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To evaluate the effectiveness of locally delivered 25 % metronidazole gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis: A randomized clinical controlled trial

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Abstract
Aim: To evaluate the clinical & microbiological effectiveness of locally delivered 25 % metronidazole gel along with scaling and root planing in the treatment of chronic periodontitis compared to placebo gel.
Methodology: A randomized controlled clinical study with a split mouth design was conducted involving 40 sites in the chronic periodontitis patients with clinical attachment loss(CAL) of ≥ 5mm and probing pocket depth (PPD) of ≥ 5mm were included in the study. Using computer generated series of random numbers, the sites are randomly assigned into two treatment groups- **i.e** Test group- Group I in which Scaling and root planing + subgingival insertion of 25% metronidazole gel was done at day 1 and day 7 and Control group – Group 2 in which Scaling and root planing + subgingival insertion of placebo gel was done at day 1 and day 7. Clinical examination for Probing pocket depth, Relative attachment level, Plaque index (PI), gingival index (GI) measurement was done. For microbiological assessment, anaerobic microbial culture was prepared to count the colonies causing periodontal destruction. Data obtained was compiled on a MS Office Excel Sheet (v 2010) and subjected to statistical analysis using Statistical package for social sciences (SPSS v 22.0, IBM).
Results: Results showed significant difference seen with intergroup comparison of Post-op GI, with higher mean for GI for Group 2.($p<0.01$).There was a statistically highly significant difference seen between Pre-op and Post-op of all variables in group 1 & 2 ($p<0.01$). There was a statistically significant difference seen between group 1 & 2 for Bacterial Count cfu/ml ($p<0.01$) with higher no of patients having lower scores in group 1 while higher no of patients with higher scores in group 2.
Conclusion: Antibiotic therapies resulted in greater improvement in microbiological parameters when compared to mechanotherapy alone.

Keywords: metronidazole, randomized, controlled, periodontitis

Introduction
Chronic periodontitis is marked with the overgrowth of micro-organisms, chiefly anaerobic. Antimicrobial regimen has been proposed to aid the non-surgical treatment of chronic periodontitis. Local drug delivery is an approach to improve the selectivity of antimicrobial therapy and increased drug potential at specific sites [1]. Localized antimicrobial therapy, in particular, has evoked growing interest because of the site-specific nature of periodontal infections, the higher concentration of anti-microbial agent subgingivally and reduced side-effects of systemic antibiotic use. Various locally delivered chemotherapeutic agents available are: Tetracycline fibers, metronidazole gel, minocycline ointment and minocycline microspheres, chlorhexidine chip, doxycycline hyclate, etc [2].
Among the various locally delivered chemotherapeutic agents metronidazole, a member of nitroimidazole class of antibiotics has bactericidal action against anaerobes, such as Prevotela intermedia, Porphyromonas gingivalis, Tannerella forsythia, Fusobacterium species and spirochetes like Treponema denticola, Treponema vincentii, which are generally believed to be the main pathogens associated with periodontitis [2, 3]. A metronidazole-containing gel (25%) (Elyzol®, Alpharma ApS, Denmark) is available for use as local drug-delivery agent. Many clinical studies have been conducted to assess the efficacy of local drug delivery systems as adjuncts to SRP or as the sole treatment for untreated periodontal lesions. Few studies have assessed the comparative efficacy of a number of currently marketed systems [4, 5].
Thus present study was conducted with the aim to evaluate the clinical & microbiological effectiveness of locally delivered 25 % metronidazole gel along with scaling and root planing in the treatment of chronic periodontitis compared to placebo gel [5].

Material and Method
A randomized controlled clinical study with a split mouth design was conducted in the Department of Periodontics, RUHS College of Dental Sciences, involving 40 sites in the chronic periodontitis patients with clinical attachment loss (CAL) of ≥ 5mm and probing pocket depth (PPD) of ≥ 5mm were included in the study.
Clinical screening was done for 40 sites, out of which 12 were excluded for the reason of providing treatment with antibiotics or periodontal treatment with in the last 6 months or pregnancy. Using computer generated series of random numbers, the sites are randomly assigned into two treatment groups- i.e Test group- Group I in which Scaling and root planing + subgingival insertion of 25% metronidazole gel was done at day 1 and day 7 and Control group – Group 2 in which Scaling and root planing + subgingival insertion of

placebo gel was done at day 1 and day 7. Clinical examination for Probing pocket depth, Relative attachment level, Plaque index (PI), gingival index (GI) measurement was done. For microbiological assessment, anaerobic microbial culture was prepared to count the colonies causing periodontal destruction. Ethical approval for carrying out the trial was sought from institutional ethical committee and written consent was obtained from each participant after providing Information sheet. Data was assessed at baseline and at one month of periodontal therapy.

Fig 1: Local drug delivery at selected site

Statistical analysis

Data obtained was compiled on a MS Office Excel Sheet (v 2010) and subjected to statistical analysis using Statistical package for social sciences (SPSS v 22.0, IBM). Descriptive variables like mean and SD of age, frequency of males and females participated in the present study has been presented. Normality of data has been checked using Kolmogorov Smirnov test for normality, it is found that data for most of the variables does not follow a normal curve ($p<0.01$, Highly Skewed), hence non parametric tests have been used for data analysis. *Intergroup comparison* of various variables like PD, CAL, GI & PI was done using Mann Whitney U test. *Intra group comparison* of these variables in each of the 2 groups pre-op and post-op was done using Wilcoxon Signed Ranks Test. Comparison of CFU pre-op and Post-op between the groups has been done using chi square test. For all the statistical tests, $p<0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results

Results showed significant difference seen with intergroup comparison of Post-op GI, with higher mean for GI for Group 2. ($p<0.01$). There was a statistically highly significant difference seen between Pre-op and Post-op of all variables in group 1 & 2 ($p<0.01$). There was a statistically significant difference seen between group 1 & 2 for Bacterial Count cfu/ml ($p<0.01$) with higher no of patients having lower scores in group 1 while higher no of patients with higher scores in group 2 as depited in figure 2-7.

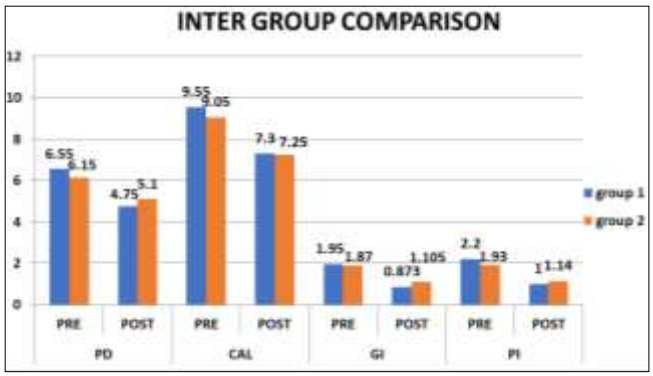

Fig 2: Intergroup comparison of PD, CAL, GI and PI

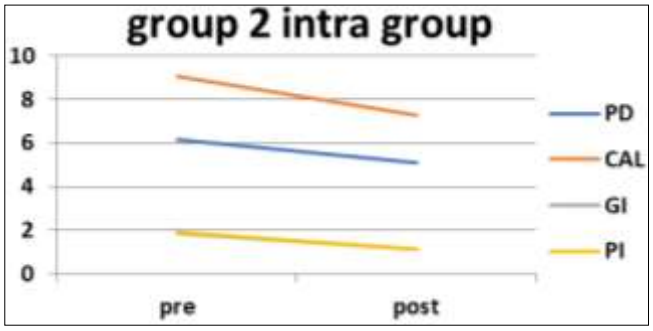

Fig 3a: Intragroup comparison of PD, CAL, GI and PI in Group 1

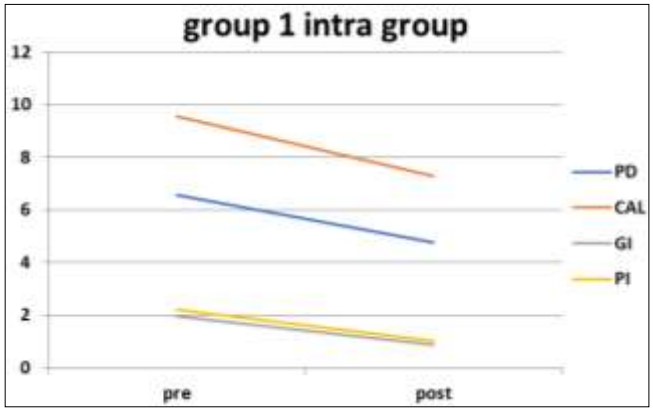

Fig 3b: Intragroup comparison of PD, CAL, GI and PI in Group 2

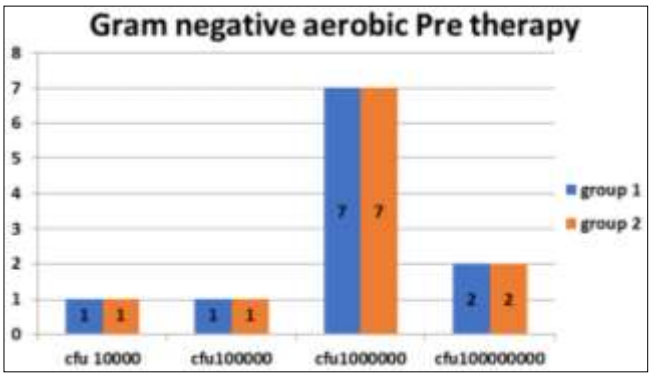

Fig 4: Gram negative aerobic CFU post therapy at different dilutions

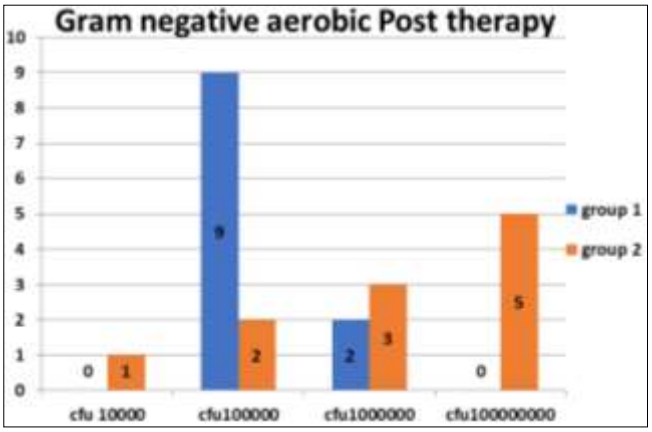

Fig 5: Gram negative aerobic CFU post therapy at different dilutions

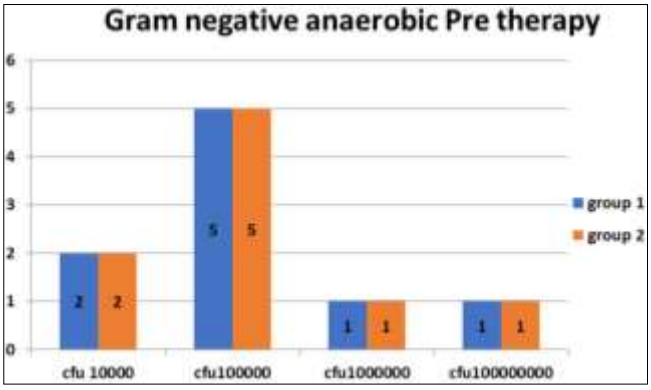

Fig 6: Gram negative anaerobic CFU pre therapy at different dilutions

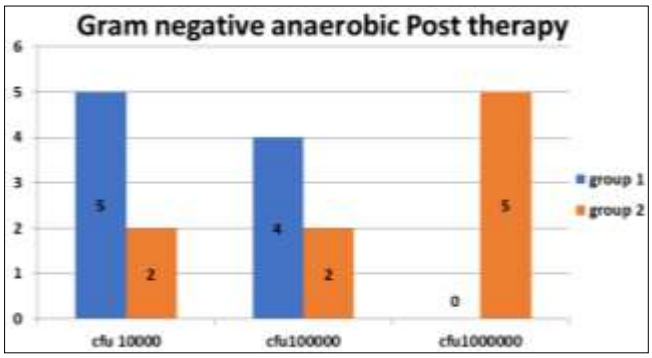

Fig 7: Gram negative anaerobic CFU post therapy at different dilutions

Discussion

The present study was designed to evaluate the clinical efficacy of locally delivered 25 % metronidazole gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis. Amongst the advantages of local drug delivery, most important is that it can attain 100-fold higher concentration of an anti-microbial agent in subgingival sites compared with a systemic drug regimen. It may employ antimicrobial agents not suitable for systemic administration, e.g., broad-spectrum antiseptic solutions. It reduces potential problems with patient compliance. It reduces systemic side effects. It reduces the risk of developing drug-resistant microbial populations at non oral body sites [6].

Metronidazole specifically targets anaerobic microorganisms but has essentially no activity against aerobic or microaerophilic bacteria. Since anaerobic bacteria are believed to be the predominant causative factor in periodontitis, it might be advantageous to use it in the treatment of chronic periodontitis [7].

A split mouth design was used in the present study. It has been suggested that a split mouth design may induce a carry-over effect of subgingival antibiotic administration due to wash out of anti-microbial agent and boosting of systemic responses.[8] Although, its' true, Imery 1986 believed that gingival crevicular fluid is relatively isolated from saliva. Moreover, split mouth design has the big advantage in that it allows paired comparisons to be made [9, 10].

Results of the present study depicted a high efficacy of local delievery of metronidazole against periodontal pathogens, clinical attachment level, periodontal pocket dept, gingival and plaque index. Similarly Sato S *et al*. conducted a study to monitor metronidazole concentrations in the gingival crevicular fluid (GCF) collected from periodontal pockets of dogs after treatment with an experimental 15% metronidazole gel. They concluded that single administration of the 15% metronidazole gel released the drug in the GCF of dogs in levels several-fold higher than the minimum inhibitory concentration for some period ontopathogens grown in subgingival biofilms for up to one hour and the drug could be detected in the GCF at least 48 hours after the gel application. Yellanki SK *et al*. also had conducted a study on six batches of metronidazole gels and were prepared using natural, biodegradable polymers chitosan, guar gum and locust bean gum in variable concentrations. They concluded that metronidazole gels could be successfully prepared using natural polymers which can be targeted in the treatment of the periodontal disease and also reduce dosing frequency, increase the bioavailability of metronidazole that will result in better patient compliance with minimal side effects. These reports demonstrated improvements related to probing depth reductions and gain in clinical attachment levels that coincided with the results of the current study.

Conclusion

The results concluded that treatment with 25% metronidazole gel and SRP improve the gram negative aerobic and anerobic bacterial count in patients with chronic periodontitis compared to SRP with placebo gel. Thus we can conclude that antibiotic therapies resulted in greater improvement in microbiological parameters when compared to mechanotherapy alone.

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