Evaluation of Efficacy of Tetracycline as a Local Drug Delivery System in the Treatment of Chronic Periodontitis as an Adjunct to Scaling and Root Planing – A Clinical and Microbiological Study

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ABSTRACT

Introduction: Tetracycline and its derivatives has shown to be highly effective in the treatment of chronic periodontitits. Since there are very limited microbiological study conducted to evaluate the efficacy of tetracycline fibers as a local drug therapy, the study has been taken up to evaluate the efficacy of locally delivered tetracycline fibers (Periodontal AB Plus) in conjuction with scaling and root planing in the treatment of chronic periodontitis in the patients who are not willing to undergo periodontal flap surgery.

Material and methods: The present study is a randomized clinical trial with split mouth design in which a total no.of 35 patients who were diagnosed with generalized chronic moderate periodontitis, consisting of both genders (Male : Female =16 : 19), aged between 25 to 60 years were selected. These selected sites were randomly divided into test group and control group Test group - included 35 sites that were selected for the placement of Periodontal Plus AB; Tetracycline fibers (local drug delivery) after scaling and root planing. Control group - included 35 sites that were treated with scaling and root planing alone (without local drug delivery).Clinical parameters taken were the PI, GI, SBI, probing depth (PD), and clinical attachment level (CAL). Anaerobic culture was done to compare the total colony forming unit before and after the treatment. Clinical parameters were assesed at base line, 30 days and 90 days whereas the total count was calculated at baseline, 30 days and 90 days.

Result: Results showed a significant improvement in all the clinical parameters. There was significant decrease in mean probing depth from base line to 90 days, and also there was significant gain in CAL in the test group as compared to control group. There was a significant reduction in the total colony count from base line to 21 days in both the group, but more reduction was observed in the test group. After 21 days to 90 days there was significant increase in the total colony count in both the group, but less increase was observed in test group.

Conclusion: Within the limits of this study and on the basis of the clinical and microbiological parameters, it can be concluded that tetracycline fiber therapy enhances the benefits of SRP in the treatment of chronic periodontitis.

Keywords: Tetracycline, Local Drug Delivery System, Chronic Periodontitis, Scaling and Root Planing, Clinical and Microbiological Study

INTRODUCTION

Periodontal diseases represent a group of localized microbial induced infections involving the gingival and supporting tissues of the teeth, resulting in progressive loss of attachment and formation of periodontal pockets. There is considerable evidence implicating facultative and anaerobic bacteria as a primary cause of periodontal disease. The control of prevalence and progression of periodontal disease requires a reduction of sub-gingival microbial plaque mass or at least a suppression of periodontopathic bacteria.[1]

Periodontal diseases are routinely treated by mechanical procedures which include meticulous scaling and root planing in conjunction with patient's proper plaque control. Mechanical therapy may however fail to eliminate the pathogenic bacteria because of their location within gingival tissues or in other areas inaccessible to periodontal instruments.[2]

Subgingival microbial recolonization after scaling and root planing occurs slowly. Periodontal debridement may not eradicate these species like A. actinomycetemcomitans and P.gingivalis due to their invasive potential into gingival epithelial cells and subepithelial connective tissue, and their high affinity for crevicular epithelium and dentinal tubule. Consequently, this has led to adjunctive use of antimicrobials, assuming that chemical aids would compensate for technical shortcomings and prevent early microbial re-colonization to ultimately ensure the best chance for clinical improvements.[3]

Antimicrobial therapy has also been directed at specific bacteria associated with clinically diseased sites to help augment the mechanical treatment aimed at the removal of sub-gingival calculus and toxins. However, the inability to achieve and maintain therapeutic concentrations of the antibiotic in the crevicular fluid with systemic administration can limit its effectiveness.[4]

Also, the Systemic administration of antimicrobial agents requires frequent dosing which is associated with the risk of developing resistant organisms and super infection as well as adverse effects such as gastrointestinal disturbances.[5]

Pitcher et al. observed that mouth rinses and agents used during supra-gingival irrigation do not predictably reach beyond 5 mm into the periodontal pocket. For antimicrobial agents to be effective, the concentration of the drug should be adequate at the site and also there should be prolonged drug microbial contact.[6]

In order to overcome the drawbacks associated with systemic and conventional mode of therapy, local drug delivery systems were developed, which is used in this study.[7]

The antimicrobial agents used as local drug delivery agents include tetracycline, ofloxacin, clindamycin, chlorhexidine, etc. Tetracycline as well its derivatives doxycycline and

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minocycline are the most commonly used antimicrobial agents in the treatment of periodontal infections. Tetracycline also binds to the root surfaces and can be released in active form over extended periods of time. The sub-lethal concentration of tetracycline reduces adherence and co-aggregation properties of a number of disease associated bacteria including P. gingivalis and P. intermedia.[8-10]

Tetracyclines are semi-synthetic chemotherapeutic agents which are bacteriostatic in action and hence are effective against rapidly multiplying bacteria. Tetracycline have been incorporated into a variety of delivery systems (nonresorbable or bioresorbable) for insertion into periodontal pockets. These include hollow fibers (Goodson et al., 1979), ethylene vinyl acetate copolymer fibers (Goodson et al., 1983), ethyl cellulose fibers (Friedman and Golomb, 1982), acrylic strips (Addy et al., 1982), collagen preparations (Minabe et al., 1989), and hydroxypropyl cellulose films (Noguchi et al., 1984).[11]

Recently, a new local drug delivery system, Periodontal Plus AB, which contains 25 mg pure fibrilar collagen with approximately 2 mg of evenly impregnated tetracycline hydrochloride (Advanced Biotech Products, Chennai, India) have been introduced for the treatment of gingival and periodontal diseases.[11]

The present three month study was designed to reduce the surgical intervention in the treatment of periodontal pocket and to use locally available material so as to reduce the financial burden on the patient and thereby making cost effective management.

Since there are limited microbiological studies conducted to evaluate the efficacy of tetracycline fibers as a local drug therapy, the study has been taken up to evaluate the efficacy of locally delivered tetracycline fibers (Periodontal AB Plus) in conjuction with scaling and root planing in the treatment of chronic periodontitis in the patients who are not willing to undergo periodontal flap surgery.

MATERIAL AND METHODS

The present study was a randomized clinical trial with split mouth design in which a total no.of 35 patients who were diagnosed with generalized chronic moderate periodontitis, consisting of both genders (Male : Female =16 : 19), aged between 25 to 60 years were selected from the outpatient department of periodontics, Rama dental college hospital and research centre, Kanpur.

The study was performed for a period of 3 months, and the patients were selected under the following criteria.

Inclusion criteria

1. Patients diagnosed as generalized chronic periodontitis.
2. Patients having
   A. two contra-lateral sites with ≥ 5 mm periodontal pocket with active lesion, and radiographic evidence of bone loss
   B. Clinical attachment loss ≥ 3 – 5 mm at the base line,
3. Patients who had not undergone any surgical or nonsurgical periodontal therapy in the past 6 months, and patient who are not willing for surgical therapy.
4. Patients able to follow verbal or written oral hygiene instructions.

Exclusion criteria

1. Patients who had taken antibiotic therapy in the past 6 months.
2. Patients with a history of using antimicrobial mouthrinses within 2 months of the baseline visit or on routine basis.
3. Patients having history of allergy to tetracycline
4. Pregnant woman and lactating mothers.
5. Patients with periodontal pockets in which the depth of the pockets corresponded to the apex of the tooth as in probable endodontic-periodontic conditions.
6. Medically compromised patients.
7. Teeth with furcation involvements.
8. Known smokers and smokeless tobacco.

Thirty five patients with a total of 70 sites who were diagnosed with generalized chronic periodontitis were selected. These selected sites were randomly divided into test group and control group.

Test group - included 35 sites that were selected for the placement of Periodontal Plus AB; Tetracycline fibers (local drug delivery) after scaling and root planing.

Control group - included 35 sites that were treated with scaling and root planing alone (without local drug delivery).

Clinical examination for the base line parameters were done after obtaining written consent from each patient who had participated in the study. The ethical clearance obtained from ethical committee of Rama dental college, hospital and research centre, Kanpur.

Clinical parameters

Sulcular Bleeding Index (Muhlemann and Sons 1971) were evaluated at base line, 1 month and 3 months post-therapy.

Soft tissue parameters

Soft tissue changes were evaluated by measuring

- Reduction in Interproximal probing pocket depth, at base line, 30 day and 3 months
- Gain in Interproximal Clinical attachment level. at base line, 30 day and 3 months

The measurement were taken using UNC -15 probe and fixed reference point (occlusal stent).

- **Interproximal Probing pocket depth** was recorded pre-operative by noting the distance from Gingival margin to the base of pocket.

Probing pocket depth = {Reference point (RP) to base of pocket (BOP) – Reference point (RP) to Gingival margin (GM)}

Probing depth measurement was done from gingival margin to the base of pocket using UNC-15 graduated probe at baseline, 30 days, and 3 months post-therapy.

Clinical attachment level = {Reference point (RP) to base of pocket (BOP) – Reference point (RP) to Cemento-enamel junction (CEJ)}

Microbiological study for total colony count

Anaerobic culture was done to compare the total colony forming unit before and after the treatment. For the collection of subgingival samples the selected sites were isolated using cotton rolls. Sterile absorbable paper points (size 45–75) were used for the collection of plaque samples.

Total Anaerobic bacterial count was measured by colony counter.

Tetracycline fibers (Periodontal Plus AB)

The product contains 25 mg pure fibrilar collagen, containing approximately 2 mg of evenly impregnated tetracycline HCl. Periodontal Plus AB Fibers are available in strips containing four individually packed and separable sterile product packs. Just before placement, fibers was soaked with saline in a sterile dappen dish. Soaked fibers was placed at the prepared site and gently pushed inside the pocket, so that the material fills the depths and curves of the pocket. The site was sealed with coe-pak to prevent ingress of oral fluids and to prevent the dislodgement of fiber.

RESULT

As shown in table -1, at base line plaque score showed no statistically difference ($p = 0.101$) between control and test group. Also after 30 days there was no significant difference in the mean plaque score between test and control group ($p = 0.749$). However at 90 days, there was a significant difference between test and control group ($p < 0.001$), with greater improvement in the test group.

At base line gingival index score showed no statistically difference ($p = 0.101$) between control and test group. After 30 days there was significant difference in the mean plaque score between test and control group ($p = 0.106$). However at 90 days, there was a greater significant difference between test and control group ($p < 0.006$), with greater improvement in the test group.

At base line mean sulcular bleeding score showed statistically difference ($p < 0.001$) between control and test group with the test group showing more mean sulcular bleeding score. However After 30 days there was not much significant difference in the mean sulcular bleeding score between test and control group ($p = 0.106$). At 90 days, there was a greater significant difference between test and control group ($p < 0.001$), with greater improvement in the test group.

Inter group Comparison of mean values for test and control for colony forming units (log CFU showed no statistically significant difference between the control group and test group ($p > 0.001$) for total anaerobic colony count at base line. However After 30 days there was significant difference in the total anaerobic colony count between test and control group ($p < 0.001$) with more reduction for total colony count seen in test group. At 90 days,there was an increase in total colony count for both the group, but still lesser than at the base line colony count and there was a greater significant difference between test and control group ($p < 0.001$), with much less rebound in the test group.($p < 0.001$).

At base line mean probing depth showed statistically difference ($p = 0.001$) between control and test group with the test group showing more mean probing depth. Mean probing depth for the control group was 6.69 ± 0.63, whereas for test group it was 6.94 ± 0.42. However After 30 days there was much significant difference in the mean probing depth between test and control group ($p = 0.106$). At 30 days the mean probing depth for test group was reduced to 4.51 ± 0.56, in comparison to control group,in which it is reduced to 5.66 ± 0.68. At 90 days, there was a greater significant difference between test and control group ($p < 0.001$), with greater

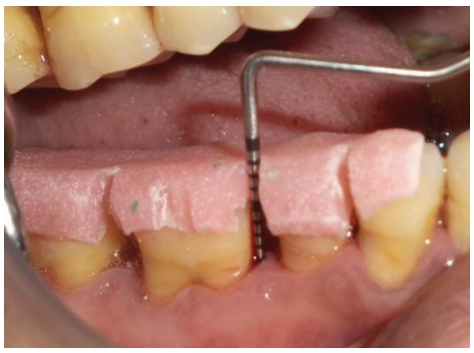

Figure-1: Test site Measuring of probing pocket depth and CAL using acrylic stent at base line.

Figure-2: Placement of Periodontal Plus AB at test site

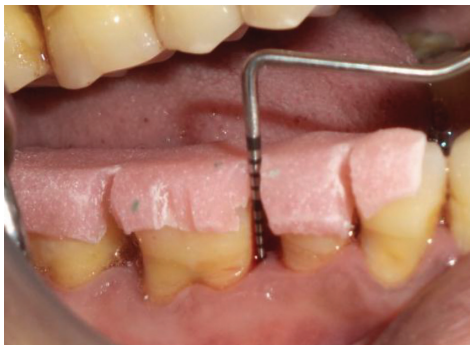

Figure-3: Measuring of probing pocket depth and CAL using acrylic stent at 3 months.

	Base line (mean ± sd)			30th day (mean ± sd)			90th day (mean ± sd)		
	Control	Test	p- value	Control	Test	p- value	Control	Test	p- value
Plaque index (PI)	2.63 ± 0.48	2.80 ± 0.36	0.101	1.29 ± 0.39	1.26 ± 0.40	0.749	1.23 ± 0.36	0.79 ± 0.53	< 0.001; sig
Gingival index (GI)	2.62 ± 0.39	2.74 ± 0.38	0.116	1.25 ± 0.67	1.09 ± 0.62	0.106	1.14 ± 0.68	0.78 ±0.45	0.006; sig
Sulcuar bleeding index (SBI)	3.47 ± 0.38	3.87 ± 0.34	<0.001; sig	2.15 ± 0.44	2.05 ± 0.46	0.090	2.28 ± 0.51	1.29 ± 0.37	< 0.001; sig
Colony forming unit (CFUs)	7.61 ± 0.07	7.63 ± 0.05		6.57 ± 0.09	3.85 ± 0.21	<0.001; sig	7.46 ± 0.07	5.65 ± 0.13	<0.001; sig
Probing depth (PD)	6.69 ± 0.63	6.94 ± 0.42	0.01	5.66 ± 0.68	4.51 ± .56	< 0.001; sig	4.71 ± 0.52	3.51 ± 0.61	< 0.001; sig
Clinical attachment loss (CAL)	6.46 ± 0.89	6.66 ± 0.73	0.051	5.90 ± 0.89	5.56 ± 0.94	0.001	5.11 ± 0.89	4.21 ± 0.38	<0.001; sig

Table-1: Intergroup comparison for test and control at base line, 30th day, and 90th day

improvement in the test group. Mean probing depth for the test group gets reduced to 3.51 ± 0.61 in comparison to control group in which it was reduced to 4,71 ± 0.52.

At base line clinical attachment level for control group was 6.46 ± 0.89, and for test group it was 6.66 ± 0.73, which was statistically significant $p < 0.051$. On 30 day clinical attachment level changes to 5.46 ± 0.89 for control group and 4.77 ± 0.94 for the test group. So the gain in clinical attachment level from base line to 30 day was 1.00 ± 0.24 for control group, whereas the gain in clinical attachment level for the test group was 1.89 ± 0.8, which was statistically significant $p < 0.001$.On 90th day, clinical attachment level changes to 4.46 ± 0.89 for control group and 3.17 ± 0.38 for the test group. So the gain in clinical attachment level from base line to 90 days was 2.00 ± 0.24 for the control group, whereas the gain in clinical attachment level for the test group was 3.49 ± 0.66, which was highly significant; $p < 0.001$. in comparison to control group.

DISCUSSION

The presence of bacterial plaque represents the principal etiological factor involved in the initiation and progression of periodontitis. These bacterial plaque or biofilms are difficult therapeutic targets as they are not easily disrupted.[12]

In a non sterile environment such as the mouth, it is virtually impossible to completely prevent their formation.[13] Essential goal of current periodontal therapy is successful management of the suspected bacterial pathogens to the extent that destruction of the periodontium is arrested. A number of different nonsurgical and surgical therapies have been successful in achieving this goal. Mechanical debridement with or without surgical manipulations, to disrupt the subgingival flora and to provide clean, smooth, and biological compatible roots surfaces, had been the therapy to treat periodontal diseases till the early 1970s. Mechanical therapy may however fail to eliminate the pathogenic bacteria because of their location within gingival tissues or in other areas inaccessible to periodontal instruments.[14]

Most widely used local drug delivery system reports in periodontal literature are of Tetracycline as reported by Goodson,[7] Metronidazole by Addy et al.[15] Chlorhexidine by Addy et al. and Ofloxacin by Hoffler et al.[16] In the present study, collagen-impregnated tetracycline fibers was used which was found to be advantageous among other drugs.

Tetracyclines are superior to other antibiotics as they are the only class of antibiotics which has the ability for retention to the tooth cementum and soft tissues. They are the only antibiotics, which can achieve higher levels of gingival fluid concentrations than serum levels.[17] Tetracycline has also been to inhibit collagenase activity, collagen degradation and bone resorption as reported by Golub et al.[18] The substantivity of tetracyclines have proved to be effective against gram-positive and gram-negative anaerobic microflora associated with chronic adult periodontitis. They exert their antimicrobial effect by inhibiting protein synthesis.[5]

Maiden et al.[19] reported that in vitro testing has shown probable periodontal pathogens including P. gingivalis, Fusobacterium nucleatum, P. intermedia, Eikenella corrodens, Wolinella recta, and A. actinomycetemcomitans are susceptible to local Tetracycline concentrations achieved in periodontal pocket with a controlled release device. Therefore, tetracycline is suitable to local delivery and as adjuncts to mechanical therapy in management of periodontal disease.

According to Betty N.A. Vandekerckhove,[22] treatment with tetracycline-impregnated fibers converted refractory sites to stable areas. The ability of locally delivered tetracycline to stop recurrent disease may be related not only to its antibacterial effect,[23] but also to its secondary effects on the collagen breakdown.[24] It also enhances Fibroblast attachment to root structure.[25] In addition, there is a substantivity of tetracycline through its binding to dentin, as proven in vitro and in vivo.

The present study was designated to access the clinical efficiency of tetracycline-impregnated bio-degradable collagen fibers, by evaluating the changes in plaque index and gingival index, sulcular bleeding index, changes in probing pocket depth and clinical attachment level. Also the changes in total anaerobic colony count was evaluated over a period of 3 months.

In the present study, statistically significant reduction in plaque score and gingival index score from baseline to 3 months for both treatment group ($P<0.001$) was observed. However better result in the reduction in plaque score and gingival index score was observed in the test group. This might be attributed to the enforced oral hygiene instruction or Howthorne phenomenon,[26] which have played a role in the reduction of the plaque score. Similar observations were made by Minabe et al.[27] Heijl et al.,[28] Mehta et al.,[5] and Friesen et al.[29] who found low levels of plaque index scores and gingival index score.

The sulcular bleeding index also showed statistically significant reduction from base line to 30 days and at 3 months in both the control and test group, however in comparison to control group, test group showed more statistically significant reduction in sulcular bleeding index. Our study is in accordance with the study conducted by Minabe and Nishimura et al[27], Heijl and Dahlen et al[28], Goodson JM and Armitage GC et al[30], Tonetti and Cortenilli et al[31], Pini Prato et al[32], D. F Kinane et al[20], Newman, Korman, Doherthy et al[4] etc.

Decrease in bleeding on probing could be attributed to the fact that these local drug delivery system maintain adequate antimicrobial drug level over a sufficient period of time. This sustained concentration of tetracyclines at very high level, greater than 1.6 mg/ml in the crevicular fluid over 10 days

Our study showed, a highly statistical significant ($P< 0.001$) reduction in probing depth from baseline to 3 months in both control and test group. On comparison between the two groups, the probing depth reduction at all time points was greater in the scaling plus tetracycline fiber group than the scaling and root planning alone group, which was statistically significant ($P<0.01$ The results are in accordance with the findings of Goodson et al.,[11] Minabe et al.[16] Newman et al.[4] Tonetti et al.[24] and Mehta et al.[5] Minabe M et al[14] observed greater reduction in probing pocket depth in tetracycline plus SRP group.

Our study reports a significant gain in clinical attachment level from baseline to 3 months in both the treated sites ($P<0.001$); On comparison between the two group, the gain in CAL at all time points was significantly greater in the scaling plus tetracycline fiber group than the scaling and root planing alone group ($P<0.01$). From base line to 3 months, mean gain in CAL was 2.45 ± 0.66 in the test group, whereas in the control group the mean gain in CAL was 1.35 ± 0.24. The percentage gain in the case of test group was 36.78% whereas in the case of control

group it was 20.89%, from base line to 3 months. Our study was in accordance to the study conducted by Goodson et al.[23] Heijl et al.[13] Minabe et al.,[22] Newman et al.,[4] Drisko et al.,[5] and Kinane and Radvar.[20] Minabe et al. found gain of clinical attachment level around 2 mm, and suggested that the local application of antibiotic using a local drug delivery in combination with root debridement may contribute to clinical attachment gain.

The reduction in probing depth and gain in CAL can be attributed to the fact that local tetracycline therapy and SRP causes the arrest of disease progression by altering the sub-gingival microbiota and to create a more healthy sub-gingival environment. In addition to the antimicrobial effects, it is possible that tetracycline fiber may have effects on the local periodontal environment. These effects may include chemical conditioning of the root surface. This concept is supported by the results of Southard et al.[10] In an experimental study with monkeys, Blomlof et al.[12] observed a New attachment on the chemically conditioned cementum surfaces. In our study, the high concentrations of tetracycline HCl over 10 days allowed clinically normal healing, achieving cliical attachment gains similar to scaling and root planning or even better than scaling and root planing. Another explanation may be that the tetracycline fiber affects the host response[15] via the anti-collagenase activity of tetracycline. Terranova et al.[22] reported that tetracycline treatment of root surfaces markedly enhanced binding of fibronectin and fibroblasts. It was also noted that pre-conditioning of root surfaces with tetracycline HCl enhanced the migration of periodontal ligament cells.

Present study reports sites receiving SRP + Periodontal Plus AB (tetracycline) and sites receiving SRP alone exhibited similar total colony count at base line. At 21 day post treatment there was a statistically significant reduction in the total anaerobic colony count in both the test and control group; $p < 0.001$; with more statistically significant reduction observed in the test group. From base line to 21 days, the mean reduction in total anaerobic colony count was (3.78 ± 0.21) in the case of test group, whereas it was (1.04 ± 0.10) for the control group. More statistically significant reduction observed in the test group at 21 days, compared with the control for total anaerobic colony count, proves the efficacy of the drug tetracycline fiber as an antimicrobial agent. However the total anaerobic colony count showed a significant increase from 21 days to 3 months in both the groups, but less significant increase in total count in the test group.

CONCLUSION

Within the limits of this study and on the basis of the clinical and microbiological parameters, it can be concluded that tetracycline fiber therapy enhances the benefits of SRP in the treatment of chronic periodontitis. There was greater improvement in all the clinical signs of priodontitis and also significant reduction in anaerobic colony count as compared to scaling and root planing alone. The adjunctive benefit of the fiber was maintained for 3 months following therapy without additional fiber treatment. SRP and locally delivered tetracycline therapy are completely different treatment modalities that work by different mechanisms. Locally delivered tetracycline therapy has a specific purpose, to control localized infection, whereas scaling is utilized to remove calculus and other deposits. Hence, a combination of scaling and local drug delivery results in added benefits in the control of periodontal disease.

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