<sup>3</sup> On the other hand; a high rate of recurrence is associated with periodontal disease. To overcome these limitations and to attain a disease-free periodontium, local drug delivery (LDD) is one of the treatment modalities. LDD is a

treatment concept that was introduced by Max Goodson,<sup>4</sup> in that a pharmacological compound was placed into a localized site in a manner that can safely achieve its desired therapeutic effect.

Combination of Metronidazole and Chlorhexidine is one of the LDD agents that has shown a marked antibacterial activity and is active against most of the periodontal pathogens. Metronidazole being a broad-spectrum antibiotic<sup>4</sup> is one of the most widely used antibacterial compound in the treatment of periodontal diseases such as aggressive periodontitis and chronic progressive periodontitis that does not react positively to conventional treatment. It is effective against widely accepted periodontal pathogens and regularly used alone or combined with amoxicillin as an empirical treatment of periodontitis<sup>5</sup> Chlorhexidine is one of the most effective topical agents, which has long been used as an effective antimicrobial agent.<sup>6</sup> The first sustained release dosage form of chlorhexidine diacetate for topical use was developed by Friedman and Golomb.<sup>7</sup> It has shown effectiveness in reducing the periodontal probing depth, clinical attachment loss, and bleeding on probing.<sup>8</sup>

Thus, with this background, a study was conducted to evaluate the effect of these gels as LDD in adjunct to conventional phase I therapy and compare the efficacy of subgingivally delivered combination of 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel with 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel for the treatment of chronic periodontitis.

## MATERIALS AND METHOD

A randomized, single-blind, split-mouth study, was conducted among patients visiting the Department of Periodontics, Government Dental College and Hospital, Srinagar. A total of 50 patients, with age groups ranging from 25 to 65 years, who were diagnosed with mild-to-moderate chronic periodontitis and willing to participate were voluntarily enrolled in the study according to the inclusion and exclusion criterion. Before the commencement of the study, ethical clearance was obtained from the ethical clearance committee of the institute. All the patients who fulfilled the inclusion criteria received detailed information regarding the study and only those patients were included who signed an informed consent. The study was conducted according to the World Medical Association Declaration of Helsinki.

## INCLUSION CRITERION

1. Patients with mild to moderate chronic periodontitis - pocket depth (PD) 4–6 mm
2. Clinical attachment loss 1–4 mm
3. No history of antibiotic therapy in the past 6 months
4. Age 25- 65 years

## EXCLUSION CRITERION

1. Any known drug allergy to any components of trial medication
2. Pregnant, lactating women
3. Smokers
4. Patient with any known medical condition
5. Patients with aggressive periodontitis

According to split-mouth design, sites with probing depths of 4–6 mm were randomly divided into two parallel treatment arms by flip of a coin with one site allocated to Group I and other site allocated to Group II in each patient.

**Group I:** comprised 50 sites wherein local delivery of combination of 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel was administered

**Group II:** comprised 50 sites wherein the local delivery of Combination of 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate was administered.

At the baseline visit, all the clinical parameters were recorded which included: Plaque Index (PI, Silness and Loe 1964)<sup>9</sup>; Gingival Index (GI, Loe and Silness 1963)<sup>9</sup>; bleeding index (BI, Muhlemann HR, Son S);<sup>10</sup> Probing Pocket Depth (PPD) and Clinical Attachment Level(CAL). After recording the parameters, full mouth scaling with ultrasonic piezoelectric scaler and root planing with Hufreidy gracey curettes was performed. The sites were irrigated gently with normal saline and left for 10 minutes to achieve haemostasis prior to placement of the respective drug. A 3 ml disposable syringe was taken and the tip of the cannula was made blunt so as to prevent tissue injury that may be caused by the sharp needle tip. The syringe was then loaded with the respective drug group for the local drug delivery. Isolation and drying followed by drug delivery subgingivally to the base of periodontal pocket was done. The confirmation of sufficient amount of drug deposition in the pocket was gained by gel seen at the gingival margin of the respective tooth being treated. Then periodontal dressing was placed. Postoperative home care instructions including brushing with a soft brush twice a day was advised and use of chemotherapeutics and irrigation devices were not recommended. Patients were recalled after 1 week, 14 days and 21 days for removal of the periodontal dressing and replacement of drug inside periodontal pocket. After 4 weeks periodontal dressing was completely removed and measurements repeated for various parameters. UNC-15 (University of North Carolina) periodontal probe was used to measure PPD and CAL.

## DATA ANALYSIS

The primary outcome of the study was probing Pocket depth (PPD). The secondary outcomes included PI, GI, BI, and clinical attachment level (CAL).

Continuous variables (PI, GI, BI, PD, and CAL) were expressed as the mean  $\pm$  standard deviation. Statistical analysis was performed with statistical

software (SPSS version 20.0, SPSS, Chicago, IL, USA). T-test for differences within the group and between the groups was performed. Statistical significance was defined as  $P < 0.001$ .

**RESULTS**

All the patients completed the study. No patients reported with any adverse reaction. There was a

statistically significant improvement in the PI, GI, BI, CAL and probing PD readings after 4 weeks in both the groups. Intergroup comparison of all the parameters showed that there was no significant difference in improvement between two concentrations used in group I and Group II. (Table 1-5).

<b>Table 1: Plaque Index (PI)</b>				
<b>Interventional Group</b>	<b>Baseline</b>	<b>4 weeks</b>	<b>Intragroup (P)</b>	<b>Intergroup (P)</b>
Group I: 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel	2.460±0.251	1.04±0.114	<0.001*	>0.001(NS)
Group II: 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel	2.48±0.277	1.08±0.130	<0.001*	

\*: Significant p value. NS: non-significant

<b>Table 2: Gingival Index (GI)</b>				
<b>Interventional Group</b>	<b>Baseline</b>	<b>4 weeks</b>	<b>Intragroup (P)</b>	<b>Intergroup (P)</b>
Group I: 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel	2.556±0.222	1.108±0.092	<0.001*	>0.001(NS)
Group II: 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel	2.554±0.275	1.136±0.094	<0.001*	

\*: Significant p value. NS: non-significant

<b>Table 3: Bleeding Index (BI)</b>				
<b>Interventional Group</b>	<b>Baseline</b>	<b>4 weeks</b>	<b>Intragroup (P)</b>	<b>Intergroup (P)</b>
Group I: 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel	2.834±0.274	1.402±0.235	<0.001*	>0.001(NS)
Group II: 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel	2.822±0.353	1.400±0.279	<0.001*	

\*Significant p value. NS: non-significant

<b>Table 4: Pocket Probing Depth (PPD)</b>				
<b>Interventional Group</b>	<b>Baseline</b>	<b>4 weeks</b>	<b>Intragroup (P)</b>	<b>Intergroup (P)</b>
Group I: 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel	5.400±0.547	2.20±0.447	<0.001*	>0.001(NS)
Group II: 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel	5.400±0.547	2.40±0.547	<0.001*	

\*: Significant p value. NS: non-significant

<b>Table 5: Clinical Attachment Level (CAL)</b>				
<b>Interventional Group</b>	<b>Baseline</b>	<b>4 weeks</b>	<b>Intragroup (P)</b>	<b>Intergroup (P)</b>
Group I: 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel	3.400±0.547	1.00±0.00	<0.001*	>0.001(NS)
Group II: 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel	3.400±0.547	1.00±0.00	<0.001*	

\*: Significant p value. NS: non-significant

**DISCUSSION**

Periodontitis is the most common multifactorial dental inflammatory disease related with several pathological conditions like inflammation of gums (gingivitis), degeneration of periodontal ligament, dental cementum and alveolar bone loss.<sup>11</sup> It leads to loss of masticatory efficacy and in severe cases, if left untreated it leads to exfoliation of teeth due to severe resorption of alveolar bone.<sup>12</sup>

Treatment of the periodontal disease is a challenging and difficult task as the infection occurs due to bacterial biofilm which is highly resistant to the antimicrobials and causes selective growth of virulent microorganisms.<sup>13</sup> In the initial stage of the disease, inflammation is limited to the gingiva (gingivitis) but later extends to the deeper tissues which in turn leads to swelling of gums and bleeding of gums. It may also lead to abscess formation and halitosis. In the late phase of disease, as the infection penetrates

deeper into the tissue, the supporting connective tissue of periodontium begins to degenerate, resorption of alveolar bone takes place and epithelial tissue of gingiva migrates which leads to formation of pockets.<sup>14</sup> The choice of the treatment strategy therefore depends upon the stage of disease progression.

Various approaches applied for the treatment of disease include mechanical therapy, use of pharmacological agents and surgical intervention.<sup>13</sup> Initial non-surgical periodontal therapy primarily consists of home care review and scaling and root planning. Periodontal scaling procedures include the removal of plaque, calculus and stain from the crown and root surfaces of teeth.<sup>15</sup> Scaling and root planning has become the “gold standard” nonsurgical treatment of periodontitis.<sup>16</sup> For patients with severe periodontitis or medically compromised adjunctive use of systemic antibiotics may be considered.<sup>17</sup> Currently systemic antibiotics are prescribed only for the treatment of rapidly progressing or refractory periodontitis.<sup>18</sup> Multiple dosing of systemic antibiotics which requires patient compliance and thus may lead to erratic antibiotic concentration at the targeted site,<sup>19</sup> a quick fall in the plasma drug concentration below the therapeutic index,<sup>20</sup> and development of resistance to antibiotics. Besides this, systemic antibiotics also leads to several side effects in patients.<sup>18</sup> These shortcomings of systemic antimicrobial treatment led to the development of interest in localized intra-pocket drug delivery systems for the treatment of periodontal diseases.

Local drug delivery systems have the advantage of lesser side effects, superior worth and improved patient compliance.<sup>11</sup> This system of delivery can provide higher concentration of medication to the targeted site for longer duration. Moreover, it can limit the adverse effects of systemic administration and prevent bacterial resistance. Despite the rapid development of a variety of adjunctive local periodontal treatments in recent years, Chlorhexidine (CHX) and Metronidazole (MTZ) remains one of the most effective local antimicrobial agents, and is widely used for the local treatment of periodontitis.<sup>21,22</sup>

The present study aimed at comparing the clinical efficacy of two local drug delivery systems in gel forms: first group-containing 1% Metronidazole and 0.25% Chlorhexidine Gluconate Gel and other group containing 1.5% Metronidazole and 0.5% Chlorhexidine Gluconate Gel in chronic periodontitis patients. The form of drug used in the study is gel which has an advantage over other forms like mouth rinse, irrigation etc due to semi-solid formulation that retains in the pocket and prevents the drug from being flushed out of the pocket by the GCF flow.

In the present study, there was a statistically significant reduction in mean plaque index score, mean gingival index score, mean bleeding index score, periodontal probing depth and clinical

attachment loss in both the groups when observed at 4 weeks follow up. A significant reduction in mean plaque index score observed in both the groups can be attributed to the antiplaque effect of CHX which is similar to the effect reported in a study where subgingival irrigation with CHX rinse demonstrated a significant reduction in formation of supragingival plaque, associated erythema and bleeding on probing when compared to control.<sup>23</sup>

The clinical parameters were recorded at baseline and 4 weeks follow up. The follow up was planned for 1 month because of the fact that substantial pocket depth reduction can take place in within 4 weeks of a single episode of root planning in association with improved oral hygiene measures to maintain low levels of supragingival plaque as concluded by Proye et al.<sup>24</sup>

The maximum change in healing that could be appreciated clinically has been noted to occur during the measurement done from baseline to 1 month. This has been explained by Cercek and coworkers<sup>25</sup> who noted clinical improvements to continue for 8 months, however, most of the healing occurred during the first month. It appears that, the maximum change in relation to probing depth reduction and clinical attachment gain can be appreciated after 4 to 6 weeks. Hence, in the present study all the groups showed a significant change in the clinical parameters during 4 weeks time.

One of the main drawbacks of this study is that microbial evaluation was not carried out. However, further studies should be done toward clinical evaluation and determination of long-term efficacy of intra-pocket application with both the gels on clinical parameters with larger sample and longer follow-up periods.

## CONCLUSION

From the study we conclude that Metronidazole and Chlorhexidine in both the concentrations are equally efficacious as an adjunct to SRP for treating chronic periodontitis patients and any of the combination can be prescribed to the patients. However, further study is required to assess long term effects of the combination gels.

## SOURCE(S) OF SUPPORT

Nil

## CONFLICTING INTEREST

We certify that we have no proprietary, financial, or other personal interest of any kind in any product, service, and/or company that is presented in this article.

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