

ORIGINAL RESEARCH

# Clinical efficacy of minocycline microspheres (arestin™) in the treatment of localised periodontitis

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## Abstract

Periodontal disease can be treated either by surgical or nonsurgical methods depending on probing pocket depth. More emphasis is given to non-surgical methods which include Scaling & root planning (SRP), the adjunctive use of medicaments, mouthwashes or patient administered irrigation systems with cannulas or syringes. The local application of antimicrobials that are effective against periodontopathogens, reduce the pocket depth and hopefully the need for surgery. *The aim* of the present study was to find out the clinical efficacy of minocycline microspheres (Arestin™) as an adjunct to SRP in the management of

localized periodontitis patients over a period of 6 months.

*Materials and Methods:* Minocycline microspheres (Arestin™ by Orapharma Inc, Warminster, PA, USA) is a subgingival sustained-release minocycline hydrochloride incorporated into a bioresorbable polymer, (poly glycolide-lactide). Each unit dose cartridge delivers 1 mg minocycline. Tooth was taken as the randomisation unit. Either buccal/labial, mesial, distal or palatal surfaces were taken. 12 sites were treated with Arestin plus SRP (Test group). 12 similar sites were treated with SRP only (Control group). Clinical parameters like probing pocket depth, clinical attachment

level, gingival index, sulcus bleeding index were recorded at baseline and at 1.5, 2.5, 3.5, 4.5 & 6 months. Supra gingival scaling and clinical measurements were done for both test and control groups at each recall visits.

*Results and conclusion:* The results of the study can be concluded that when used as an adjunct to mechanical debridement, the subgingival application of minocycline microspheres (Arestin™) is more efficacious than SRP alone in the treatment of localized periodontitis patients.

## **Introduction**

The periodontal disease represents a group of localized microbial induced infections. Around 300 or 400 bacterial species are found in the human sub gingival plaque samples. Out of these 10-20 species may play a role in the pathogenesis of periodontal disease. There is considerable evidence implicating facultative and obligate anaerobic bacteria as the primary cause of periodontal disease<sup>1,2,3,4</sup> Periodontal pathogens produce a variety of enzymes and toxins that can damage the tissues and initiate inflammation.<sup>5</sup>

Periodontal disease can be treated either by surgical or nonsurgical methods depending on the probing pocket depth and nature of the disease. More emphasis is given to non-surgical methods which include scaling & root planning (SRP), adjunctive use of medicaments, mouthwashes or patient administered irrigation systems with cannulas or syringes. Various antimicrobial

agents have been tested as irrigants including chlorhexidine, iodine, sanguinarine and essential oils. The disadvantages of these methods include inability to maintain adequate concentration of the drug in the periodontal pocket and require patient compliance and dexterity.

The initial attempt to utilize controlled delivery for the management of periodontitis is the work of Goodson *et al* in which tetracycline was delivered to the periodontal pocket via hollow dialysis tube.<sup>6</sup> More recent development has focused on injectable systems, which offer greater ease of use. Eg: 25% metronidazole gel, 2% Minocycline gel, films and microspheres, 35% tetracycline hydrochloride gel and 10% doxycycline gel.

Tetracyclines comprise a group of broad-spectrum antibiotics in the management of periodontal diseases. Minocycline, a semi synthetic tetracycline has the most marked substantivity and greater lipid solubility than tetracycline along with the features of tetracycline like antibacterial activity, and anticollagenase activity. Therefore, minocycline is one of the most suitable antibiotics for controlling periodontal disease especially for local therapy.

In this clinical trial an attempt has been made to evaluate the effects of local delivery of sustained release Minocycline microspheres (Arestin™), as an adjunct to SRP in the management of localized periodontitis.

## **Aims and objectives**

To find out the clinical efficacy of Minocycline microspheres (Arestin™) as an adjunct to SRP in the management of localised periodontitis as measured by reduction in probing depth.

### **Materials and Methods**

Minocycline microspheres (Arestin™ by Orapharma Inc, Warminster, PA, USA) is a subgingival sustained-release minocycline hydrochloride incorporated into a bioresorbable polymer, (poly glycolide-lactide). Each unit dose cartridge delivers 1 mg minocycline. Arestin's microspheres are bioadhesive, bioresorbable polymer in powder form produced by microencapsulation process. Once Arestin is inserted, it immediately adheres to the periodontal pocket. Crevicular fluid hydrolyses the polymer causing water-filled channels which provide "escape routes" for the encapsulated antibiotic for sustained release. The active drug diffuses through the channels and eventually, the microspheres themselves are fragmented through polymer hydrolysis and completely bioresorbed. Arestin™ can be administered quickly right after SRP and no anesthesia is needed.

Study population comprised of patients with chronic periodontitis.

#### *Criteria for patient selection*

##### **Inclusion criteria**

1. Subjects between 21-48 years of age belonging to both sexes with localized periodontitis.
2. Periodontal pocket depth of 4-7mm.

3. Single rooted teeth
4. Patients who are willing to participate and able to give informed consent.

##### **Exclusion criteria**

1. Prior antibiotic treatment for any illness during the past 2 weeks.
2. Any systemic disease as evident from the history.
3. Habitual smokers.
4. Allergy to tetracycline.
5. Pregnancy, lactating mothers.

##### *Site selection*

Study setting and period: Government Dental College, Trivandrum; one year -2002.

Study was done under the approval of Human Ethics Committee, Medical College, Trivandrum.

All the patients after randomisation had received supra gingival scaling using ultrasonic instruments. Oral hygiene instructions were given. After 1 week patients were recalled for evaluation of periodontal status. Tooth was taken as the randomisation unit. Either buccal/labial, mesial, distal or palatal surfaces were taken. If more than one surface was involved, it was not taken for the study. 12 sites each were treated in the test and control group.

##### *Clinical evaluation*

After selection of the appropriate sites, clinical parameters at base line, like probing pocket depth (PPD), clinical attachment level (CAL), gingival index (GI), sulcus

bleeding index (SBI) were recorded. For standardisation of probing measurements, impressions were made and customised acrylic occlusal stents prepared. The stents covered the occlusal surface of the teeth and extended on the buccal and lingual surfaces. The groove that was prepared provided the reproducible alignment for the periodontal probe. The base of the stent served as the reference point for measurements like PPD and CAL which was measured with William's graduated probe.

*Criteria for GI (Loe and Silness 1964)*

1. Normal gingiva
2. Mild inflammation, slight change in colour, slight edema, no bleeding on probing.
3. Moderate inflammation, redness, edema and glazing, bleeding on probing.
4. Severe inflammation, marked redness and edema, ulceration and tendency to bleed spontaneously

*Criteria for SBI (Mombelli et al 1987)*

1. No bleeding
2. Isolated bleeding spots
3. Blood formed a confluent red line
4. Heavy/profuse bleeding

*Intervention*

After recording the baseline clinical measurements, a thorough subgingival scaling and root planing were done using hand instruments under local anaesthesia for

the test and control sites. Following subgingival scaling, test sites were dried and Arestin placed subgingivally using plastic disposable syringes. To avoid dislodging of Arestin, periodontal dressings were placed. Patients were instructed to refrain from brushing and flossing those sites for seven days. Patients were asked to report untoward reactions if any.

*Recall check up*

Patients in both groups were recalled after seven days for the removal of periodontal pack and also recalled at 1.5, 2.5, 3.5, 4.5 & 6 months. Supra gingival scaling and clinical measurements were done for both groups at each recall visits.

**Statistical analysis**

Analysis were done using SPSS statistical package (version 7.5). Using the normal probability plot, it was found that the clinical parameters followed the distribution normality. Therefore the parametric test to compare means was used, i.e. Independent 't' test . It was used to assess the statistical significance between each variable reduction for the test and control group at 1.5 and 6 months compared to base line values. Statistical significance was declared if the 'p value' was found less than or equal to 0.05.

**Results**

There is no difference in baseline characteristics for the test and control groups.

**Table 1.** Mean baseline values for each group

Parameters	Sample size in each group	Test group Mean $\pm$ SD	Control group Mean $\pm$ SD
Age	12	35.25 $\pm$ 8.48	38.25 $\pm$ 7.21
PPD	12	1.83 $\pm$ 0.83	5.17 $\pm$ 0.83
CAL	12	5.83 $\pm$ 0.83	5.17 $\pm$ 0.83
GI	12	1.92 $\pm$ 0.29	2 $\pm$ 0.00
SBI	12	2.42 $\pm$ 0.51	2.42 $\pm$ 0.51

**Table 2:** Probing Pocket Depth Reduction (PPDR)

Procedure	Mean baseline PPD (PPDB)	PPDR in mm at			
		1.5 month	2.5months	3.5 months	4.5 months
Test	5.83 $\pm$ 0.83	1.83 $\pm$ 0.94	2.42 $\pm$ 1.31	3.08 $\pm$ 1.08	3.17 $\pm$ 1.1
Control	5.17 $\pm$ 0.83	0.67 $\pm$ 0.98	0.5 $\pm$ 1.7	1 $\pm$ 1.8	1.08 $\pm$ 1.8

**Table 3.** Comparison of PPDR for the test and control groups at 1.5 and 6 months to mean baseline PPD

Variable	Procedure	Mean $\pm$ SD	T value	p value	Inference
PPDR at 1.5 month	Test	1.83 $\pm$ 0.94	2.97	0.007	Significant
	Control	0.67 $\pm$ 0.98			
PPDR at 6 months	Test	3.25 $\pm$ 1.14	3.55	0.002	Significant
	Control	1.08 $\pm$ 1.78			

**Table 4.** Gain in CAL (CALG)

Procedure	Mean baseline CAL(CALB) 1.5 months	Mean gain in CAL(CALG) in mm at			
		2.5months	3.5months	4.5months	6months
Test	5.83 $\pm$ 0.83	1.83 $\pm$ 0.94	2.42 $\pm$ 1.3	3 $\pm$ 1.04	3.3 $\pm$ 1.2
Control	5.17 $\pm$ 0.83	0.75 $\pm$ 1.22	0.5 $\pm$ 1.68	1.08 $\pm$ 1.88	1.08 $\pm$ 1.8

**Table 5.** Comparison of gain in CAL for the test and control group at 1.5 and 6 months to mean baseline CAL

Variable	Procedure	Mean $\pm$ SD	t value	p value	Inference
Gain in CAL at 1.5 months	Test	1.83 $\pm$ 0.94	2.44	0.02	Significant
	Control	0.75 $\pm$ 1.22			
Gain in CAL AT 6 Months	Test	3.17 $\pm$ 1.11	3.43	0.002	Significant
	Control	1.08 $\pm$ 1.78			

**Table 6.** GI reduction (GIR)

Procedure	Mean baselineGI (GIB) 1.5 months	GIR at			
		2.5months	3.5months	4.5months	6months
Test	1.92 $\pm$ 0.29	1.25 $\pm$ 0.45	1.6 $\pm$ 0.5	1.75 $\pm$ 0.45	1.75 $\pm$ 0.45
Control	2 $\pm$ 0.00	0.67 $\pm$ 0.89	0.42 $\pm$ 2.43	0.75 $\pm$ 2.53	0.83 $\pm$ 2.55

**Table 7.** Comparison of GI reduction for the test and control groups at 1.5 and 6 months to mean baseline GI

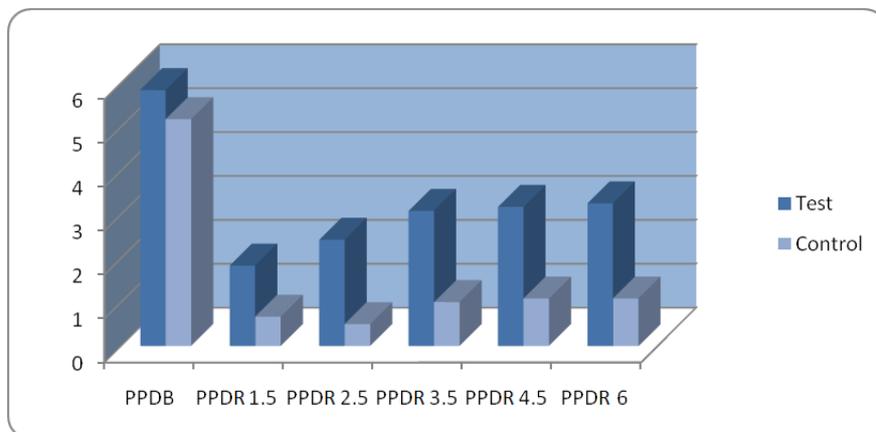
Variable	Procedure	Mean $\pm$ SD	t value	p value	Inference
GIR at 1.5 months	Test	1.25 $\pm$ 0.45	2.4	0.05	Significant
	Control	0.67 $\pm$ 0.89			
GIR at 6 months	Test	1.5 $\pm$ 0.9	0.75	0.461	Not Significant
	Control	0.92 $\pm$ 2.54			

**Table 8.** SBI reduction (SBIR)

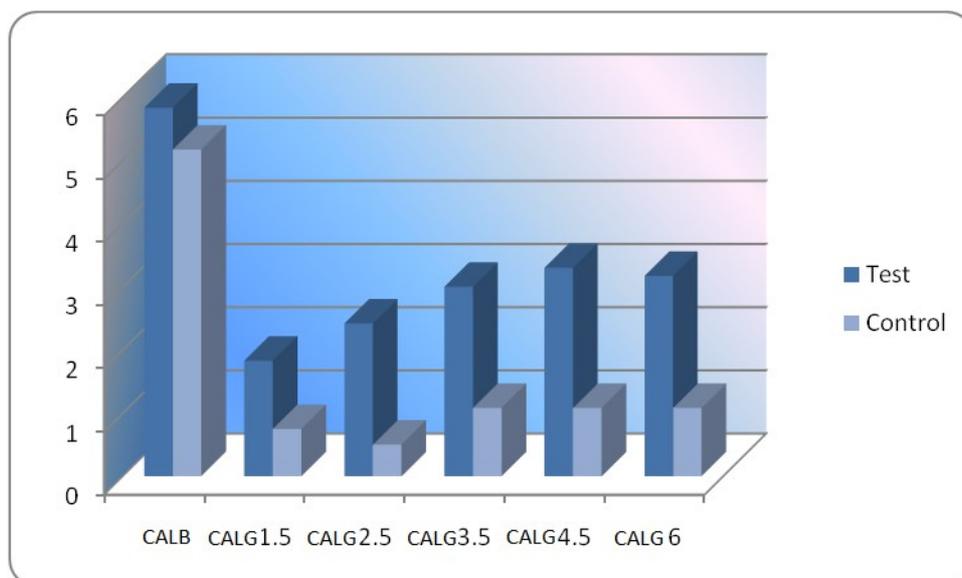
Procedure	Mean baselineSBI (SBIB)	SBIR at			
		1.5 months	2.5months	3.5months	
Test	2.42 $\pm$ 0.51	1.42 $\pm$ 0.67	1.7 $\pm$ 0.5	2.25 $\pm$ 0.62	2.33 $\pm$ 0.65
Control	2.42 $\pm$ 0.51	0.75 $\pm$ 0.75	1.08 $\pm$ 0.67	1.08 $\pm$ 2.3	1.08 $\pm$ 2.31

**Table 9.** Comparison of SBIR for the test and control groups at 1.5 and 6 months to mean baseline SBI

Variable	Procedure	Mean $\pm$ SD	T value	p value	Inference
SBIR at 1.5 months	Test	1.4 $\pm$ 0.7	2.4	0.03	Significant
	Control	0.75 $\pm$ 0.75			
SBIR at 6 months	Test	2.3 $\pm$ 0.7	1.5	0.14	Not Significant
	Control	1.25 $\pm$ 2.4			



**Figure 1.** PPDB and PPDR at 1.5, 2.5, 3.5, 4.5 and 6 months for the test and control groups



**Figure 2.** CALB and CALG at 1.5, 2.5, 3.5, 4.5 and 6 months for the test and control groups.

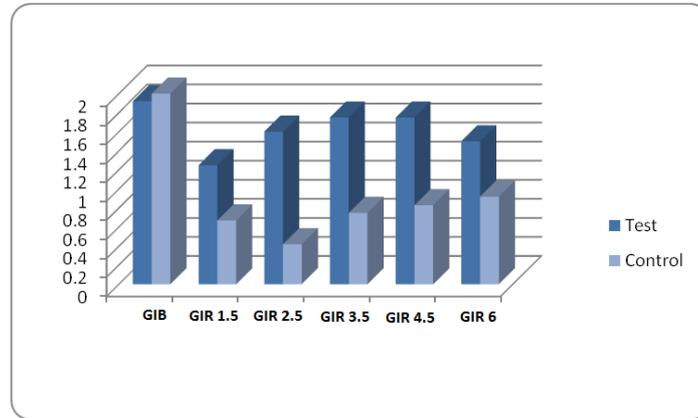


Figure 3. GIB and GIR at 1.5, 2.5, 3.5, 4.5 and 6 months for the test and control groups

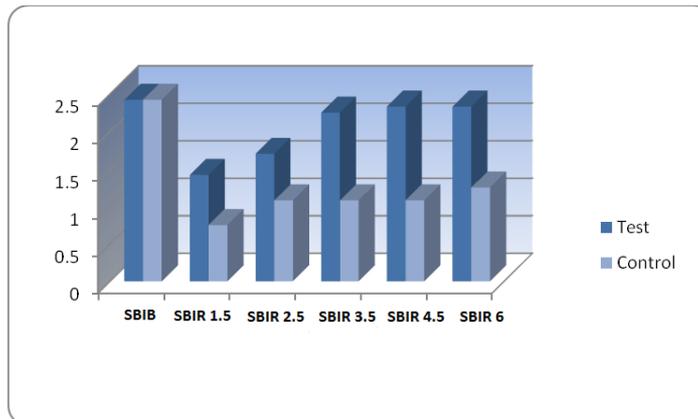
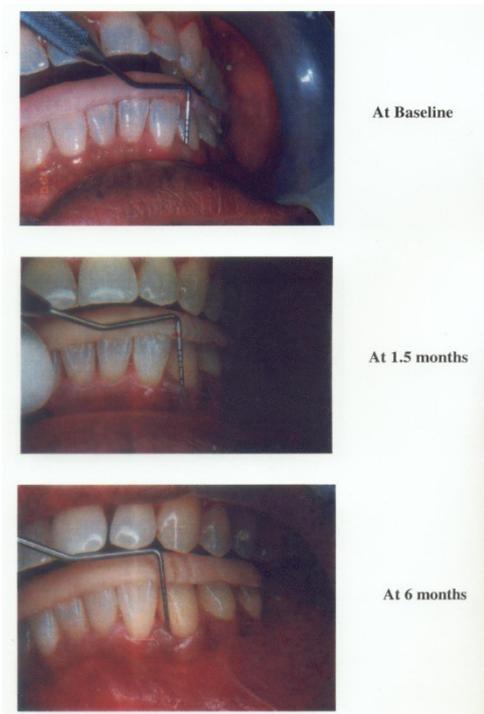
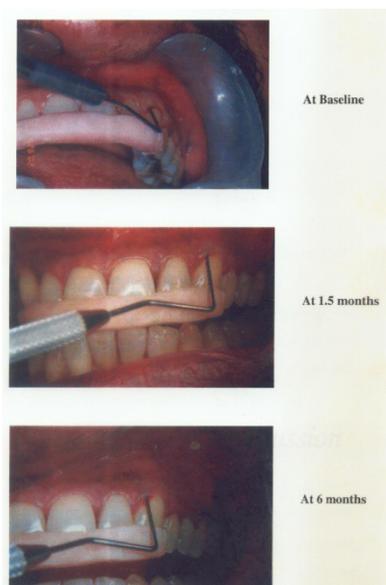


Figure 4. SBIB and SBIR at 1.5, 2.5, 3.5, 4.5 and 6 months for the test and control groups



**Figure 5.** Test site treated with Arestin™ + SRP



**Figure 6.** Control site treated with SRP only.

## Discussion

Bacterial etiology in periodontal disease allows the clinician to use chemotherapeutic agents for the management of the disease. This clinical trial was done to find out the efficacy of 1 mg minocycline microspheres (Arestin™) local application as an adjunct to SRP in the treatment of patients with localised periodontitis over a period of 6 months. 13 patients selected, (8 females, 5 males). Mean age of test and control group  $35.25 \pm 8$ ,  $38.25 \pm 7$  years, respectively.

Mean reduction in PPD at 1.5 and 6 months for the test group was  $1.83 \pm 0.94\text{mm}$ ,  $3.25 \pm 1.14\text{mm}$  and that of control was  $0.67 \pm 0.98\text{mm}$ ,  $1.08 \pm 1.78\text{mm}$  respectively. The mean reduction in PPD was higher for the test group. 't' test was used to find out the statistical significance between groups. Mean reduction in PPD was found to be significant for the test group at 1.5 ( $1.83 \pm 0.94\text{mm}$ ,  $t=2.97$ ,  $p$  value- $0.007$ ) and 6 months ( $3.25 \pm 1.14\text{mm}$ ,  $t=3.55$ ,  $P$  value- $0.002$ ).

Mean gain in CAL at 1.5 and 6 months for the test group was  $1.83 \pm 0.94\text{mm}$  and  $3.17 \pm 1.11\text{mm}$  and that of control group was  $0.75 \pm 1.22\text{mm}$  &  $1.08 \pm 1.78\text{mm}$ , respectively. So there is statistically significant gain in CAL for the test group at 1.5 ( $t=2.44$ ,  $P=0.02$ ) and 6 months ( $t=3.43$ ,  $p=0.002$ ). The reduction in PPD and gain in CAL was similar to the observations of several earlier studies.<sup>7-17</sup> The mean GI reduction at 1.5 months for the test group was  $1.25 \pm 0.45\text{mm}$  and that of control

group was  $0.67 \pm 0.89$  mm. ( $t=2.4$ ,  $p$  value=0.05). The mean GI reduction at 6 months for the test group was  $1.5 \pm 0.9$  mm and that of control group was  $0.92 \pm 2.54$  mm. There is a significant reduction in GI for the test group at 1.5 months. Although there is a reduction in GI at 6 months for the test group, it is not statistically significant. ( $t=0.75$ ,  $p$  value=-0.461). Similar results with SBI. At 1.5 months for the test group  $1.4 \pm 0.7$  mm, control group  $0.75 \pm 0.75$ mm. ( $t=2.4$ ,  $P$  value=0.03) The mean SBI reduction at 6 months for the test group  $2.3 \pm 0.7$  mm, control group  $1.25 \pm 2.4$ mm. ( $t=1.5$ ,  $p$  value=0.14).It may be due to bacterial recolonisation. This increase in gingival bleeding is similar to the observations by others earlier.<sup>9,14,18</sup>

The effect on the clinical parameters of Arestin may be due to the following properties. Minocycline exhibited strong effects on bacterial growth with 95% or more inhibition at concentration of  $1\mu\text{g/ml}$ . Against black pigmented *Bacteroides* there was 100% inhibition at  $1\mu\text{g/ml}$  and 97% at  $0.1\mu\text{g/ml}$  of minocycline.<sup>19</sup> Hagiwara et al 1998 conducted a study to search the resistance of minocycline in periodontal bacterial strains.<sup>20</sup>The minimum inhibitory concentration (MIC) for each organism showed that most were inhibited by a minocycline concentration equal to or less than the MIC. However, *Prevotella intermedia* exhibited low susceptibility to minocycline. Grossi et al(2007), Bland PS et al(2010) in their studies showed that the addition of minocycline to SRP led to a reduction of red complex bacteria.<sup>15,16</sup>

In addition to its antibacterial activity, the anticollagenase activity was reported by Maehara et al (1988).<sup>21</sup> Against *P.gingivalis* collagenase, minocycline caused 48% and 80% inhibition at 25 and  $250\mu\text{g/ml}$  respectively. Against human polymorphonuclear leukocyte (PMN) collagenase; minocycline caused 22% and 100% inhibition at 25 and  $250\mu\text{g/ml}$ , respectively which shows a greater degree of inhibition than with tetracycline at the same concentrations. Human fibroblast collagenase (MMP-1) is relatively resistant to tetracycline inhibition compared with human polymorphonuclear collagenase (MMP-8) (Golub LM 1991).<sup>22</sup> Polymorphonuclear neutrophils provide the principal source of collagenase for tissue destruction in periodontitis. Fibroblast collagenase may be required for normal connective tissue remodeling (Sorsa T et al 1988).<sup>23</sup>This differential sensitivity of tetracycline to collagenases, may have therapeutic benefits (Rifkin BR et al 1993).<sup>24</sup> 1980's Golub et al discovered a novel non antimicrobial property of tetracyclines, the ability to inhibit the activity of interstitial collagenases from a variety of cells such as neutrophils, macrophages, osteoblasts etc. In germ free rats, minocycline reduced gingival collagenase activity in vitro by 70%, confirming that tetracyclines decreased tissue collagenase activity which is not dependent on the drug's antibacterial efficacy (Golub et al1983).<sup>25</sup> The effects of tetracycline on bone resorption were studied (Gomes BC et al 1984), which showed that collagenase activity may be a rate-limiting step in bone resorption.<sup>26</sup>It (i)inhibit directly

active extra cellular osteoblast(OB) or osteoclast(OC) collagenase/gelatinase (2)altering the responsiveness of osteoclasts to elevated extra cellular calcium.(3)reduce the available concentration of OC generated super oxide radicals reactive oxygen species (ROS); and thereby (4) inhibit super oxide radical conversion of extra cellular OB or OC procollagenase/progelatinase to active enzyme (5)reduce the secretion of osteoclast cysteine proteinases( cys-pro) such as cathepsin L; and thereby (6) reduce resorption of bone collagen.

In addition, Minocycline have several key properties. 1) An avidity for skeletal tissue 2) concentration in GCF 3) long recognized history of safety in daily treatment 4). bind to the tooth surface and then be released slowly in an active form. From this clinical trial it was found that sustained release minocycline microspheres can be effectively used as an adjunct to routine scaling and root planing without any serious adverse effects.

### **Summary and conclusions**

In this clinical trial Arestin™ was used along with SRP to treat localized periodontitis patients of 4-7mm of PPD. 12 sites were treated with Arestin™ +SRP and 12 sites treated only with SRP alone. Reduction in clinical variables of both the groups of 1.5 and 6 months were statistically compared with mean base line values. The following conclusions were made from this study. Adjunctive use of Arestin™ resulted in significant reduction in

1. PPD and gain in CAL from base line up to 6 months compared to controls.
2. Gingivitis from base line up to 4.5 months compared to controls.
3. It was not associated with any serious adverse effects.
4. Found to be safe, efficacious and easy to use.

From the above clinical results, it can be concluded that when used as an adjunct to mechanical debridement, the sub gingival application of minocycline microspheres (Arestin™) is more efficacious than SRP alone in the treatment of patients with localized periodontitis.

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