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Evaluation of Effectiveness of Ornidazole (Ornigreat Gel^{Tm}), Metronidazole (Metrohex Plus^{Tm}), Silver Nanoparticle Gel (Megaheal Gel^{Tm}) And Oxygen Releasing Formula (Blue M Gel^{Tm}) Gel as an Adjunct to Phase I Therapy in The Management of Stage I Grade A/B Periodontitis: A Clinico-Microbiological Study

[1]Dr Navneet Kaur, PhD Scholar, Department of Periodontology & Oral Implantology, Desh Bhagat University, Mandi, Gobindgarh. Punjab.

[2]Dr Vikram Bali, Professor & Head, Department of Periodontology & Oral Implantology, Desh Bhagat University, Mandi, Gobindgarh.

[3]Dr Vaneet Gupta, Associate Professor, Department of Periodontology & Oral Implantology, Yamuna Institute of Dental Sciences & Research, Yamuna Nagar, Haryana.

Corresponding Author: Dr Navneet Kaur, PhD Scholar, Department of Periodontology & Oral Implantology, Desh Bhagat University, Mandi, Gobindgarh. Punjab.

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Abstract

Background: Periodontitis is an inflammatory disease induced by complex interactions between the host immune system and pathogens that affect the integrity of teeth supporting tissues. The primary goal of periodontal treatment is the elimination or reduction in the number of pathogenic bacteria. Local drug delivery agents have been used as an adjunct to SRP has been successfully used as non-surgical treatment and helps to eradicate the pathogenic bacteria which are present into the deeper structure of periodontium. The purpose of the study is to evaluate the clinical and microbiological efficacy of subgingival application of ornidazole, metronidazole, silver nano particle gel and blue M gel used as an adjunct to Phase I therapy in the treatment of Stage I Grade A/B periodontitis.

Material and Methods: Following non-surgical therapy, a total of 140 patients diagnosed with Stage I Grade A/B periodontitis having minimum of 5 teeth with PPD between 5-6 mm were randomly selected. Treatment consisted of subgingival application of ornidazole, metronidazole, silver nano particle gel and blue M gel as an adjunct to SRP in group 1/site1, group 2/site 2, group 3/site 3 and group 4/Site 4 respectively. Baseline and follow up measurements included PI, GI, PPD, CAL and

evaluation of the total microbial load (Colony Forming Units/ml).

Results: On clinical measurement, all the four groups (ornidazole, metronidazole, silver nano particle gel and blue M gel) showed significant improvement in PI, GI, PPD and CAL gain from baseline to 3 months of time interval. On microbiological analysis, group 4/site 4 and group 3/sites 3 showed a significant reduction in total microbial load from $20.09\times10^2\pm14.75$ to $4.30\times10^2\pm6.11$ and $21.72\times10^2\pm18.13$ to $3.67\times10^2\pm4.72$ respectively from baseline to 3 months of intervention. On intragroup comparison the $p<0.001$ found to be statistically significant for all the four groups/sites with less concentration of anaerobic microflora in comparison with aerobic microflora.

Conclusion: Local drug delivery agent (ornidazole, metronidazole, silver nano particle gel and blue M gel) as additional therapy with SRP manifested promising outcome along with substantial improvement as clinical and microbiological parameter.

Keywords: Periodontitis, adjunctive treatment, local drug delivery agent, anaerobic flora, microbial load

Introduction

Periodontal disease is a collective term for a number of pathological conditions characterized by inflammation and degeneration of the gums (gingiva), supporting bone (alveolar bone), periodontal ligament and cementum. Periodontitis is an inflammation of the supporting tissue surrounding teeth caused by anaerobic bacteria and in the diseased state, supporting collagen of the periodontium is destroyed and the alveolar bones begin to resorb. More severe stages of the disease lead to the loosening and ultimately loss of teeth. Periodontal disease is marked by bacterial overgrowth. The periodontal pathogens such as P. intermedia, P. gingivalis, and A. actinomycetemcomitans along with anaerobic species such as Capnocytophaga, Bacteroides melaninogenicus and Fusobacterium nucleatum species. The importance of bacteria in the etiology of periodontitis has been clearly established and the treatment is directed towards controlling the bacterial flora in the periodontal pocket.[1] As periodontal disease is associated with bacteria, treatment by antibiotics which are specifically active against gram negative or gram positive or both appears to be appropriate. However, the systemic route of antibiotic administration may not be ideal because of the concern over the development of bacterial resistance that may be induced over long periods of time.[2] Systemic antibiotic therapy over a long period of time also raises the risk of undesirable side effects such as nausea, diarrhoea, fever, abdominal pain and pseudo-membranous colitis. The local delivery of antibiotic therapy to periodontal pockets has the benefit of putting more drugs at the target site while minimizing exposure of the total body to the drug.[2] Local delivery of antibiotics by sustained release delivery systems has been an active area of pharmaceutical development and clinical research since the early pioneering papers of Goodson. Goodson et al. placed tetracycline fibres incorporated with cellulose acetate in to the periodontal pocket results in improvement of clinical signs and number of spirochaetes generated by the fibres. The attractiveness of treating periodontal disease by the sustained release of antibiotics in the periodontal pocket is based on the prospects of maintaining effective high levels of drag in the gingival crevicular fluid (GCF) for a sustained period of time to produce the desirable clinical benefits of attachment level gain, pocket depth reduction and bleeding on probing reduction. Periodontitis has been evaluated locally by chemotherapeutic agents such as minocycline, doxycycline, tetracycline, metronidazole, ornidazole etc. Various formulations of delivery systems are

commercially available in the market such as fibres, films, gels, strips, injectable systems, microparticles which contains different active agents as a major component. Gels are semisolid formulations used in numerous biomedical pharmaceutical applications. They are crosslinked polymer-based systems in which therapeutic agents can be physically or chemically incorporated to provide a sustained-release kinetic. Several hydrogels and oleo gels receive intensive attention for the localized delivery of therapeutics into periodontal pockets since they are easy to prepare and administer and also their bio-adhesive property enhances the retention time in the periodontal pocket.

Metronidazole and other drugs of that genre are bactericidal and exert their action by interfering with bacterial DNA synthesis. They are active against anaerobic bacteria such as P. gingivalis and other G-negative bacteria. However, they seem to have little effect on a major player in periodontal disease; A. actinomycetemcomitans.[3,4] Silver nanoparticles has become an emerging biomaterial with antimicrobial and anti-inflammatory properties.[6] Silver and silver nanoparticles (AgNPs) in the prevention and or reduction of gram-positive and/or gram-negative bacteria have been successfully applied.[7] Silver nanoparticles causes bacterial cell wall damage, interacts with the bacterial cytoplasm, prevents DNA replication, involves in the disruption of bacterial protein, releases free silver ions, and generates reactive oxygen species.[5,8] Furthermore, AgNPs act on a broad range of bacterial tar gets, hence the potential for the development of antimicrobial resistance is quite rare.

Oxygen plays an essential and vital role in cellular metabolism, protein synthesis and tissue repair as a whole. The role of topical oxygen therapy is emerged as an evidence and gain popularity in oral soft tissue and wound healing care. Blue M oral gel contain an active oxygen molecule as main component which offers multiple benefits to enhance collagen synthesis, release of growth factors during the regeneration process, maintain an adequate blood supply during healing tissues.[9] Because of its therapeutic role the gel promises a beneficial effects on oral soft tissues and can be applied as an adjunctive measure during surgical or non-surgical intervention.

Several studies have, over the years, been done on the effect of local drug delivery approach as adjunct to non-surgical periodontal treatment. The results have ranged from showing no or little effect to significant benefit from the local antibiotics. Therefore, the purpose of the study is to evaluate the clinical and microbiological efficacy of subgingival application of ornidazole, metronidazole, silver nano particle gel and blue M gel used as an adjunct to Phase I therapy in the treatment of Stage I Grade A/B periodontitis.

Materials and Methodology

Study Population

The study was a randomized controlled clinical trial. It was conducted in the Department of Periodontics and Oral Implantology and an ethical clearance was obtained from the Institutional Ethical Committee. The protocol was explained to the patients and subjects were requested to sign a consent form. For the present study, 140 Stage I, Grade A/B periodontitis patients were included based on the following inclusion and exclusion criteria:

Inclusion Criteria

- Patient of both genders between age group 20-50 years.
- Patients diagnosed with Stage I Grade A/B periodontitis having minimum of 5 teeth with PPD between 5-6 mm.

- Patient had not experienced any periodontal therapy or any antibiotic therapy from past 6 months.
- Systemically healthy patient without known allergic conditions

Exclusion Criteria

- Patients with known allergy to metronidazole, chlorhexidine, silver nanoparticles or ornidazole
- Patient with systemic disease
- Smoker and Chronic alcoholic patients
- Any tooth with periapical disease
- Teeth with furcation involvement
- Pregnancy, lactation and use of oral contraceptives

Sampling

Patients who satisfied the conditions for selection to enter the trial were assigned randomly into four study groups/sites consisting of 35 participants as follows:

Group 1 / Site 1- treated with Ornidazole (Ornigreat gel™) as an adjunct to SRP.

Group 2 / Site 2 – treated with Metronidazole (Metrohex plus gel™) as an adjunct to SRP.

Group 3 / Site 3- treated with Siver nanoparticle gel (Megaheal gel™) as an adjunct to SRP.

Group 4 / Site 4- treated with oxygen releasing formula (Blue M gel™) as an adjunct to SRP.

Methodology

A thorough scaling and root planing was performed in each group/site along with education and motivation to mechanical plaque control measures.

Group 1 / Site 1- 35 patients treated with subgingival application of Ornidazole (Ornigreat Gel™) in 5-6 mm of periodontal pocket depth. The drug was injected with a disposable syringe by blunting the cannula tip so that to avoid the soft tissue trauma. A periodontal dressing was placed over the treated site.

Group 2 / Site 2 – 35 patients treated with subgingival delivery of Metronidazole (Metrohex Plus Gel™) in 5-6 mm of periodontal pocket depth. The drug was injected with a disposable syringe by blunting the cannula tip so that to avoid the soft tissue trauma. A periodontal dressing was placed over the treated site.

Group 3 / Site 3- 35 patients received subgingival application of silver nanoparticle gel (Megaheal Gel™) in 5-6 mm of periodontal pocket depth. The drug was injected with a disposable syringe by blunting the cannula tip so that to avoid the soft tissue trauma. A periodontal dressing was placed over the treated site.

Group 4 / Site 4- 35 patients received subgingival application of an oxygen-releasing formulation (Blue M Gel™) in 5-6 mm of periodontal pocket depth. The drug was injected with a disposable syringe by blunting the cannula tip so that to avoid the soft tissue trauma. A periodontal dressing was placed over the treated site.

Postoperative instructions included mechanical plaque control measures such a soft bristle tooth brush twice a day. Patient should be instructed to refrain from not using any type of chemical plaque control measures.

Subgingival Plaque Sample Collection

Sub gingival plaque samples were collected at baseline and after 3 months with sterile paper points. The collected sample were directly put into sterile glass vial which was filled with 2.5 ml of thioglycolate medium and carried to the Microbiology Department for anaerobic bacterial quantification. The serial dilution was done with same medium to reach a final dilution factor of 10^2. From each dilution, 0.1 ml was injected on blood agar plate and evenly spread using a sterile glass spreader through spread plate technique. The culture media composed of blood agar enriched with 5–10% fresh sheep or human blood and nutrient agar supplemented with 5–10% defibrinated fresh blood. The injected plate was kept down under anaerobic jar equipped with a GasPak system by maintaining a temperature of 37°C for

48 -72 hours. After incubation, plate was checked for growth of bacteria in the form of colonies. The total colony count on each plate was analysed and bacterial colonies were counted as colony-forming units per millilitre (cfu/ml) using the standard formula:

$$CFU/ml = \frac{\text{Total number of colonies x dilution factor}}{\text{volume of inoculum transferred}}$$

Assessment of Clinical and Microbiological Parameter

Clinical parameters were recorded such as Plaque index, Gingival index, Probing Pocket depth and Clinical attachment level (UNC-15 Probe). The follow up time period of parameters were at baseline, 1 month and 3 months. Colony-forming units were recorded at baseline and after 3 months in all the four groups.

Statistical Analysis

The data were tabulated and analysed through Statistical Package SPSS 23.0 version. The descriptive statistics included mean, standard deviation frequency and percentage were recoded and calculated. Parameters were compared through One-way analysis of variance (ANOVA), Bonferroni post hoc ANOVA and Paired t test for intergroup and intragroup comparison.

Results

Table 1: Intragroup comparison of all clinical parameters between different time interval within the groups

Group/Site	Time Period	Plaque Index (PI)		Gingival Index (GI)		Probing Pocket Depth (PPD)		Clinical Attachment Level (CAL)	
		Mean±SD	p value	Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
Group1/ Site 1	Baseline	1.88±0.31	<0.001*	2.12±0.27	<0.001*	5.55±0.39	<0.001*	7.54±0.39	<0.001*
	1 Month	1.26±0.35		1.62±0.31		4.61±0.53		6.66±0.38	
	3 Months	1.08±0.29		0.81±0.26		3.54±0.56		5.80±0.50	
Group 2/Site 2	Baseline	2.01±0.23	<0.001*	2.33±0.25	<0.001*	5.68±0.31	<0.001*	7.62±0.33	<0.001*
	1 Month	1.44±0.39		1.43±0.36		4.66±0.41		6.58±0.48	
	3 Months	1.13±0.30		0.76±0.35		3.57±0.56		5.60±0.55	
Group 3/Site 3	Baseline	1.83±0.36	<0.001*	2.15±0.39	<0.001*	5.73±0.25	<0.001*	7.47±0.38	<0.001*
	1 Month	1.47±0.38		1.39±0.39		4.82±0.59		6.62±0.53	
	3 Months	1.12±0.30		0.85±0.28		3.71±0.52		5.56±0.46	
Group 4/site 4	Baseline	2.04±0.33	<0.001*	2.25±0.31	<0.001*	5.69±0.28	<0.001*	7.60±0.37	<0.001*
	1 Month	1.29±0.50		1.28±0.40		4.66±0.56		6.62±0.50	
	3 Months	0.96±0.16		0.73±0.27		3.46±0.56		5.53±0.53	

* Statistically significant

Table 1 showed intragroup comparison of all the clinical parameters was compared in group 1, group 2, group 3 and group 4 at baseline, 1 month and after 3 months. The intragroup comparison of plaque index (PI), gingival index (GI), probing pocket depth (PPD) and clinical attachment level (CAL) was at baseline, 1 month and 3 months was found to be statistically significant (<0.001) for all the four groups/sites. There was a significant improvement in all the clinical parameters from baseline to 3 months of time interval.

At baseline, group 1/site 1 plaque index value was 1.88 ± 0.31, after 1 month it was 1.26 ± 0.35 and three months

later, it was 1.08 ± 0.29. Group 2/ site 2 mean score at baseline was 2.01 ± 0.23, after 1 month it was 1.44 ± 0.39 and after three months it was 1.13 ± 0.30. Group 3/ site 3 mean score at baseline was 1.83 ± 0.36, after 1 month it was 1.47± 0.38 and after three months it was 1.12 ± 0.30. Group 4/ site 4 mean score at baseline was 2.04 ± 0.33, after 1 month it was 1.29± 0.50 and after three months it was 0.96 ± 0.16. There was a statistically significant (<0.001) difference in the mean reduction in the plaque index scores within the groups /site when mean scores was compared at baseline, 1 month and after 3 months.

After three months, the gingival index score in group 1/site 1 were 0.81 ± 0.26, compared to 2.12 ± 0.27 at baseline and 1.62 ± 0.31 after 1 month of time interval. The mean score in group 2/site 2 was 2.33 ± 0.25 at baseline, after 1 month it was 1.43 ± 0.36 and 0.76 ± 0.35 after 3 months. Group 3/ site 3 mean score at baseline was 2.15 ± 0.39, after 1 month it was 1.39± 0.39 and after three months it was 0.85 ± 0.28. Group 4/ site 4 mean score at baseline was 2.25 ± 0.31, after 1 month it was 1.28± 0.40 and after three months it was 0.73 ± 0.27. In group 1/ site 1, group 2/ site 2, group 3/ site 3 and group 4/ site 4 the intragroup comparison of the mean reduction in the gingival index scores at baseline, 1 month and 3 months was found to be statistically significant (<0.001).

The PPD at the baseline in group 1/site 1 was 5.55 ± 0.39, after 1 month it was 4.61 ± 0.53 and 3.54 ± 0.56 after 3 months. In group 2/site 2 the mean score was 5.68 ± 0.31 at baseline, 4.66 ± 0.41 and 3.57 ± 0.56 after 3 months. In group 3/site 3 the mean score was 5.73 ± 0.25 at baseline, 4.82 ± 0.59 and 3.71 ± 0.52 after 3 months. In group 4/site 4 the mean score was 5.69 ± 0.28 at baseline, 4.66 ± 0.56 and 3.46 ± 0.56 after 3 months. The intragroup comparison of mean reduction in probing pocket depth from baseline to 1 month and 3 months was found to be statistically significant (<0.001) in all the four groups/sites.

The CAL at the baseline in group 1/site 1 was 7.54 ± 0.39, after 1 month it was 6.66 ± 0.38 and 5.80 ± 0.50 after 3 months. In group 2/site 2 the mean score was 7.62 ± 0.33 at baseline, 6.58 ± 0.48 and 5.60 ± 0.55 after 3 months. In group 3/site 3 the mean score was 7.47 ± 0.38 at baseline, 6.62 ± 0.53 and 5.56 ± 0.46 after 3 months. In group 4/site 4 the mean score was 7.60 ± 0.37 at baseline, 6.62 ± 0.50 and 5.53 ± 0.53 after 3 months. The intragroup comparison of mean gain in clinical attachment level from baseline to 1 month and 3 months was found to be statistically significant (<0.001) in all the four groups/sites.

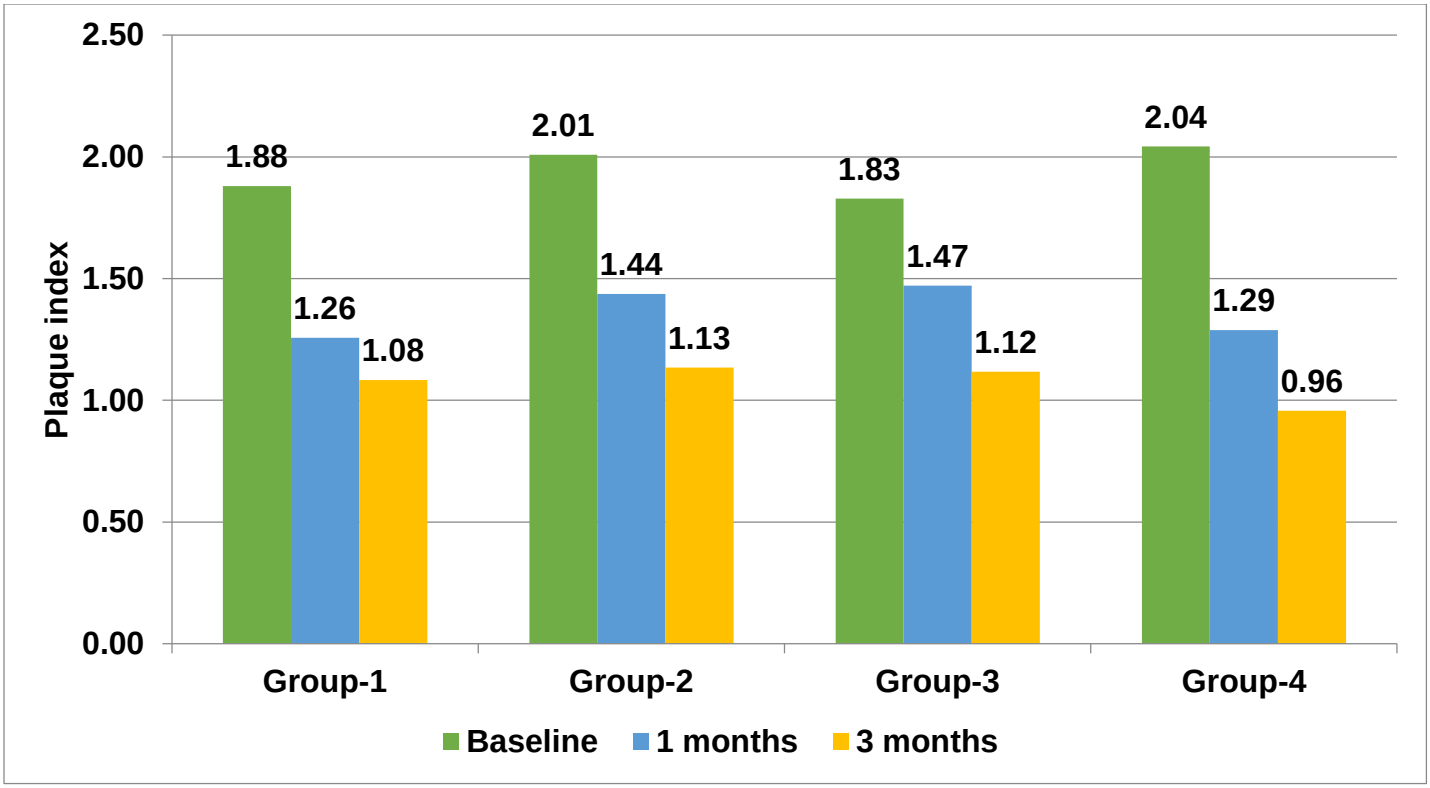
Multiple Group Comparison of Plaque Index score (Table 2; Graph 1):

The multiple group comparison of PI score between the groups with each other at different intervals of time has been accomplished through Bonferroni post hoc ANOVA**.** Multiple comparison of Group 1/site 1 Versus Group 2/site 2, Group 1/site 1 Versus Group 3/site 3, Group 1/site 1 Versus Group 4/site 4, Group 2/site 2 Versus Group 3/site 3 at baseline, 1 month and 3 months yielded statistically non-significant. Group 2/site 2 Versus Group 4/site 4 at baseline and after 1 month yielded statistically non-significant however, at 3 months of time interval it yielded statistically significant. Group 3/site 3 Versus Group 4/site 4 at baseline yielded statistically significant however, it was found be statistically non-significant at 1 month and 3 months of time interval.

Table 2: Multiple comparison of plaque index score between the groups with each other at different time interval (Using Bonferroni post hoc ANOVA)

Groups	Time Interval	Group 1/Site 1	Group 2/ Site 2	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group1/Site 1 Vs Group 2/Site 2	Baseline	1.88±0.31	2.01±0.23	-0.13	0.509**
	1 month	1.26±0.35	1.44±0.39	-0.18	0.404**
	3 months	1.08±0.29	1.13±0.30	-0.05	1.000**
		Group 1/ Site1	Group 3/ Site 3	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 3/ Site 3	Baseline	1.88±0.31	1.83±0.36	0.05	1.000**
	1 month	1.26±0.35	1.47±0.38	-0.21	0.179**
	3 months	1.08±0.29	1.12±0.30	-0.03	1.000**
		Group 1/ Site1	Group 4/ Site 4	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 4/ Site 4	Baseline	1.88±0.31	2.04±0.33	-0.16	0.178**
	1 month	1.26±0.35	1.29±0.50	-0.03	1.000**
	3 months	1.08±0.29	0.96±0.16	0.13	0.319**
		Group 2/ Site 2	Group 3/ Site 3	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 3/ Site 3	Baseline	2.01±0.23	1.83±0.36	0.18	0.098**
	1 month	1.44±0.39	1.47±0.38	-0.03	1.000**
	3 months	1.13±0.30	1.12±0.30	0.02	1.000**
		Group 2/ Site 2	Group 4/ Site 4	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 4/ Site 4	Baseline	2.01±0.23	2.04±0.33	-0.03	1.000**
	1 month	1.44±0.39	1.29±0.50	0.15	0.782**
	3 months	1.13±0.30	0.96±0.16	0.18	0.041*
		Group 3/ Site 3	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 3/ Site 3 Vs Group 4/ Site 4	Baseline	1.83±0.36	2.04±0.33	-0.21	0.027*
	1 month	1.47±0.38	1.29±0.50	0.18	0.329**
	3 months	1.12±0.30	0.96±0.16	0.16	0.086**

* Statistically significant; ** statistically non-significant



Graph 1: Intragroup comparison of plaque index score between different time interval within the groups

Multiple group comparison of GI score (Table 3; Graph 2):

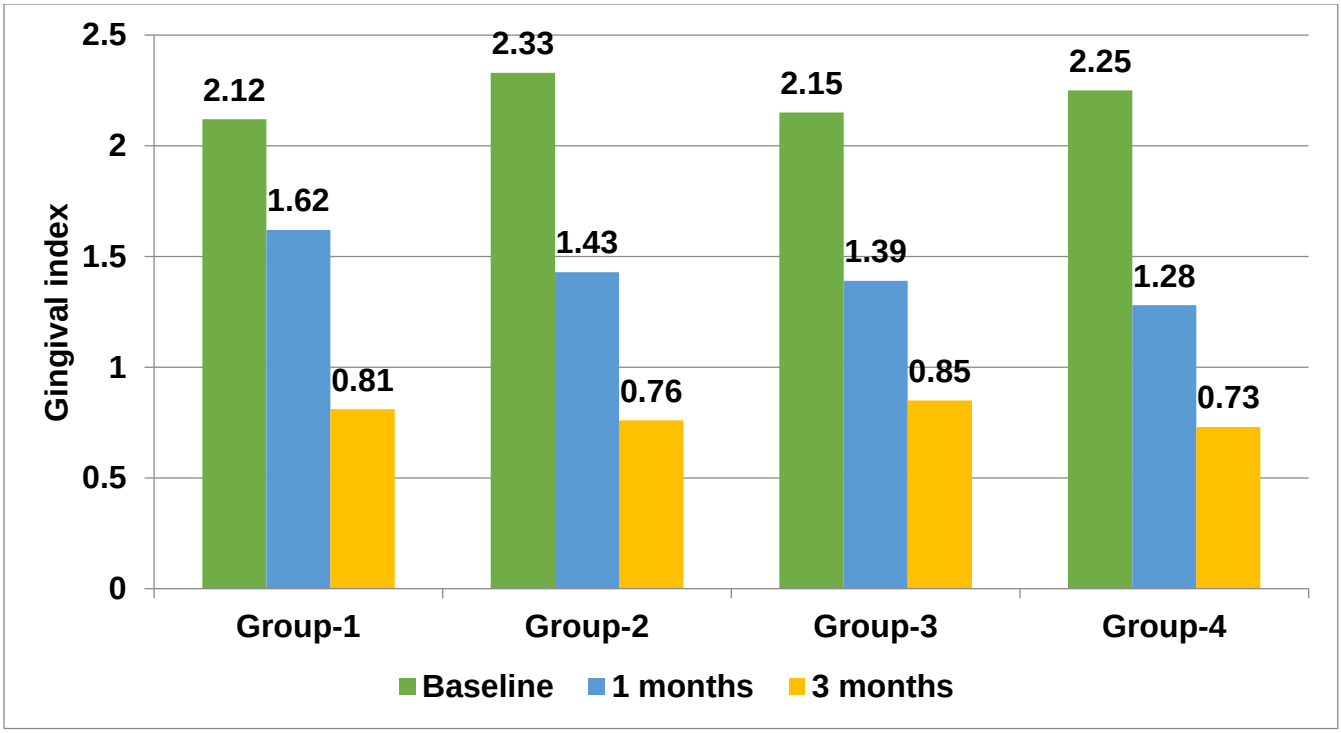
The multiple group comparison for GI score between groups for each other at various intervals of time has been accomplished through Bonferroni post hoc ANOVA. Multiple comparison of Group 1/site 1 Versus Group 2/site 2, Group 2/site 2 Versus Group 3/site 3, Group 2/site 2 Versus Group 4/site 4 and Group 3/site 3 Versus Group 4/site 4 at baseline, 1 month and 3 months yielded statistically non-significant. Group 1/site 1 Versus Group 3/site 3 and Group 1/site 1 Versus Group 4/site 4 at baseline and after 3 months yielded statistically non-significant however, at 1-month time interval it yielded statistically significant.

Table 3: Multiple comparison of gingival index score between the groups with each other at different time interval (Using Bonferroni post hoc ANOVA)

Groups	Time Interval	Group 1/Site 1	Group 2/ Site 2	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group1/Site 1 Vs Group 2/Site 2	Baseline	2.12±0.27	2.33±0.25	-0.21	0.027**
	1 month	1.62±0.31	1.43±0.36	0.19	0.197**
	3 months	0.81±0.26	0.76±0.35	0.05	1.000**
		Group1/ Site1	Group 3/ Site 3	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs	Baseline	2.12±0.27	2.15±0.39	-0.03	1.000**
	1 month	1.62±0.31	1.39±0.39	0.23	0.050*

Group 3/ Site 3	3 months	0.81±0.26	0.85±0.28	-0.04	1.000**
		Group1/ Site1	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1	Baseline	1.88±0.31	2.04±0.33	-0.13	0.178**
Vs	1 month	1.26±0.35	1.29±0.50	0.35	1.000*
Group 4/ Site 4	3 months	1.08±0.29	0.96±0.16	0.08	0.319**
		Group2/ Site 2	Group 3/ Site 3	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2	Baseline	2.33±0.25	2.15±0.39	0.18	0.100**
Vs	1 month	1.43±0.36	1.39±0.39	0.05	1.000**
Group 3/ Site 3	3 months	0.76±0.35	0.85±0.28	-0.09	1.000**
		Group2/ Site 2	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2	Baseline	2.33±0.25	2.25±0.31	0.09	1.000**
Vs	1 month	1.43±0.36	1.28±0.40	0.16	0.448**
Group 4/ Site 4	3 months	0.76±0.35	0.73±0.27	0.03	1.000**
		Group 3/ Site 3	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 3/ Site 3	Baseline	2.15±0.39	2.25±0.31	-0.09	1.000**
Vs	1 month	1.39±0.39	1.28±0.40	0.11	1.000**
Group 4/ Site 4	3 months	0.85±0.28	0.73±0.27	0.12	0.476**

* Statistically significant; ** statistically non-significant



Graph 2: Intragroup comparison of gingival index score between different time interval within the groups

Multiple group comparison of Probing Pocket Depth (Table 4; Graph 3):

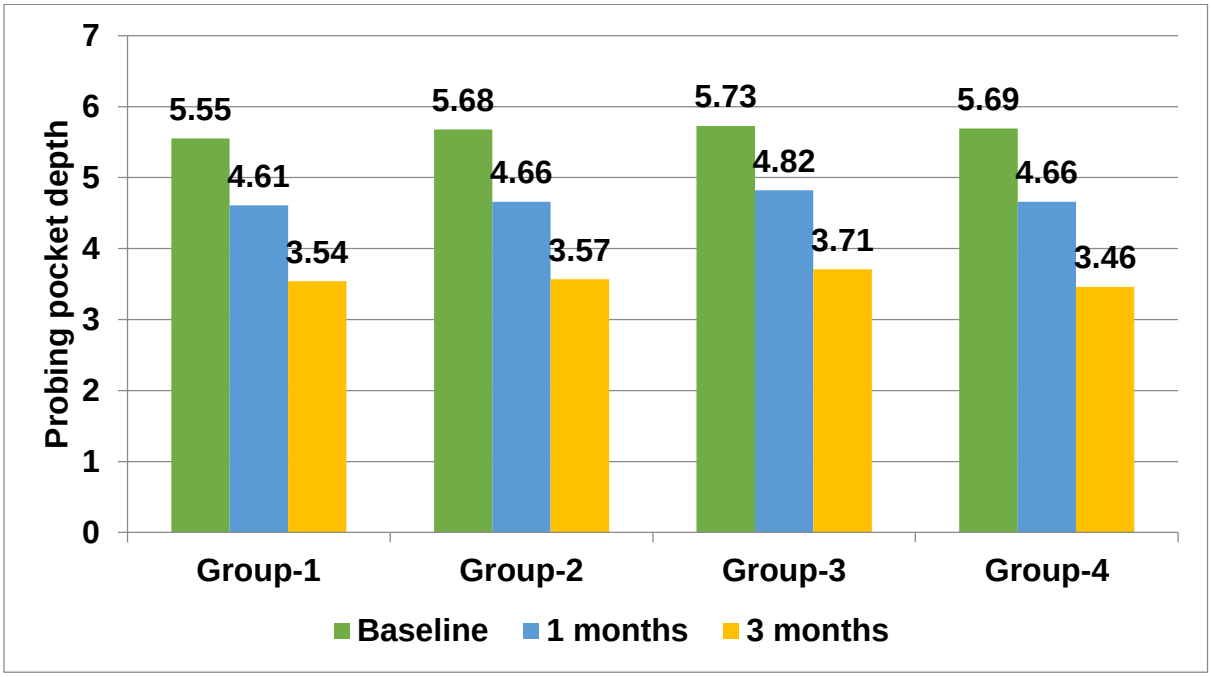
The multiple group comparison for PPD between groups with each other at different time frame has been accomplished through Bonferroni post hoc ANOVA. Multiple comparison of Group 1/site 1 Versus Group 2/site 2, Group 1/site 1 Versus Group 3/site 3, Group 1/site 1 Versus Group 4/site 4, Group 2/site 2 Versus Group 3/site 3, Group 2/site 2 Versus Group 4/site 4 and Group 3/site 3 Versus Group 4/site 4 at baseline, 1 month and 3 months yielded statistically non-significant.

Table 4: Multiple comparison of probing pocket depth between the groups with each other at different time interval (Using Bonferroni post hoc ANOVA)

Groups	Time Interval	Group 1/Site 1	Group 2/ Site 2	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group1/Site 1 Vs Group 2/Site 2	Baseline	5.55±0.39	5.68±0.31	-0.13	0.519**
	1 month	4.61±0.53	4.66±0.41	0.05	1.000**
	3 months	3.54±0.56	3.57±0.56	0.03	1.000**
		Group1/ Site1	Group 3/ Site 3	Mean Difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 3/ Site 3	Baseline	5.55±0.39	5.73±0.25	-0.19	0.083**
	1 month	4.61±0.53	4.82±0.59	-0.22	0.526**
	3 months	3.54±0.56	3.71±0.52	-0.17	1.000**
		Group1/ Site1	Group 4/ Site 4	Mean difference	p-value

		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 4/ Site 4	Baseline	5.55±0.39	5.69±0.28	-0.14	0.343**
	1 month	4.61±0.53	4.66±0.56	-0.05	1.000*
	3 months	3.54±0.56	3.46±0.56	0.09	1.000**
		Group2/ Site 2	Group 3/ Site 3	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 3/ Site 3	Baseline	5.68±0.31	5.73±0.25	-0.06	1.000**
	1 month	4.66±0.41	4.82±0.59	-0.17	1.000**
	3 months	3.57±0.56	3.71±0.52	-0.14	1.000**
		Group2/ Site 2	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 4/ Site 4	Baseline	5.68±0.31	5.69±0.28	-0.01	1.000**
	1 month	4.66±0.41	4.66±0.56	-0.003	1.000**
	3 months	3.57±0.56	3.46±0.56	0.11	1.000**
		Group 3/ Site 3	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 3/ Site 3 Vs Group 4/ Site 4	Baseline	5.73±0.25	5.69±0.28	0.04	1.000**
	1 month	4.82±0.59	4.66±0.56	0.16	1.000**
	3 months	3.71±0.52	3.46±0.56	0.26	0.304**

** statistically non-significant



Graph 3: Intragroup comparison of probing pocket depth between different time interval within the groups

Multiple Group Comparison of CAL (Table 5; Graph 4):

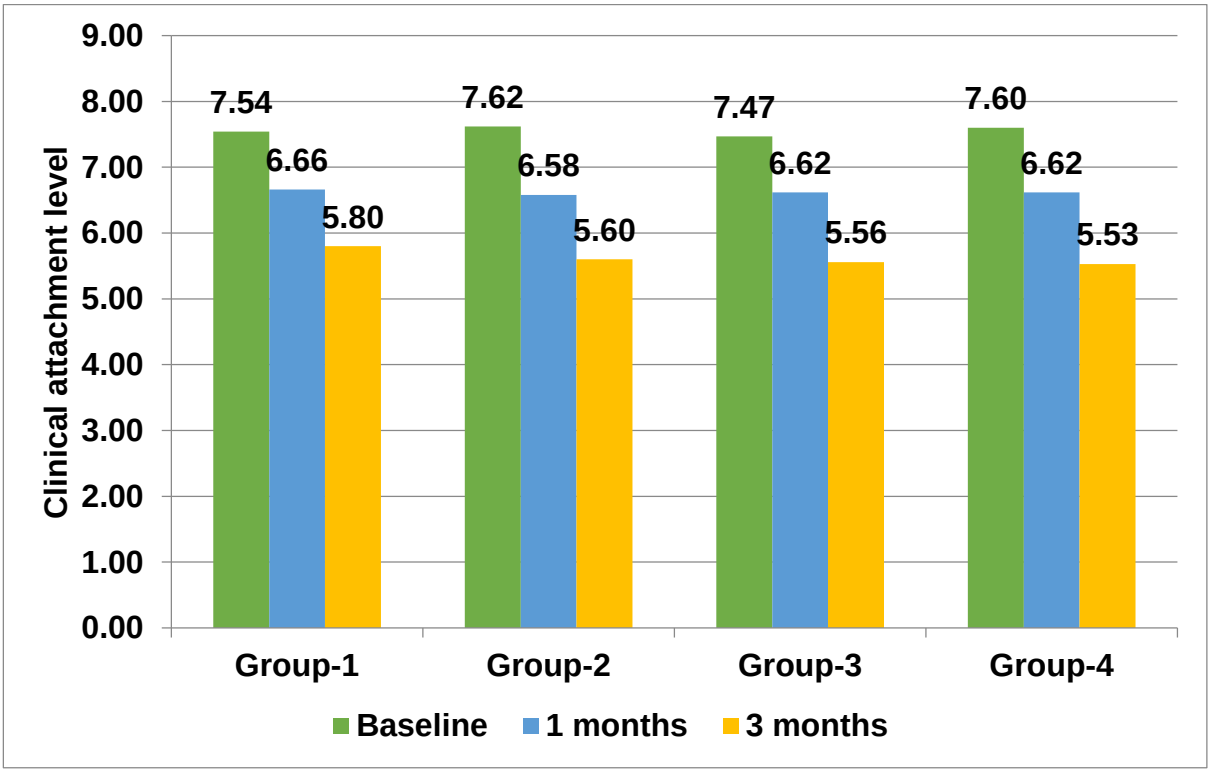
The multiple group comparison of CAL between group with each other at different intervals of time has been accomplished through Bonferroni post hoc ANOVA. Multiple comparison of Group 1/site 1 Versus Group 2/site 2, Group 1/site 1 Versus Group 3/site 3, Group 1/site 1 Versus Group 4/site 4, Group 2/site 2 Versus Group 3/site 3, Group 2/site 2 Versus Group 4/site 4 and Group 3/site 3 Versus Group 4/site 4 at baseline, 1 month and 3 months yielded statistically non-significant.

Table 5: Multiple comparison of clinical attachment level between the groups with each other at different time interval (Using Bonferroni post hoc ANOVA)

Groups	Time Interval	Group 1/Site 1	Group 2/ Site 2	Mean difference	p-value
		Mean±SD	Mean±SD		
Group1/Site 1 Vs Group 2/Site 2	Baseline	7.54±0.39	7.62±0.33	-0.08	1.000**
	1 month	6.66±0.53	6.58±0.48	0.09	1.000**
	3 months	5.80±0.56	5.60±0.55	0.20	0.623**
		Group1/ Site1	Group 3/ Site 3	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 3/ Site 3	Baseline	7.54±0.39	7.47±0.38	0.07	1.000**
	1 month	6.66±0.53	6.62±0.53	0.04	1.000**
	3 months	5.80±0.56	5.56±0.46	0.24	0.308**
		Group1/ Site1	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 1/ Site 1 Vs Group 4/ Site 4	Baseline	7.54±0.39	7.60±0.37	-0.06	1.000**
	1 month	6.66±0.53	6.62±0.50	-0.04	1.000*
	3 months	5.80±0.56	5.53±0.53	0.27	0.167**
		Group2/ Site 2	Group 3/ Site 3	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 3/ Site 3	Baseline	7.62±0.33	7.47±0.38	0.15	0.527**
	1 month	6.58±0.48	6.62±0.53	-0.05	1.000**
	3 months	5.60±0.55	5.56±0.46	0.04	1.000**
		Group2/ Site 2	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		
Group 2/ Site 2 Vs Group 4/ Site 4	Baseline	7.62±0.33	7.60±0.37	0.02	1.000**
	1 month	6.58±0.48	6.62±0.50	-0.05	1.000**
	3 months	5.60±0.55	5.53±0.53	0.07	1.000**
		Group 3/ Site 3	Group 4/ Site 4	Mean difference	p-value
		Mean±SD	Mean±SD		

Group 3/ Site 3 Vs Group 4/ Site 4	Baseline	7.47±0.38	7.60±0.37	-0.13	0.827**
	1 month	6.62±0.53	6.62±0.50	0.00	1.000**
	3 months	5.56±0.46	5.53±0.53	0.03	1.000**

** statistically non-significant



Graph 4: Intragroup comparison of clinical attachment level between different time interval within the groups

Table 6: Intragroup comparison of colony forming unit between different time interval within the groups

Group/Site	Time Interval	Mean±SD	Mean Difference	p value
Group 1/site 1	Baseline	$24.11\times10^2\pm20.83$	16.02	<0.001*
	3 Months	$8.09\times10^2\pm10.92$		
Group 2/site 2	Baseline	$30.67\times10^2\pm25.49$	24.34	<0.001*
	3 Months	$6.33\times10^2\pm6.00$		
Group 3/site 3	Baseline	$21.72\times10^2\pm18.13$	18.05	<0.001*
	3 Months	$3.67\times10^2\pm4.72$		
Group 4/site 4	Baseline	$20.09\times10^2\pm14.75$	15.79	<0.001*
	3 Months	$4.30\times10^2\pm6.11$		

* Statistically significant

Mean ±SD CFU recorded in group 1/site 1 at baseline was $24.11\times10^2\pm20.83$ and at 3 months was $8.09\times10^2\pm10.92$. The intra group comparison of Colony Forming Unit in group 1/site 1 differs significantly between different interval i.e., baseline and 3 months ($p<0.001$). There was significantly less concentration of anaerobic microflora in comparison with aerobic

microflora in group 1/site 1 when compared from baseline to 3 months' time interval.

Mean ±SD CFU recorded in group 2/site 2 at baseline was $30.67\times10^2\pm25.49$ and at 3 months was $6.33\times10^2\pm6.00$. The intra group comparison of Colony Forming Unit in group 2/site 2 differs significantly between different interval i.e., baseline and 3 months ($p<0.001$). There was significantly less concentration of anaerobic microflora in comparison with aerobic microflora in group 2/site 2 when compared from baseline to 3 months' time interval.

Mean ±SD CFU recorded in group 3/site 3 at baseline was $21.72\times10^2\pm18.13$ and at 3 months was $3.67\times10^2\pm4.72$. The intra group comparison of Colony Forming Unit in group 3/site 3 differs significantly between different interval i.e., baseline and 3 months ($p<0.001$). There was significantly less concentration of anaerobic microflora in comparison with aerobic microflora in group 3/site 3 when compared from baseline to 3 months' time interval.

Mean ±SD CFU recorded in group 4/site 4 at baseline was $20.09\times10^2\pm14.75$ and at 3 months was $4.30\times10^2\pm6.11$. The intra group comparison of Colony Forming Unit in group 4/site 4 differs significantly between different interval i.e., baseline and 3 months ($p<0.001$). There was a significantly less concentration of anaerobic microflora in comparison with aerobic microflora in group 4/site 4 when compared from baseline to 3 months' time interval.

Multiple Group Comparison of CFU (Table 7; Graph 5):

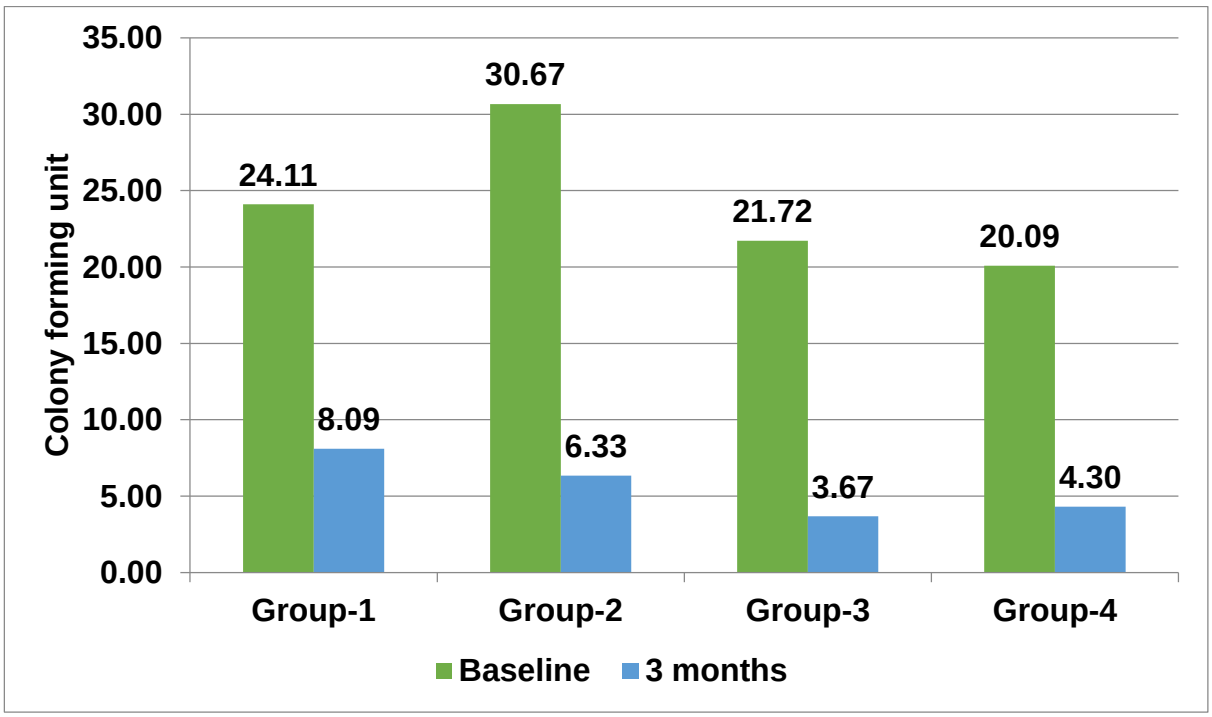
The multiple group comparison of CFU between group with each other at different intervals of time has been accomplished through Bonferroni post hoc ANOVA. Multiple comparison of Group 1/site 1 Versus Group 2/site 2, Group 1/site 1 Versus Group 3/site 3, Group 1/site 1 Versus Group 4/site 4, Group 2/site 2 Versus Group 3/site 3, Group 2/site 2 Versus Group 4/site 4 and Group 3/site 3 Versus Group 4/site 4 at baseline and 3 months yielded statistically non-significant.

Table 7: Multiple comparison of colony forming unit between the groups with each other at different time interval (Using Bonferroni post hoc ANOVA)

Groups	Time Interval	Group 1/Site 1 Mean±SD	Group 2/ Site 2 Mean±SD	Mean difference	p-value
Group1/Site 1 Vs Group 2/Site 2	Baseline	$24.11\times10^2\pm20.83$	$30.67\times10^2\pm25.49$	-6.56	1.000**
	3 months	$8.09\times10^2\pm10.92$	$6.33\times10^2\pm6.00$	1.77	1.000**
		Group1/ Site1 Mean±SD	Group 3/ Site 3 Mean±SD	Mean difference	p-value
Group 1/ Site 1 Vs Group 3/ Site 3	Baseline	$24.11\times10^2\pm20.83$	$21.72\times10^2\pm18.13$	2.39	1.000**
	3 months	$8.09\times10^2\pm10.92$	$3.67\times10^2\pm4.72$	4.42	0.077**
		Group1/ Site 1 Mean±SD	Group 4/ Site 4 Mean±SD	Mean difference	p-value
Group 1/ Site 1	Baseline	$24.11\times10^2\pm20.83$	$20.09\times10^2\pm14.75$	4.02	1.000**

Vs Group 4/ Site 4	3 months	$8.09\times10^2\pm10.92$	$4.30\times10^2\pm6.11$	3.79	0.193**
		Group2/ Site 2 Mean±SD	Group 3/ Site 3 Mean±SD	Mean difference	p-value
Group 2/ Site 2 Vs Group 3/ Site 3	Baseline	$30.67\times10^2\pm25.49$	$21.72\times10^2\pm18.13$	8.95	0.395**
	3 months	$6.33\times10^2\pm6.00$	$3.67\times10^2\pm4.72$	2.65	0.792**
		Group2/ Site 2 Mean±SD	Group 4/ Site 4 Mean±SD	Mean difference	p-value
Group 2/ Site 2 Vs Group 4/ Site 4	Baseline	$30.67\times10^2\pm25.49$	$20.09\times10^2\pm14.75$	10.58	0.181**
	3 months	$6.33\times10^2\pm6.00$	$4.30\times10^2\pm6.11$	2.03	1.000**
		Group 3/ Site 3 Mean±SD	Group 4/ Site 4 Mean±SD	Mean difference	p-value
Group 3/ Site 3 Vs Group 4/ Site 4	Baseline	$21.72\times10^2\pm18.13$	$20.09\times10^2\pm14.75$	1.63	1.000**
	3 months	$3.67\times10^2\pm4.72$	$4.30\times10^2\pm6.11$	-0.63	1.000**

** statistically non-significant



Graph 5: Intragroup comparison of Colony Forming Unit ($\times 10^2$) between different time interval within the groups

Discussion

Periodontal disease is now considered to be a group of diseases or infections. Each disease is associated with a different group of microorganisms. The resulting clinical signs and symptoms can be similar or unique. The mechanisms by which sub-gingival bacteria may contribute to the pathogenesis of periodontal disease are varied. The periodontal pathogens possess numerous factors that permit them to directly damage the periodontium or to indirectly trigger a pathologic host response. Recently widespread interest has been generated among researchers in use of local controlled drug delivery system to release the drug directly into the periodontal cavity as an alternative method for drug delivery to reduce the drug toxicity and drug resistivity.

Recent development of a new approach using local, site-specific controlled delivery systems containing antibiotics into the periodontal cavity has been introduced, which produces more constant and prolonged concentration profiles at the targeted site. Local delivery devices are the systems designed to deliver agents locally into the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time, hence the approach claims to be of several folds. The periodic use of local delivery systems in reducing probing depths, stabilizing attachment levels and minimizing bleeding would allow better control of the disease. The effectiveness of this form of therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the prolonged and controlled effect to occur. However, periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a periodontal drug delivery device. Controlled release delivery of antibiotics directly into the periodontal pocket has received greatest interest and appears to hold some promise in periodontal therapy.

Therefore, the purpose of the present study compared four treatment modalities of periodontal therapy evaluating the clinical and microbial changes that occurred after an initial therapy that consisted of SRP with subgingival application of ornidazole, metronidazole, silver nano particle gel and blue M gel used as an adjunct in the treatment of Stage I Grade A/B periodontitis. clinical measurement was made at baseline, 1 month and after 3 months of time interval. In the present study, there was a significant difference in the baseline plaque scores among four groups/sites ($p=0.012$). Group 4/Site 4 (2.04±0.33) was found to be with highest value followed by Group 2/Site 2 (2.01±0.23), Group 1/Site 1 (1.88±0.31) and the lowest in Group 3/Site 3 (1.83±0.36). After 3 months, the plaque score value was found to be statistically significant. Group 2/Site 2 (1.13±0.30) was found to be with highest value followed by Group 3/Site 3 (1.12±0.30) and Group 1/Site 1 (1.08±0.29) and the lowest in Group 4/Site 4 (0.96±0.16). The significant reduction in plaque index score could be due to periodic re-evaluation and reinforcement of oral hygiene instructions. On intragroup comparison the mean plaque index score was found with significant difference (<0.001) at baseline, 1 month and after 3 months of time interval in all the four groups/sites. Multiple comparison of mean plaque index score was done based on different time interval, the mean plaque score was found to be statistically significant from baseline to 1 month, baseline to 3 months and from 1 month to 3 months of time interval. Among the four groups Siver nanoparticle gel (Megaheal gel™) and oxygen releasing formula (Blue M gel™) showed superior results in terms of reduction in mean plaque index score. The results are in line with the studies which

supported the present study results by Kadam P et al 2020; Nedumaran et al 2024 and Agarwal S et al 2024.[10,11,12] Silver ions reduces the plaque associated biofilm by preventing the bacterial adhesion factor around the hard tissue structures in the oral cavity. Blue-m gel has the property of improving the wound healing status and prevents formation of dental plaque associated biofilm. Anisha Koul et al 2019 conducted the efficacy of Chlorhexidine gel and Blue-m gel as an adjunct to SRP and prove their efficacy with superiority in terms of anti-bacterial properties.[13]

On the other hand, the maximum change in mean gingival index score from baseline to 1 month was observed and non-significant change was observed after 3 months of time interval. Group 1/Site 1 and Group 4/Site 4 was found to be superior as compared to Group 2/Site 2 and Group 3/Site 3. The significant change was might be because of efforts put on by the patients to stick with oral hygiene measures and performances as maintenance therapy. On intragroup comparison the mean gingival index score was found with significant difference (<0.001) at baseline, 1 month and after 3 months of time interval in all the four groups/sites. Multiple comparison of mean gingival index score was done based on different time interval, the mean gingival index score was found to be was found to be statistically significant from baseline to 1 month, baseline to 3 months and from 1 month to 3 months of time interval. Among the four groups Ornidazole (Ornigreat gel^{TM}) and oxygen releasing formula (Blue M gel^{TM}) showed superior results in terms of reduction in mean gingival index score. These results are in accordance with other studies that have proved the efficacy of ornidazole gel successfully used as an adjunct to SRP conducted by Bhavin Patel et al 2014; Mishra et al. 2015 and Nagasree M et al 2016.[14,15,16] In the literature studies Ornidazole had shown better potency for all clinical parameters and microbial analysis in comparison with SRP alone. Blue-m gel has been well established with the property of anti-inflammatory which reduces the inflammation cascade and further improved the gingival status. Singh A et al 2024 highlighted adjunctive therapy of oxygen-releasing gel have shown more superior effects for the treatment of periodontitis cases resulting in improvement of clinical parameters.[17]

The obtained results demonstrated that therapeutic modalities applied in the form of local drug delivery agents could result in statistically significant improvement in periodontal parameters (PPD and CAL) after the intervention. The positive clinical outcomes of group1/site 1 and Group 4/Site 4 after three months of intervention was highly appreciable as compared to group 3/site3 and group 2/site2. Ornidazole (Ornigreat gel^{TM}) and blue M gel as additional therapy with SRP showed a meaningful reduction in PPD as compared to the other groups/sites. The positive outcome of the study corresponds with the previous findings concerning clinical efficacy of local drug delivery agent as an adjunct in treatment of periodontitis cases. Bashir B et al 2019; Penmetsa GS et al 2020; Upendra Prasad et al 2021 supported the results of present study.[18,19,20] Reduction in PPD and gain in CAL may be due to short-term gingival inflammation, and sustained reduction of periodontal pathogenic bacteria. Sharmishtha Vijay et al 2023; Nedumaran et al 2024 pointed out a significant periodontal parameter in favor of reduction in PPD score after the intervention.[21,11] At baseline Group 3/Site 3 and after 3 months of Group 4/Site 4 is more appreciable for gain in CAL as compared to other groups/sites. Silver nano particle gel and blue M gel contributed a beneficial and sustained release of LDD agent into periodontal pocket resulting in gaining CAL. Silver nano particle gel

attributed the top-tier characteristics of anti-inflammatory, antimicrobial and bactericidal property against the microflora. Nymphea et al 2013 evaluate efficiency for metronidazole gel and minocycline microsphere as LDD agent with key findings for both gels improve PPD and CAL for periodontitis patients in comparison with SRP alone.[22]

Present study reports that all the four groups/sites showed a significant reduction in CFU count on intragroup comparison. However, the change was found to statistically non-significant after 3 months of intervention. At baseline the mean CFU was highest in Group 2/Site 2 ($30.67\times10^2\pm25.49$), followed by Group 1/Site (1 $24.11\times10^2\pm20.83$), Group 3/Site 3 ($21.72\times10^2\pm18.13$) and the lowest in Group 4/Site 4 ($20.09\times10^2\pm14.75$). After 3 months the mean of CFU was highest in Group 1/Site 1 ($8.09\times10^2\pm0.50$), followed by Group 2/Site 2 ($6.33\times10^2\pm6.00$) and Group 4/Site 4 ($4.30\times10^2\pm6.11$) and the lowest in Group 3/Site 3 ($3.67\times10^2\pm4.72$). Shao J et al 2017 hypothesized an antibacterial quality of silver nanoparticles in chitosan-based membranes against P. gingivalis and F. nucleatum.[23] This reduction in CFU is at the point for delivery of silver ions into periodontal pocket which is biologically showed activity in case of plaque biofilm. In contrast to the results of the present study, Daneshmand et al 2002 and Medaiah et al 2014 suggested that trial group failed to capitulate substantial outcome from baseline to follow up.[24,25]

The literature studies compared and evaluate numerous local drug delivery agents as an adjunct to scaling and root planing emphasized promising outcome along with statistically improvement in both clinical and microbiological parameter. In the present study no adverse effects was observed with the application of Ornidazole/ Metronidazole / Siver nanoparticle gel/ Blue M gel. Since the present study is only limited to smaller sample size, there is a need to elucidate by comparing with larger and greater cross section of people to evaluate the greater benefits of this local administration of antimicrobial therapy in periodontitis.

Conclusion

The adjunctive use of local drug delivery agents reduces or eliminate the growth of pathogenic bacteria by inhibiting the plaque microflora, decreased probing pocket depth, decreased bleeding results in arresting of disease. Therefore, LDD system can be used alone or as an adjunct to scaling and root planing. It is the safe treatment option and beneficial in terms of managing the cases of Stage I Grade A/B Periodontitis.

Within the limitation of present study, it can be concluded that adjunctive use of oxygen releasing formula (Blue M gel™) and Siver nanoparticle gel (Megaheal gel™) followed by Ornidazole (Ornigreat gel™) and Metronidazole (Metrohex plus gel™) showed a significant improvement in clinical and microbiological parameters. The overall results showed an improvement in the management of periodontitis. The subgingival delivery of local drug delivery agents into the pocket depth disrupts the plaque biofilm and improved the clinical status of the oral cavity. However, further studies are required on large sample size with long term investigations with evaluation of biochemical parameter by collecting the gingival crevicular fluid to assess the biomarkers with use of local drug delivery agent in Stage I Grade A/B periodontitis.

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