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RESEARCH ARTICLE

A COMPARATIVE STUDY OF THE EFFECT OF MINOCYCLINE MICROSPHERES AS AN ADJUNCT TO SCALING AND ROOT PLANING VERSUS SCALING AND ROOT PLANING ALONE IN THE TREATMENT OF CHRONIC PERIODONTITIS

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ABSTRACT

Background: Periodontal diseases are localized to the immediate environment of pocket making the pocket a natural site for treatment with local sustained delivery systems. Adjunctive therapy with locally delivered antimicrobials has resulted in improved clinical outcomes.

Aim and objectives: The aim of the present study was to evaluate the efficacy of the adjunctive use of minocycline plus scaling / root planing as compared with scaling / root planing alone in the treatment of the chronic periodontitis and to compare the effects of local drug delivery of minocycline microspheres as an adjunct to scaling and root planing with scaling and root planing alone.

Materials and Methods: A total number of 72 sites from 18 patients were selected for the study who had periodontal pockets measuring ≥5 mm and had been diagnosed with chronic periodontitis, were selected for the study. The selected groups were randomly assigned to either the control group (group I) or the treatment/test group (group II). Only scaling and root planing were done at the base line visit for the control sites and for test sites scaling and root planing were done at the base line visit followed by local application of Arestin™ (1 mg) and reapplication of Arestin™ (1 mg) was done on 30th day. Clinical parameters such as plaque index, gingival index, and gingival bleeding index were recorded at baseline, day 30, day 90, and day 180 in the selected sites of both the groups. Probing pocket depth and Clinical attachment level also was recorded at baseline, day 90, and day 180 for both the groups.

Results: A statistically significant reduction was observed in both groups. Group II showed statistically significant reduction in all the clinical parameters than Group I ($p<0.001$).

Conclusion: The results of this study confirm that Arestin (1mg Minocycline microspheres) delivered in biodegradable system, are a safe and efficient adjunct to scaling and root planing, and can produce significant clinical benefits when compared to scaling and root planing alone.

INTRODUCTION

Periodontitis is an inflammatory disease of the supporting tissues of the teeth caused by the presence of subgingival gram negative bacteria, including porphyromonas gingivalis, bacteroides forsythia, and Treponema denticola. This pathogenesis coexists with hundreds of other species in a highly organized plaque biofilms. The pathogenesis attributed to these bacteria may involve ; 1) direct release of proteolytic enzymes; 2) production of toxins such as lipopolysaccharide that trigger the expression of degradable enzymes; and 3)stimulation of an immune response resulting in the release of cytokines from lymphocytes and macrophages that activate degradative pathways.[1]

Antimicrobial treatments in periodontics range from mechanical debridement of tooth surfaces and home plaque removal to local and systemic delivery of chemical antimicrobial agents.[2] Periodontitis is usually treated with scaling and root planing (SRP), which removes subgingival plaque mechanically. This procedure, even when meticulously performed, improves periodontal status, but is ineffective in the complete removal of plaque or periodontal pathogens.[1] Systemic administration has been useful in treating periodontal pockets, but repeated, long-term use of systemic antibiotics is fraught with potential danger including resistant strains and superimposed infections. Inability to achieve and maintain therapeutic concentrations of the drug in the periodontal pocket, risk of adverse drug reactions and dependence of patient compliance are some of the disadvantages, making local drug delivery a viable option.[2]

Antibiotic therapy is administered systemically or locally, either as a single therapy or in combination with non-surgical

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periodontal treatment. Local antibiotic therapy involves the direct placement of an antimicrobial agent into subgingival sites, minimizing the impact of the agent on non oral body sites. Periodontal diseases are localized to the immediate environment of pocket making the pocket a natural site for treatment with local sustained delivery systems. The various local delivery antimicrobials available are Tetracycline – non resorbable fibre, Metronidazole gel, Minocycline ointment, Chlorhexidine chips, Doxycycline hyclate in a resorbable polymer, Resorbable tetracycline in fibrillar collagen, Azithromycin gel and Minocycline microspheres.

Minocycline is an antimicrobial tetracycline derivative which is active against a broad spectrum of Gram negative and Gram-positive anaerobes including pathogens associated with adult periodontitis (Drisko 1996). Arestin™ is made up of minocycline, a semi-derivative of tetracycline, and a very potent broad-spectrum antibiotic. Minocycline has a wide range of anticollagenase effect. Minocycline works by interfering with protein synthesis in the bacterial cell wall.[4] Delivery of Arestin (21-day, controlled, non-systemic release, bioresorbable polymer formulation of microspheres containing minocycline HCl), subgingivally administered, provides bactericidal action against anaerobes and facultative anaerobes residing in the periodontal pocket.[3]

Arestin™ delivers minocycline in a powdered microsphere delivery system. The microspheres have diameters ranging from 20 to 60 µ. The active ingredient is minocycline hydrochloride which exists as particles distributed throughout the interior of the microspheres. When Arestin™ is administered, it immediately adheres to the periodontal pocket.[4] Gingival crevicular fluid hydrolyzes the polymer, causing water-filled channels to form inside the microspheres. These holes provide escape routes for the encapsulated minocycline for sustained release. The active drug dissolves and diffuses out of the microspheres through the channels into the surrounding tissues. After ten days, the microspheres are fragmented and continue to release minocycline for 14 days or longer; eventually, these microspheres completely bioresorb.[4] These concentrations exceed the minimum inhibitory concentrations (MICs) for periodontal pathogens.

The aim of the present study was to compare the clinical effects of minocycline microspheres as an adjunct to scaling and root planing versus scaling and root planing alone in the treatment of chronic periodontitis. Objective is to assess the efficacy of local drug delivery of minocycline microspheres in combination with scaling & root planing on subjects with chronic periodontitis, to compare the effects of local drug delivery of minocycline microspheres as an adjunct to scaling and root planing with scaling and root planing alone.

MATERIALS AND METHODS

Study Design: A randomized split mouth and single blinded study was undertaken to evaluate the effect of minocycline microspheres as an adjunct to SRP versus SRP alone in the treatment of chronic periodontitis. Approval of the study was obtained from the ethical committee of Mamata Educational Society and an informed consent was taken from all participants before commencing the study.

Study Population: The study population included subjects who reported to the Department of Periodontics, Mamata Dental College, Khammam between June 2011 to June 2012 and were subsequently diagnosed as Chronic Periodontitis patients.

Inclusion Criteria

- Subjects in the age group > 30years with good general health who have test teeth with both mesial and distal neighbouring teeth.
- Patient diagnosed as suffering from chronic periodontitis having a probing periodontal pocket depth of > 5 mm as well as radiographic evidence of bone loss.
- Patients willing to take part in the study and maintain appointments regularly.
- Patient with > 16 natural teeth.

Exclusion criteria

- Patients having systemic diseases like diabetes mellitus, hypertension, bleeding disorders, hyperparathyroidism and compromised medical conditions.
- Pregnant women and lactating mothers.
- Patients allergic to tetracyclines/ minocyclines.
- Patients who have had periodontal treatment in last six months.
- Antibiotic therapy within 2 weeks prior to treatment.
- Patients who underwent periodontal surgery, restorative procedures and tooth extraction adjacent to either of test area in the previous 3 months.
- Long-term therapy within a month prior to enrollment with medications that could affect periodontal status or healing.
- Patients with medical or dental therapy scheduled or expected to occur during the course of this study that could have an impact on the subjects ability to complete the study.

Study Procedure

A total number of 72 sites from 18 patients were selected for the study. The duration of the study was for six months. On Screening day (day 0), For all patients, general, oral and full mouth periodontal examination was carried out and informed consent was obtained from the patients and was followed by impressions for the fabrication of acrylic stents required for the measurement of pocket depths in the control and test sites during the study period. Four sites were identified for the study in each patient: Two sites served as control sites (Group I) and two sites on the contra lateral side served as test sites (Group II). Variables associated were recorded on baseline day (day 0) before treatment to provide baseline data. The following parameters were recorded:

1. Plaque index (Silness and Loe, 1964).

2. Gingival bleeding index (Papillary Bleeding Index - Muhlemann H.R 1977)
3. Gingival index (Loe and Silness, 1963)
4. Probing depth.
5. Clinical attachment level.

Probing Depth

Probing depth was measured from the free gingival margin to the base of the periodontal pocket with a slight manual force (of 0.25 N) using a UNC #15 periodontal probe calibrated in 1-mm intervals. Measurements were taken at six sites per tooth at the baseline appointment, and at 90th, and 180th day.

Clinical Attachment Level

Clinical attachment level was measured from a fixed reference such as crown margin to the base of the periodontal pocket. Six sites per tooth were measured for all selected teeth of both groups. Measurements were taken at six sites per tooth at the baseline appointment, and at 90th, and 180th day.

Occlusal stent

The stent is made up of 1mm polyvinyl silicone sheet (3A MEDES Inc.KOREA) in a Biostar unit (Jaypee Instruments Corp.Kerala).

The control and test sites were grouped and treated as follows: **Group I (control)** - Comprised of 36 sites; only scaling and root planing was done at the baseline visit. **Fig 1-4 Group II (test)** - Comprised of 36 sites; scaling and root planing was followed by local application of Arestin™ (1mg) at the baseline visit. For test group, Arestin 1 mg were dispensed subgingivally to base of pocket by means of a disposable plastic cartridge affixed to stainless steel handle. **Fig 5-10.**

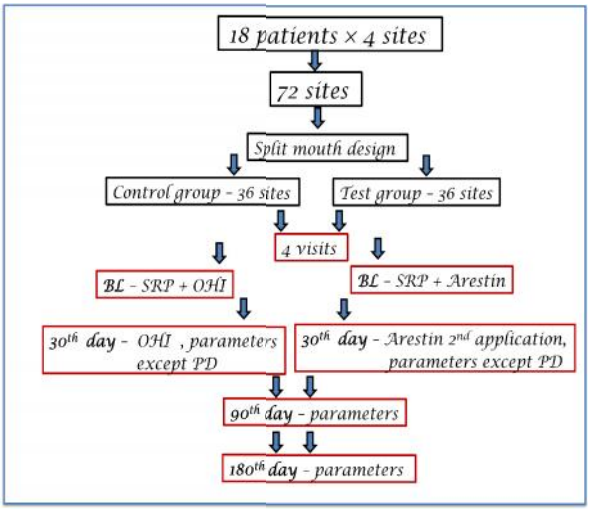
Both the control and test sites were again examined on the 30 th day. During this visit, all clinical parameters, except probing depth, were measured. An additional application of Arestin™ (1mg) was given in the test sites, the control and test sites were also examined on the 90 th and 180 th days, and all clinical parameters including probing pocket depth were recorded.

Application of minocycline microspheres

Arestin 1 mg were dispensed subgingivally to base of pocket by means of a disposable plastic cartridge affixed to stainless steel handle. Subgingival administration is accomplished by inserting the unit dose cartridge to the base of the periodontal pocket and then pressing the thumb ring in the handle mechanism to expel the powder while gradually with drawing the tip from base of the pocket. The handle mechanism should be sterilized between patients. Arestin does not have to be removed, as it is bioresorbable, nor is an adhesive or dressing required.

Instruction for Patients

After treatment, patients were asked to avoid chewing hard, crunchy, or sticky foods (i.e., carrots, taffy, and gum) with the treated teeth for 1 week, as well as avoid touching treated areas. Patients were asked also to postpone the use of interproximal cleaning devices around the treated sites for 10 days after administration of Arestin®. Patients were advised that although some mild to moderate sensitivity is expected during the first week after SRP and administration of Arestin®, they were asked to notify the dentist promptly if pain, swelling, or other problems occur. Patients were asked to inform the dentist if itching, swelling, rash, papules, reddening, difficulty breathing or other signs and symptoms of possible hypersensitivity occur.



RESULTS

The present study was conducted in the Department Of Periodontics, Mamata Dental College, Khammam from June 2011 to June 2012. The study population included 18 patients of age greater than 30 years with chronic periodontitis, having probing depths of greater than or equal to 5mm. A split mouth study was designed in which a total of 72 sites were treated for 180 days. On Screening day (day 0), For all patients, general, oral and full mouth periodontal examination was carried out and informed consent was obtained from the patients and was followed by impressions for the fabrication of acrylic stents required for the measurement of pocket depths in the control and test sites during the study period. Four sites were identified for the study in each patient: Two sites served as control sites (Group I) and two sites on the contra lateral side served as test sites (Group II).

Group I (control) - Comprised of 36 sites; only scaling and root planing was done at the baseline visit. Group II (test) - Comprised of 36 sites; scaling and root planing was followed by local application of Arestin™ (1mg) at the baseline and 30th day. For test group, Arestin 1 mg were dispensed subgingivally to base of pocket by means of a disposable plastic cartridge affixed to stainless steel handle.

The participants were asked to make 4 visits for both control and test sites in the following order:

Baseline, 30th, 90th .180th day

At the baseline, the following assessments were recorded to the nearest mm using a UNC 15mm probe.

1. Plaque index (Silness and Loe, 1964)
2. Gingival bleeding index (Papillary Bleeding Index - Muhlemann H.R 1977)
3. Gingival index (Loe and Silness, 1963)
4. Probing depth.
5. Clinical attachment level.

PI,GI and GBI were recorded at Baseline, 30th,90th, 180th day post treatment visits, while PD and CAL were recorded at Baseline,90th, 180th day for control sites . Next, contralateral test sites received the identical protocol with an additional application of Arestin™ (1mg), at all selected sites following SRP at baseline visit. The minocycline microsphere (Arestin) was re-applied at 30th day post treatment. The study ended at 6th month visit.

Statistical Analysis

Statistical analysis was performed on the data available from the subjects who participated in the study. The data was collected from selected sites in each at Baseline, 30th, 90th, 180th day, All the analysis was performed using SPSS 18 version. Intragroup comparison of mean scores from baseline through follow-ups was done using repeated measures ANOVA followed by post-hoc Bonferroni test. Comparison of baseline with follow-up was done within the groups by paired t-test. Intergroup comparison between test and control group at each follow-up was done using student's t test. A p-value of <0.05 was considered to be statistically significant.

Table 1 Inter and Intra-group comparison of mean values of Plaque index between Control (group I) and Test (group II) at baseline to 180th day follow up visits. Graph 1a,1b.

PI	Control (group I)		Test (group II)		p-value
	Mean	SD	Mean	SD	
1. Baseline	2.30	0.24	2.47	1.16	0.495
2. 30 days	1.63	0.27	1.35	0.29	<0.001
3. 90 days	1.14	0.30	0.84	0.22	<0.001
4. 180 days	0.58	0.16	0.42	0.14	<0.001
p-value	<0.001		<0.001		
Post-hoc test	1>2>3>4		1>2>3>4		

Inter group comparison: At baseline there was no significant difference in the mean PI between control (2.30±0.24) and test group (2.47±1.16) (p=0.495). At 30, 90 and 180 days, the mean PI was significantly higher in control than test group. (p<0.001).

Intra-group comparison: The mean PI values in control group at baseline, 30, 90 and 180 days were 2.3±0.24, 1.63±0.27, 1.14±0.3 and 0.58±0.16 respectively. The mean PI values in test group at baseline, 30, 90 and 180 days were 2.47±1.16, 1.35±0.29, 0.84±0.22 and 0.42±0.14 respectively. There was significant difference in the mean PI values in control and test group from baseline through 180 days follow-ups (p<0.001). Post hoc analysis showed significant trend which showed that baseline was higher followed by 30, 90 and 180 days being the lowest value for both the groups.

Intergroup analysis: At baseline there was no significant difference in the mean GBI between control (1.85±0.49) and test group (1.74±0.43) (p=0.079). At 30, 90 and 180 days, the mean GBI was significantly higher in control than test group. (p<0.001).

Table 2 Shows Inter and Intra-group comparison of mean values of Gingival bleeding index from baseline to 180th day follow up visits. Graph 2a, 2b.

GBI	Control (group I)		Test (group II)		p-value
	Mean	SD	Mean	SD	[Inter-group]
1. Baseline	1.85	0.49	1.74	0.43	0.079
2. 30 days	1.31	0.35	1.08	0.32	<0.001
3. 90 days	0.84	0.22	0.64	0.19	<0.001
4. 180 days	0.53	0.17	0.36	0.15	<0.001
p-value [Intra group]	<0.001		<0.001		
Post-hoc test	1>2>3>4		1>2>3>4		

Intra-group analysis: The mean GBI values in control group at baseline, 30, 90 and 180 days were 1.85±0.49, 1.31±0.35, 0.84±0.22 and 0.53±0.17 respectively. The mean GBI values in test group at baseline, 30, 90 and 180 days were 1.74±0.43, 1.08±0.32, 0.64±0.19 and 0.36±0.15 respectively. There was significant difference in the mean GBI values from baseline through 180 days follow-ups (p<0.001) in both the groups. Post hoc analysis showed significant trend which showed that baseline was higher followed by 30, 90 and 180 days being the lowest value for control and test groups.

Table 3 shows Inter and Intra-group comparison of mean values of Gingival index between Control (group I) and Test (group II)at baseline to 180th day follow up visits. Graph 3a, 3b.

GI	Control (group I)		Test (group II)		p-value
	Mean	SD	Mean	SD	
1. Baseline	2.19	0.28	2.14	0.26	0.006
2. 30 days	1.56	0.23	1.29	0.27	<0.001
3. 90 days	1.06	0.24	0.81	0.27	<0.001
4. 180 days	0.62	0.15	0.43	0.13	<0.001
p-value	<0.001		<0.001		
Post-hoc test	1>2>3>4		1>2>3>4		

Intergroup analysis: At baseline there was no significant difference in the mean GI between control (2.19±0.28) and test group (2.14±0.26) (p=0.006). At 30, 90 and 180 days, the mean GI was significantly higher in control than test group. (p<0.001).

Intra-group analysis: The mean GI values in control group at baseline, 30, 90 and 180 days were 2.19±0.28, 1.56±0.23, 1.06±0.24 and 0.62±0.15 respectively. The mean GI values in test group at baseline, 30, 90 and 180 days were 2.14±0.26, 1.29±0.27, 0.81±0.27 and 0.43±0.13 respectively. There was significant difference in the mean GI values in both control and test group from baseline through 180 days follow-ups (p<0.001). Post hoc analysis showed significant trend which showed that baseline was higher followed by 30, 90 and 180 days being the lowest value in both the groups.

Table 4 shows Inter and Intra-group comparison of mean values of Probing depth between Control (group I)and Test (group II)at baseline to 180th day follow up visits. Graph 4a, 4b.

PD	Control (group I)		Test (group II)		p-value
	Mean	SD	Mean	SD	
1. Baseline	5.82	0.48	6.13	0.79	0.054
2. 90 days	3.36	0.37	2.84	0.44	<0.001
3. 180 days	2.60	0.47	2.25	0.46	<0.001
p-value	<0.001		<0.001		
Post-hoc test	1>2>3		1>2>3		

Intergroup analysis: At baseline there was no significant difference in the mean PD between control (5.82±0.48) and test group (6.13±0.79) (p=0.054).But at 90 days, there was significant difference in the mean PD between control (3.36±0.37) and test group (2.84±0.44) (p<0.001). Similarly at 180 days the mean PD was significantly higher in control (2.6±0.47) than test group (2.25±0.46) (p<0.001).

Intra-group analysis: The mean PD values in control group at baseline, 90 and 180 days were 5.82±0.48, 3.36±0.37 and 2.6±0.47 respectively. The mean PD values in test group at baseline, 90 and 180 days were 6.13±0.79, 2.84±0.44 and 2.25±0.46 respectively. There was significant difference in the mean PD values in both control and test group from baseline through 180 days follow-ups (p<0.001). Post hoc analysis showed significant trend which showed that baseline was higher followed by 90 and 180 days being the lowest value both the groups.

Table 5 shows Inter and Intra-group comparison of means of Clinical attachment level between Control (group I) and group II (test) at baseline to 180th day follow up visits. Graph 5a, 5b.

CAL	Control (group I)		Test (group II)		p-value
	Mean	SD	Mean	SD	
1. Baseline	5.97	0.68	6.19	0.85	0.211
2. 90 days	3.51	0.43	2.79	0.53	<0.001
3. 180 days	2.66	0.38	2.31	0.42	<0.001
p-value	<0.001		<0.001		
Post-hoc test	1>2>3		1>2>3		

Intergroup analysis: At baseline there was no significant difference in the mean CAL between control (5.97±0.68) and test group (6.19±0.85) (p=0.211). But at 90 days, there was significant difference in the mean CAL between control (3.51±0.43) and test group (2.79±0.53) (p<0.001). Similarly at 180 days the mean CAL was significantly higher in control (2.66±0.38) than test group (2.31±0.42) (p<0.001).

Intra-group analysis: The mean CAL values in control group at baseline, 90 and 180 days were 5.97±0.68, 3.51±0.43 and 2.66±0.38 respectively. The mean CAL values in test group at baseline, 90 and 180 days were 6.19±0.85, 2.79±0.53 and 2.31±0.42 respectively. There was significant difference in the mean CAL values in test group from baseline through 180 days follow-ups (p<0.001) in both the groups. Post hoc analysis showed significant trend which showed that baseline was higher followed by 90 and 180 days being the lowest value in both groups.

Table 6 shows the comparison of mean percentage change of various study parameters between Test (group II) and Control (group I). Graph -6.

	Test (group II)		Control (group I)		p-value
	Mean	SD	Mean	SD	
PI	81.54	7.69	74.43	8.18	<0.001
GI	79.09	6.75	71.25	7.34	<0.001
GBI	78.39	9.56	69.54	12.38	<0.001
PD	62.57	9.95	55.10	9.10	<0.001
CAL	61.85	9.48	54.76	8.68	<0.001

The mean percentage change in PI, GI, GBI, PD and CAL was significantly higher in test than control (<0.001).

Group I (Control Group)

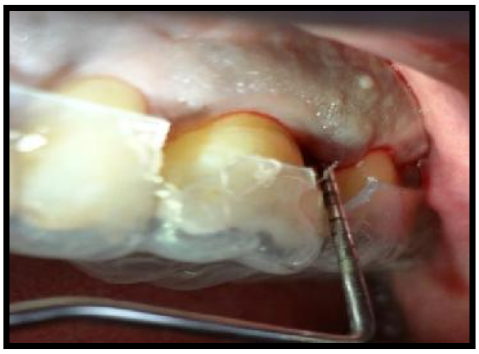


Fig 1 Control Group Probing Depth At Base Line (Buccal Site)

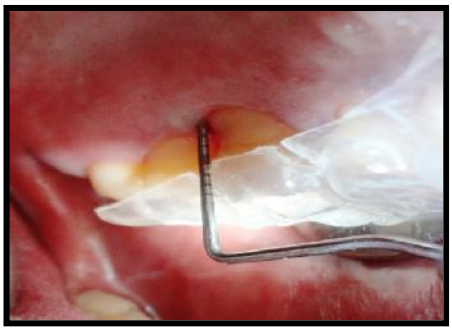


Fig 2 Control Group Probing Depth At Base Line (Palatal Site)

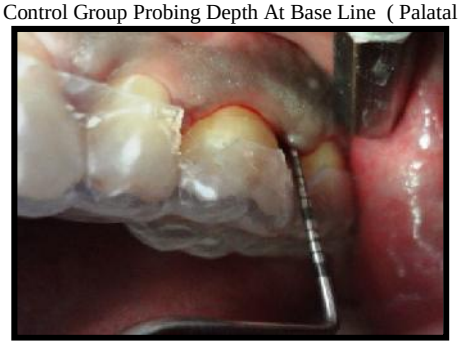


Fig 3 Control Group Probing Depth At 180th Day (Buccal Site)

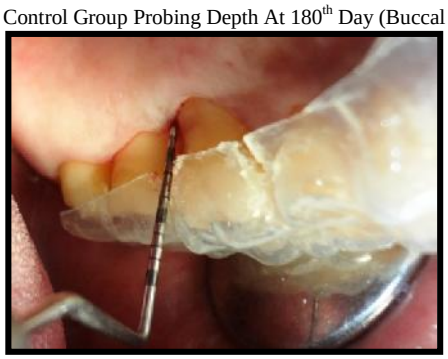


Fig 4 Control Group Probing Depth At 180th Day (Palatal Site)

Group II (Test Group)

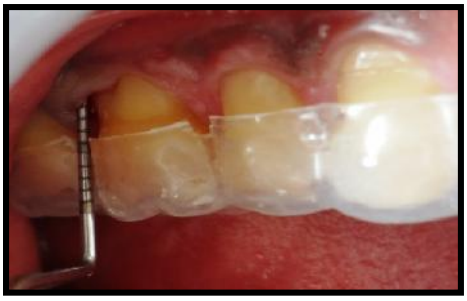


Fig 5 Test Group Probing Depth At Base Line (Buccal Site)

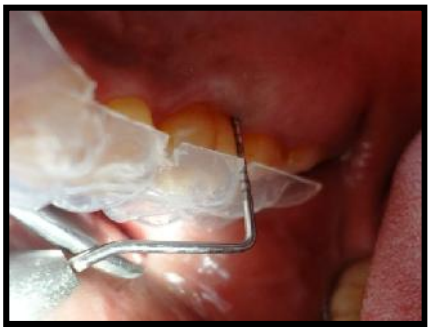


Fig 6 Test Group Probing Depth At Base Line (Palatal Site)

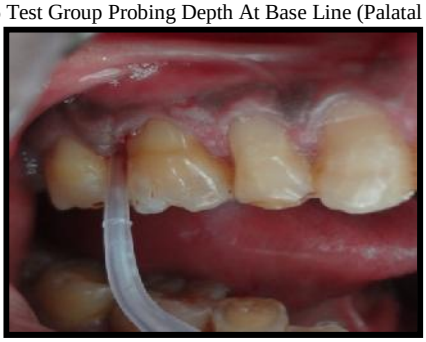


Fig 7 Local Drug Delivery Of Arestin (Buccal Site)

Fig 8 Local Drug Delivery Of Arestin (Palatal Site)

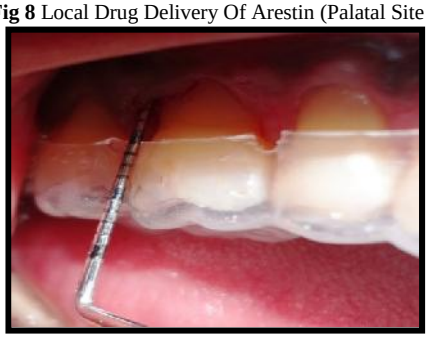


Fig 9 Test Group Probing Depth At 180th Day (Buccal Site)

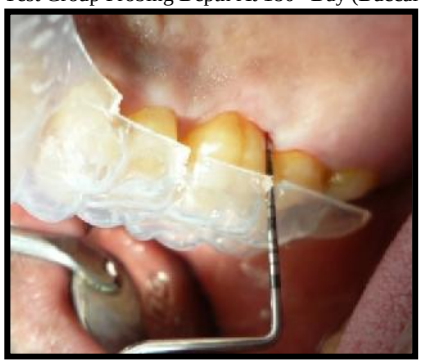
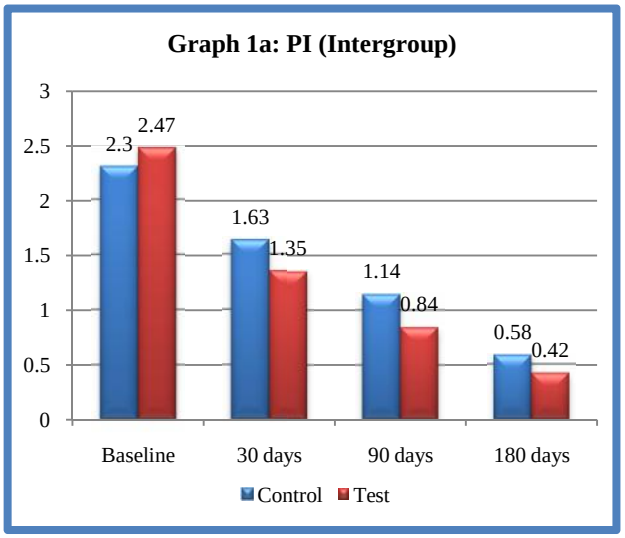
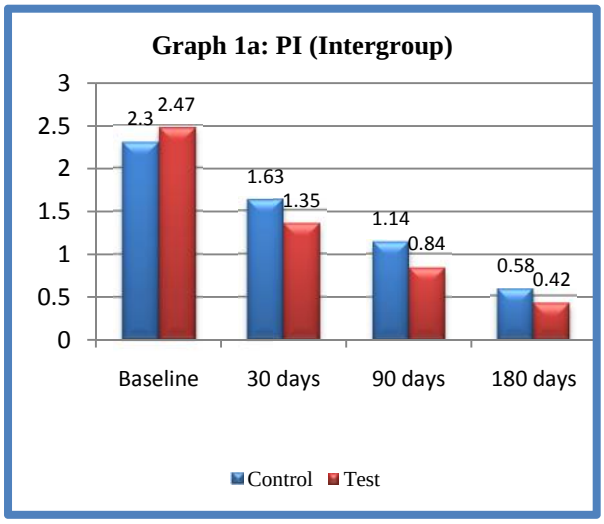


Fig 10 Test Group Probing Depth At 180th Day (Palatal Site)

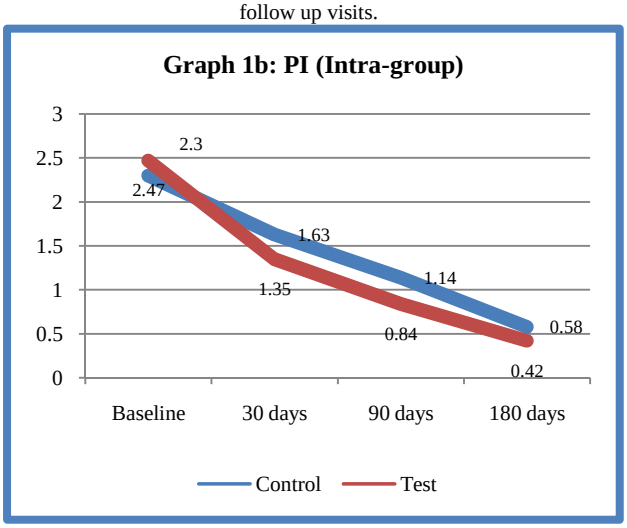
Graphs



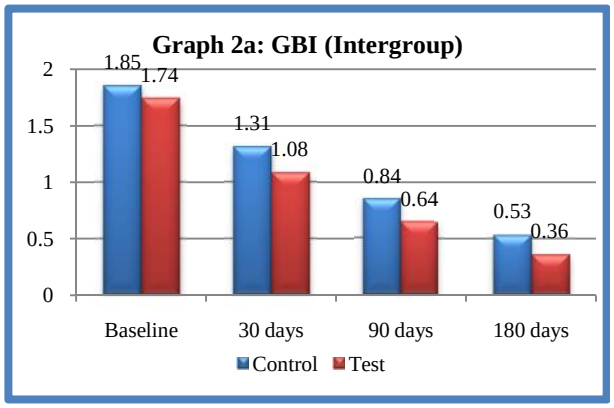
Graph 1a Inter group comparison of mean values of Plaque index between group I (control) and group II (test) at baseline to 180th day follow up visits.



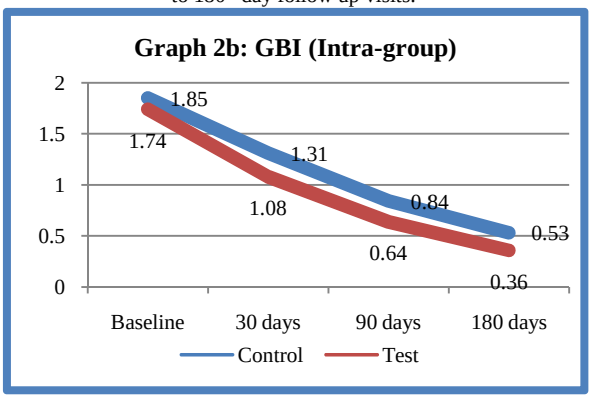
Graph 1b Intra-group comparison of mean values of Plaque index within group I (control) and group II (test) from baseline to 180th day follow up visits.



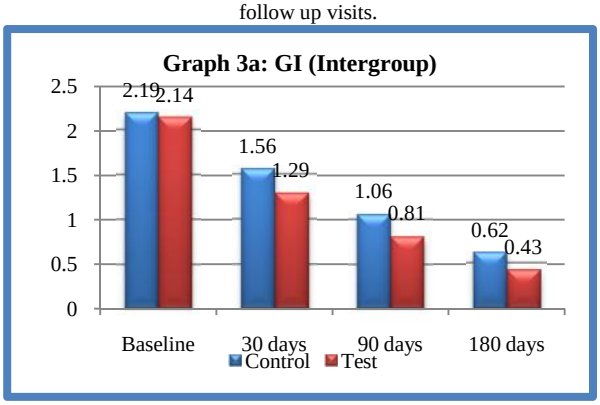
Graph 2a Inter group comparison of mean values of Gingival bleeding index between group I (control) and group II (test) at baseline to 180th day follow up visits.



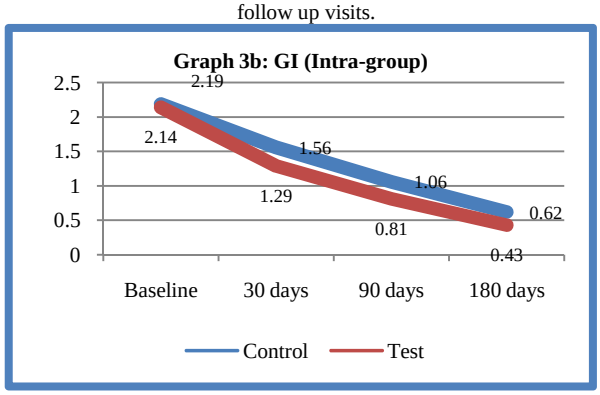
Graph 2b Intra-group comparison of mean values of Gingival bleeding index within group I (control) and group II (test) from baseline to 180th day follow up visits.



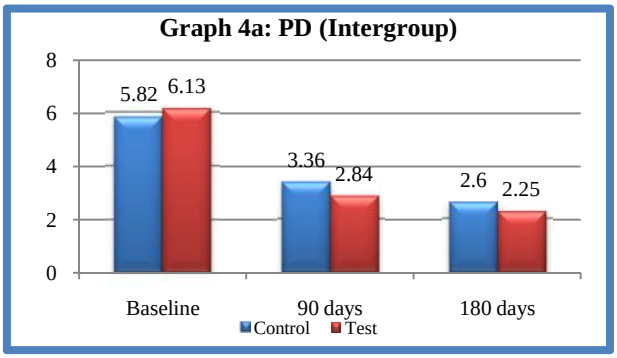
Graph 3a Inter group comparison of mean values of Gingival index between group I (control) and group II (test) at baseline to 180th day follow up visits.



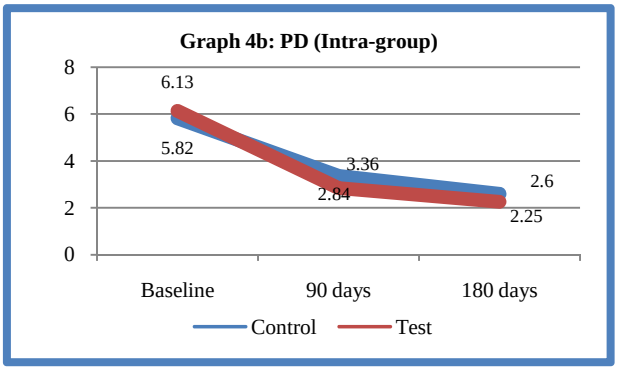
Graph 3b Intra-group comparison of mean values of Gingival index within group I (control) and group II (test) from baseline to 180th day follow up visits.



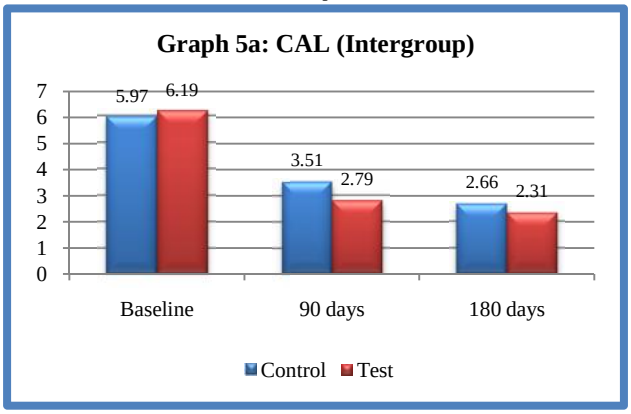
Graph 4a Inter group comparison of mean values of Probing depth between group I (control) and group II (test) at baseline to 180th day follow up visits.



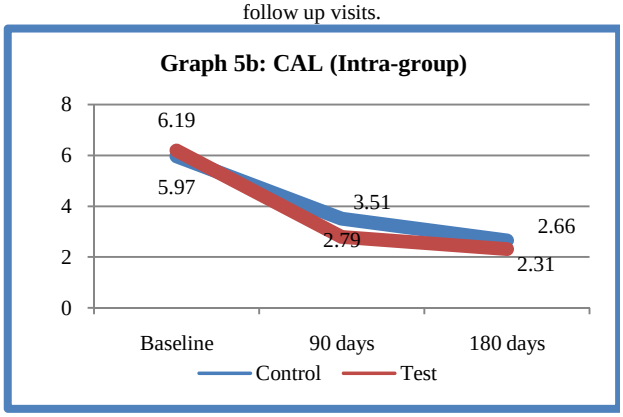
Graph 4b Intra-group comparison of mean values of Probing depth within group I (control) and group II (test) from baseline to 180th day follow up visits.



Graph 5a Inter group comparison of mean values of Clinical attachment level between group I (control) and group II (test) at baseline to 180th day follow up visits.



Graph 5b Intra-group comparison of mean values of Clinical attachment level within group I (control) and group II (test) from baseline to 180th day follow up visits.



Graph 6 The comparison of mean percentage change of various study parameters between test and control group.

DISCUSSION

In the present study, a split mouth study was designed in which a total of 72 sites from 18 patients who were treated for 180 days. The split mouth design used in this study has the additional advantage over two groups of unmatched patients where subject variation would otherwise play a large role. It has been suggested that a split-mouth design may induce a carryover effect of subgingival antibiotic administration due to wash-out of antimicrobial agents and boosting of systemic responses. [34]

An attempt is made to evaluate the efficacy of the adjunctive use of minocycline plus scaling / root planing as compared with scaling / root planing alone in the treatment of the chronic periodontitis The Objective of the study was 1. To assess the efficacy of local drug delivery of minocycline microspheres in combination with scaling & root planning on subjects with chronic periodontitis. 2. To compare the effects of local drug delivery of minocycline microspheres as an adjunct to scaling and root planing with scaling and root planing alone.

The results of this investigation demonstrated an overall improvement in all parameters at various time intervals both in test and control groups. In this study the mean PI values showed significant difference in control and test group from baseline, 30th, 90th and 180th days follow-ups (p<0.001).These findings are in accordance with studies of Kalsi R *et al* (2011)[49] , Cortelli JR *et al* (2008)[46] , Hagiwara S (1998)[22] , Timmerman *et al* (1996)[15] , these studies showed significant reduction in plaque scores This improvement achieved may be accounted to adequate maintenance of oral hygiene which was instructed to each patient at each visit. This supports the observation that a reduction in plaque scores seen following scaling and root planing and local delivery of minocycline are due primarily to a change in the subgingival plaque. In the study of Gopinath *et al* (2009)[4] , no statistically significant difference between the two groups on the 30th day from the baseline were observed in PI, but there was a significant difference in the plaque index on the 90th and 180th days between the two groups. The study conducted by Jones *et al* (1994)[13] has shown only significant differences in PI change from baseline to 3 months. The PI in present study is in contrast to the studies of Jain *et al* (2012)[51], Muller *et al* (1993)[12]. In the above mentioned studies plaque scores showed significant improvement from baseline to three months , but by the end of six months plaque scores returned to baseline. This may be due to lack of adequate maintenance of oral hygiene. This observation was supported by Cortelli JR *et al* (2006)[36] who reported that absence of periodontal maintenance resulted in worsening of PI.

A significant difference in the **mean GBI values and mean change in % of BOP sites** from baseline, 30th 90th and 180 days follow-ups (p<0.001) in both the groups were observed in present study. Our results are similar to studies done by Jain R *et al* (2012)[51] , Graca *et al.* (1997)[18] ,Hanes *et al* (2003) ,Emingil, (2006) which showed substantial reduction in bleeding scores. The possible cause for this reduction in bleeding scores is related to the inflammatory status and there is decrease in inflammatory markers like prostaglandin E2 and MMP 8 with LDD, which is possibly due to modulation of the host response, which was probably the cause of decreased BI in the test group.[49] In contrast Lu H-K, Chei C-J(2005)[34] study showed no statistical difference in bleeding scores between the experimental and control groups after subgingival minocycline application, further they concluded that , bleeding on probing is not sensitive enough to detect the difference of SRP alone and SRP in combination with subgingival minocycline application in the 6–18-week follow-up period.

In the present study **the mean GI values** showed significant difference in control and test group from baseline, 30th, 90th and 180th days follow-ups (p<0.001). These findings are consistent with the reports of Muller *et al.* (1993)[12], Vansteenberghe *et al.*,(1999)[26] Jones *et al.*,(1994)[13] Timmerman *et al.*,(1996)[15] Radvar *et al.*,(1996)[17] , Hagiwara *et al.*,(1998)[22] and Kinane *et al.*(1999)[25] , Gopinath *et al* (2009)[4] . In contrast study of Cortelli JR *et al* (2006)[36] reported that absence of periodontal maintenance resulted in worsening of GI.

Pocket depth is an important variable and has an impact on the type of subgingival flora and the treatment outcome. A significant difference in the mean PD values from baseline, 90th and 180 days follow-ups (p<0.001) in both the groups were observed in the present study. Our study is in accordance with the studies conducted by Mullur *et al.*,(1993)[12] Vansteenberghe *et al.*,(1990)[26] Jones *et al.*,(1994)[13] Timmerman *et al.*,(1996)[15] Radvar *et al.*,(1996)[17] , Hagiwara *et al.*,(1998)[22] and Kinane *et al.*(1999)[25] , Makoto Umeda *et al.*,(1996)[16] Hey-Riyeom *et al*,(1997)[20] Williams *et al.*,(2001)[1], Gopinath *et al* (2009)[4] , Jain R *et al* (2012)[51]. However, Graca *et al.* (1997)[18] reported marked reductions in probing depth in both groups from baseline to 6 and 12 weeks, but their results did not show significant difference between the test and control groups.

Reports from the meta-analyses of Pavia *et al.* (2003) and Hanes *et al.*(2003), supports the hypothesis that association of mechanical debridement and antimicrobial effect can be more effective than SRP as monotherapy. This metaanalysis also revealed that some sustained-release antimicrobial agents combined with SRP provided a relatively small but statistically significant reduction in PD compared with SRP alone.[49] The differences between these studies may arise from their different study designs and methodology.[18] In contrast study of McColl E *et al* (2006)[37] showed majority of sites with residual PPD of 5 mm. They failed to detect a difference in the effect of local drug delivery of minocycline as a mono-therapy in SPT and subgingival debridement over a 12-month period. This may be attributed to the poor patients compliance and insufficient treatment thus making the periodontal tissues more susceptibile for further breakdown.[37] This observation is supported by the findings from the study of Cortelli JR *et al* (2006)[36] that absence of periodontal maintenance would result in worsening of PD .

A significant difference in the mean CAL values from baseline, 90th and 180 days follow-ups (p<0.001) in both the groups were observed in present study. Our findings are in accordance to the studies done by Lu H-K, Chei C-J(2005)[34] , Goodson

J.(1982), Newman MG,(1994). Whereas, the study of Jain R *et al* (2012)[51] observed that the relative attachment levels also showed significant improvement in both test and control groups from baseline to three and six months , which is in accordance to our study results. But , when two groups were compared, the values did not reach statistical significance at any time. This may be because chronic periodontitis is a chronic disease which progresses in an episodic manner and the rate of progression of disease is very slow, so a 9-month period may not be sufficient to record noticeable differences in attachment loss.

The mean percentage change in PI, GI, GBI, PD and CAL was significantly higher in test than control (<0.001) in our study. This was statistically significant and consistent with the findings of Mullur *et al*., (1993)[12] Vansteenberghe *et al*.,(1990)[26] and Timmerman *et al*.,(1996)[15],Hellstorm MK *et al* (2008)[2], Gopinath *et al* (2009)[4].

The above results show that scaling and root planing plus Minocycline microspheres provide significantly greater probing depth reduction than scaling and root planing alone. This significant change in all the clinical parameters examined in the test group, is because Arestin™ releases therapeutic doses of the drug for more than 14 days, well above the minimum inhibitory concentration needed to kill most putative pathogens for periodontal disease. Paquette D *et al* (2000) in their study also revealed mean dose salivary levels of minocycline was approximately 1,000 times higher than those in serum. This finding suggests that minocycline has minimal absorption through the periodontal pocket into serum and stays concentrated in saliva. In addition, levels of minocycline were found in saliva for longer than 14 days, suggesting a sustained release of minocycline from the local delivery system[4]

The present study did not report any patient-centered undesirable effects when adjunctive antimicrobial agents were used. Their use apparently does no harm. The lack of significant adverse events is possibly due to the non irritating nature of the medications and delivery vehicles employed. In addition, one of the advantages of local drug delivery systems for periodontal therapy is that the total amount of drug used is quite small. When systemic administration of antimicrobials were compared with LDD, the total body dose of drug delivered with local sustained-release systems was meagre . Therefore, side-effects associated with relatively high doses of systemically administered antimicrobials are less likely to occur when local drug delivery systems are used. [44]

Adverse events, treatment time, patient compliance and cost factor are all important in determining whether a given procedure is worth the effort. Determining clinical significance is a highly complex and variable task and involves both the patient's and the therapist's perceptions of benefits gained from the procedure.[49] The efficacy of subgingival minocycline is clearly attributed to the dose level. The repeated administration of minocycline as an adjunct to SRP could result in continued improvements in periodontal clinical status associated with substantial reductions in periodontal pathogens.[26]

The locally delivered antimicrobial are efficacious, particularly when number of sites treated is large. The study of Williams RC (2001)[1] reported that the Clinicians found minocycline microspheres are very easy to administer and there was no evidence of fatigue factor and were able to treat more than 30 sites without prolonging SRP visit. The minocycline microspheres powder, begins to hydrolyze upon contact with the moisture and it would immediately becomes bio adhesive and self retentive. These attributes would likely to be favorably impact the efficacy.[1]

The results of this study confirm that Arestin (1mg Minocycline microspheres) delivered in biodegradable system, are a safe and efficient adjunct to scaling and root planing, and can produce significant clinical benefits when compared to scaling and root planing alone.

SUMMARY AND CONCLUSION

The present study evaluated the efficacy of the adjunctive use of minocycline plus scaling / root planing as compared with scaling / root planing alone in the treatment of the chronic periodontitis. In this split mouth study, 72 sites in 18 patients diagnosed with chronic periodontitis were randomly divided into two groups and treated with SRP+Arestin (Test group) or SRP alone (Control group). Plaque formation, bleeding on probing,Gingival index, probing depth and clinical attachment level were evaluated for 180 days for each group. Significant differences with and between the groups were analyzed using students paired-test and ANOVA. The following conclusions may be drawn from the present study:

1. Test sites where Minocycline microspheres were employed, displayed a statistically significant reduction in all the clinical parameters (Plaque index, Gingival index, Gingival bleeding index, Probing pocket depth) after treatment as compared to control sites, which showed only minimal changes.
2. A degradable, subgingivally placed drug delivery system containing 1 mg Minocycline microspheres, is a safe and efficient adjunct to scaling and root planing in the treatment of chronic periodontitis.
3. No side effects were found in the adjunctive local application of Arestin in subjects with chronic periodontitis undergoing non-surgical periodontal therapy.
4. This study demonstrated that minocycline microspheres is safe & efficient local drug delivery in reducing clinical signs of periodontitis. However, it calls for further advanced histological and microbiological studies clarifying the efficacy, long term effects and bacterial resistance to minocycline.

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