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Clinical Evaluation of Locally Delivered 10% Doxycycline Hyclate Gel as An Adjunct to Scaling and Root Planing in the Treatment of Chronic Periodontitis

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ABSTRACT

To evaluate and compare the efficacy of locally administered 10 % doxycycline hyclate gel and scaling and root planing (SRP) in the treatment of chronic periodontitis. Randomized, controlled study was conducted involving 64 treatment sites in 32 patients suffering from chronic periodontitis. The selected two sites in each subject were randomized to two treatment groups: Group A – SRP + placement of 10% doxycycline gel immediately, and Group B – SRP alone. The gingival index (GI), plaque index (PI), probing pocket depth (PPD), and clinical attachment level (CAL) were recorded at baseline and subsequently after 1 month and 3 months. Significant improvement in GI and PI values in all the subjects were observed at 1 and 3 months ($p<0.001$) from baseline. Reductions in PPD values in Group A and Group B were significant ($p <0.001$) from baseline to 3 months, but was statistically non significant in Group B from 1 month to 3 months. Gain in CAL from baseline to 3 months was significant in both the groups ($p<0.001$), and was non significant ($p =0.365$) in Group B from 1 month to 3 months. On comparing Group A to Group B, reduction in PPD and gain in CAL were statistically significant ($p <0.001$) at the termination of study. SRP along with subgingival placement of doxycycline improves the clinical condition of periodontitis.

Key words: *Doxycycline hyclate, local drug delivery, periodontal therapy, randomized clinical trial, scaling and root planning.*

INTRODUCTION

Bacterial plaque represents the principal etiological factor involved in the initiation and progression of inflammatory periodontal diseases.[1,2] Therefore, one of the key elements of periodontal therapy is to achieve a significant reduction or even eradication of suspected periodontal pathogens. Regular and adequate oral hygiene combined with non-surgical mechanical debridement such as SRP and, in some instances, additional surgical therapy using access flaps have been documented to successfully arrest the progression of periodontal tissue destruction.[1]

The rationale for use of antibiotics in the management of periodontal diseases is based on the concept that conventional mechanical debridement cannot eradicate all periopathogenic bacteria from the subgingival environment, especially those inhabiting inaccessible areas. Periodontal pathogens have been detected from other intraoral sites and dentinal tubules, which are also beyond the reach of conventional mechanical therapy. Thus it appears logical to use antimicrobial agents, either systemically or locally, to suppress the remaining pathogens.

Systemic drug treatment has many adverse reactions such as toxicity, acquired bacterial resistance, drug interactions and very less drug concentration at the target site. Patient compliance is also a recognized problem.[2] Local drug delivery can avoid most of these problems by limiting the drug to its target site with little or no systemic uptake.[3]

Various antimicrobials like chlorhexidine, tetracyclines, doxycycline, minocycline, metronidazole, clindamycin and ofloxacin are available in various forms like hollow fiber systems, gel delivery systems, polymer chips and microspheres are being used as local delivery devices in the treatment of periodontitis. Out of them doxycycline has been found to contain host modulatory as well as antibacterial properties. Different studies have found beneficial effect of doxycycline along with SRP. So, it can be assumed that its 1 month delayed subgingival placement can bring further improvement in periodontal condition. In this study doxycycline was used as an antimicrobial agent.

The aim of the present study was to evaluate and compare the efficacy of locally administered 10% doxycycline hyclate gel (Atridox^{TM}, Block drug corporation, Inc., Jersey City, NJ, U.S.A.) as an adjunct to SRP by immediate subgingival placement in the treatment of chronic periodontitis.

MATERIALS & METHODS

32 subjects, between the age of 25-55 years with minimum of two sites, at least one tooth apart, probing pocket depth measuring 5-8mm, were selected from the outpatient Department of Periodontics, D.A.V. (C) Dental College and Hospital, Yamunanagar, Haryana, India. Medically compromised patients, pregnant and lactating mothers, patients receiving systemic or local antibiotic therapy and allergic to doxycycline hyclate were excluded from the study.

Study design:

A total of 64 sites were randomly divided into following 2 groups, by chit picking method:

Group A (32 sites): SRP & placement of 10% Doxycycline hyclate gel at the same time.

Group B (Control site) (32 sites): SRP alone.

Full mouth **Plaque index (P.I.)** *(Silness and Loe 1964),*[4] **Gingival index (G.I.)** *(Loe and Silness 1963),*[5] and site specific **Probing pocket depth (PPD)** and **Level of attachment (LOA**) were recorded at baseline, 1 month, and 3 months respectively using UNC–15 probe. Occlusal acrylic stent was fabricated, vertical groove was made, and following measurements were recorded from a reference point, lower border of stent, at the selected sites-

Reference point (RP) to base of the pocket (BOP).

Reference point (RP) to the gingival margin (GM)

Reference point (RP) to the cementoenamel junction(CEJ)

PPD and level of attachment were assessed as following:

1. Pocket depth: (RP to BOP) ± (RP to GM)
2. Clinical attachment level: (RP to BOP) ± (RP to CEJ).

After recording clinical parameters, scaling and root planing was done.

Preparation and placement of Doxycycline Hyclate gel

Following the manufacturer's instructions the doxycycline hyclate gel (Atridox^{TM}) (Figure-1),

having two components; vehicle and doxycycline hyclate in syringes, were mixed prior to use by coupling together (Figure-2) forming a gel.[6] The syringes were uncoupled and a cannula was attached for delivering the gel in periodontal pocket. The cannula was inserted up to base of the pocket and the gel was pushed until it reached top of the gingival margin (Figure-3). The cannula tip was withdrawn from the pocket very gently.[6]

The gel hardened within 1 to 2 minutes, during which it was packed into pocket with moistened blunt instrument.[7] Sites were covered with periodontal dressing (Coe-Pak ™, GC America Inc., Alsip, IL, U.S.A). Patients were recalled after 7 days for removal of the dressing.[8]

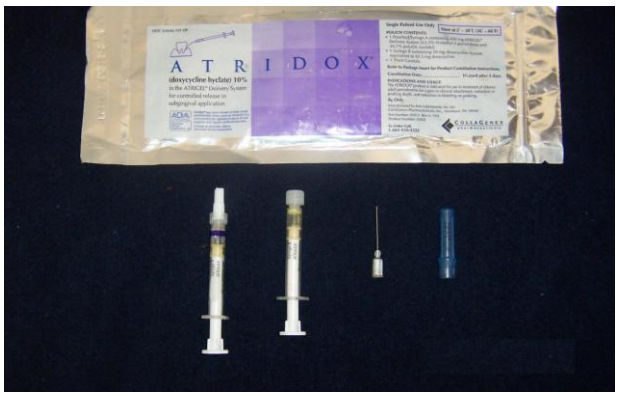

Fig. 1: 10 % Doxycycline gel and syringe A and syringe B.

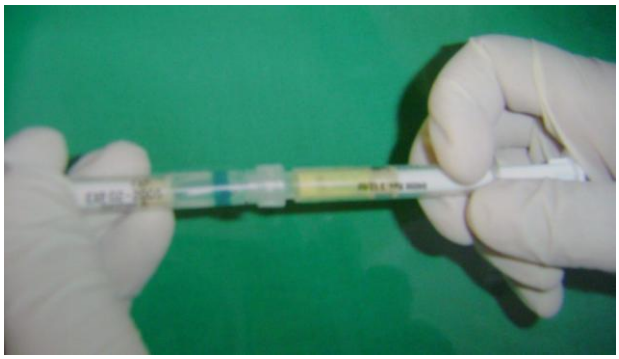

Fig. 2: syringes coupled together

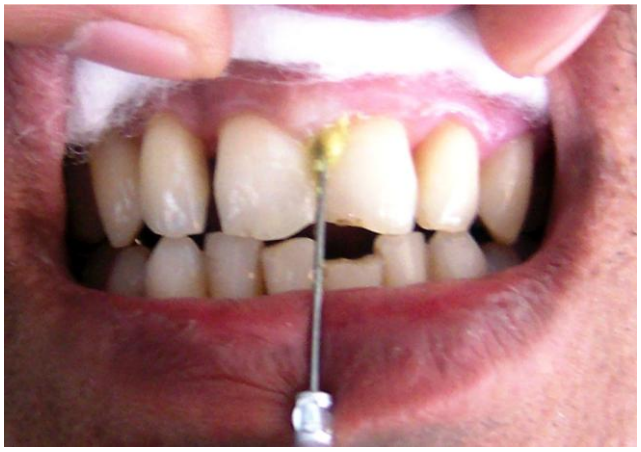

Fig. 3: Insertion of 10 % Doxycycline gel.

DISCUSSION

Elimination or adequate suppression of putative periodontopathic microorganisms in subgingival plaque is virtually impossible for the patient to achieve on their own. Highly organized subgingival bacterial plaques (biofilms) are difficult to reach, as they form the apically advancing front of periodontal pockets in close proximity to the degrading connective tissue and alveolar bone.

Different antibiotics have been used in different forms in its treatment. Doxycycline is one of them. Doxycycline is an antibiotic synthetically derived from oxytetracycline. It is bacteriostatic, inhibiting bacterial protein synthesis (30S) due to disruption of transfer RNA and messenger RNA at ribosomal sites. Doxycycline and minocycline are third generation tetracyclines which are favoured today over original tetracyclines because they offer better resorption, protein binding, diffusion into tissue structures and have prolonged action. Doxycycline, used as an adjunct to periodontal therapy due to its broad spectrum bacteriostatic

activity, could shift the potentially harmful gram-negative subgingival flora into gram positive flora which is more compatible with periodontal health.[9] The other properties of doxycycline which seem to be useful in periodontal treatment include antiproteolytic activity, anti-collagenase activity, anti-inflammatory properties to suppress PMN activity, high degree substantivity, inhibition of bone resorption and scavenging action on reactive oxygen metabolites.[9,10]

Doxycycline inhibits proteases by blocking the conversion of latent proteases into active mature forms and the activation of MMP's by chelating metal ions, reduces the activity of tissue degradation enzymes such as collagenase, gelatinase, MMP 8, and elastase, and down regulated bone resorption .[11]

High degree substantivity is one of the most important characteristics of drugs to be used as microbial plaque control.[12] Substantive effects of the tetracyclines within the periodontal pocket - adjacent tooth surface environment have been well documented.[13] The tetracyclines are known to be adsorbed to the crown and root surface through a process of demineralization / chelation[13], and they may also be absorbed into the adjacent gingival connective tissues. This latter effect could be enhanced in the case of doxycycline because it is more lipophilic than tetracycline.[13]

Hence, the present study was done to evaluate and compare the clinical efficacy of locally delivered 10% doxycycline hyclate gel when used as an adjunct to SRP, because it is a well established fact that the organized structure of biofilm can block proper diffusion or even inactivate pharmacological agents subgingivally.[14]Thus, previous biofilm removal could favour greater effectiveness of the antibiotic against subgingival pathgens, favouring the adjunctive therapy done in the present study.

In the present study two groups A and B (each containing 32 sites) were constituted to assess the effect of immediate subgingival placement of doxycycline hyclate gel over SRP. From each subject, 2 sites were selected; one for each group to eliminate the subject related confounding factors. The selected sites were at least one tooth apart to minimize the interaction of different therapy modes. Randomization can be considered to be satisfactory as there were no significant differences among the two groups in clinical parameters at baseline.

Post therapy evaluation at one and three months is done because changes in inflammation and probing pocket depth requires minimum of 30 days and maximum effect observed at 3 months.[2]

All measurements were highly standardized using a reference stent as used by *Eickholz P. et al, 2002*: *Machion L, 2004.* Reliability and reproducibility of measurements is better using occlusal stent reference (*Gibbs et al, 1988*).

All the patients showed statistically and clinically significant improvements in gingival and plaque scores at both follow up visits indicating the good oral hygiene maintenance by the patients ($p < 0.05$).

Reduction in pocket probing depth and gain of attachment in Group B are apparently due to reduction of inflammation secondary to alteration in the subgingival bacteria.[15] In addition to the elimination of local etiological factors, it has been recently proposed that scaling procedure may also elicit a local and systemic host response that would aid in eliminating local infection and promote healing.[16] In addition, the intentional and / or inadvertent removal of inflamed tissue and pocket epithelium associated with scaling and root planing would be followed by a healing phase in which new epithelial attachment and connective tissue attachment would form a regenerated periodontal support.

In Group A, the clinical reduction in probing depth was substantial and significant with a reduction of inflammation in the adjacent gingival tissues. This reduction and presence of healing in the connective tissue subjacent to the junctional epithelium has been shown to be the primary reason for reducing the probing pocket depth after non-surgical therapy.[13] The enhanced response may be, in part, related to the additional property of doxycycline to inhibit tissue collagenase activity.[13] The greater gain in clinical attachment level in this group could be attributed to the absence of bacterial challenge during critical initial phase of healing following scaling and root planing. It seems that greater reduction of pocket depth and gain in clinical attachment level could have been enhanced by the possibility of adsorption of doxycycline onto the mineralized dental structures, where it acted as a transient reservoir of doxycycline during a period of substantivity.[13]This suggests that immediate placement of doxycycline has further helped in inflammatory resolution of tissue and repopulation of bacteria.

On intergroup comparison, at 1 month, the difference in mean pocket depth reduction between Group A – Group B was 0.28 ± .99, statistically non significant. But, at the termination of the study (at 3 months) there is statistically significant reduction of 0.84 ± .98 in probing pocket depth between Group A- Group B, as compared with those obtained by scaling and root planing alone.[17] Relative gain in attachment levels was observed in Group A when compared with the pretreatment values at all time intervals. Gain in CAL from baseline to 3 months was significant in group C ($p<0.001$), but was non significant ($p =0.365$) in Group B from 1 month to 3 months. All these observations show a positive correlation between doxycycline and gain in CAL.

The most plausible explanation for such results is that the magnitude of the infection is reduced to a level where a significant reduction of inflammation results in positive clinical effects. Maintenance of the reduction of inflammation has been shown to arrest attachment loss *(Lang et al. 1986, 1990)*. This supports the observation that clinical effects seen following SRP and local delivery of doxycycline are primarily due to a change in the subgingival plaque activity and not the effect of the removal of subgingival calculus and contaminated cementum.

CONCLUSION

The present study was planned to prove the clinical benefits of adjunctive subgingival application of antimicrobials with SRP. In this study biodegradable 10% doxycycline hyclate gel was used as an adjunct to SRP and it was evaluated that 10% doxycycline hyclate gel is safe and reduced PPD non-invasively. We found statistically significant results of 10% doxycycline hyclate gel with SRP in comparison to SRP alone. Placement of 10% doxycycline hyclate can further reduce the bacterial load and improve clinical parameters. These results shows the efficacy of 10% doxycycline hyclate gel as local drug delivery system against biofilm bacteria, avoiding the adverse effects associated with mechanical instrumentation of the root surface.

In future, incorporation of antimicrobials and other local drug delivery agents into the membranes and guided tissue devices to enhance regenerative outcomes are expected to be available for clinical use.

RESULT

Plaque index:

The mean reduction in plaque score at 1 month and 3 months from baseline value (1.68 ± 0.33) was 0.99 ± 0.36 and 1.19 ± 0.33 respectively, which were significant ($p<0.05$) and reduction at 3 months from 1 month was 0.21 ± 0.08, which was also significant ($p<0.05$) (Table 1).

Table: 1 Comparison of Mean Values of Plaque Index Scores at Baseline, 1 Month and 3 Months

Time Interval	Mean ± SD	Difference from baseline	P. value	Difference From1 month	P. value
Baseline	1.68 ± 0.33				
1 Month	0.69 ± 0.09	0.99 ± 0.36	0.001		
3 Months	0.49 ± 0.09	1.19 ± 0.33	0.001	0.21 ± 0.08	0.001

Paired t-test, $P<0.05$- Significant

Gingival index:

The mean reduction in gingival score at 1 month and 3 months from baseline value (1.54 ± 0.45) was 0.89 ± 0.47 and 1.09 ± 0.44 respectively, which were significant ($p<0.05$) and reduction at 3 months from 1 month was 0.20 ± 0.11, which was also significant ($p<0.05$) (Table 2).

Table: 2 Comparison of Mean Values of Gingival Index Scores at Baseline, 1 Month and 3 Months

Time Interval	Mean ± SD	Difference from baseline	P. value	Difference from 1 month	P. value
Baseline	1.54 ± 0.45				
1 Month	0.64 ± 0.12	0.89 ± 0.47	0.001		
3 Months	0.45 ± 0.12	1.09 ± 0.44	0.001	0.20 ± 0.11	0.001

Paired t-test, P<0.05- Significant

Probing pocket depth

The mean pocket depth for Group A at baseline, 1 month and 3 months was 6.18 ± 1.20, 4.18 ± 1.02 and 3.43 ± 0.71 respectively. The mean pocket depth reductions from baseline to 1 month and 3 months were 2.00 ± 0.80 and 2.75 ± 1.31, respectively, which were significant ($p < 0.05$) and when compared from 1 month to 3 months, it was 0.75 ± 1.01, which was also statistically significant ($p<0.05$) (Table 3).

Table: 3 Comparison of Mean Values of Pocket Depth at Baseline, 1 Month and 3 Months - Group A, Group B

Group	Observation period	Mean ± S.D (in mm)	Comparison	Mean ± S.D (in mm)	t' value	P value
Group A	Baseline (BL)	6.18 ± 1.20				
	1 Month (1M)	4.18 ± 1.02	BL Vs 1M	2.0 ± .80	14.08^{S}	0.001
	3 Month (3M)	3.43 ± 0.71	BL Vs 3M	2.75 ± 1.31	11.78^{S}	0.001
			1M Vs 3M	0.75 ± 1.01	4.17^{S}	0.001
Group B	Baseline (BL)	6.03 ± 1.14				
	1 Month (1M)	4.46 ± 0.67	BL Vs 1M	1.56± 1.45	6.06^{s}	0.001
	3 Month (3M)	4.28 ± 0.80	BL Vs 3M	1.75 ± 0.91	10.81^{S}	0.001
			1M Vs 3M	0.18 ± 1.14	$.924^{NS}$	0.363

Charted value of 't' (from distribution table by Fisher & Yates) for $p < 0.05 = 2.042$

S= significant; NS= Non- significant

The mean pocket depth for Group B at baseline, 1 month and 3 months was 6.03± 1.14, 4.46 ± 0.67 and 4.28 ± 0.80, respectively. The mean pocket depth reductions from baseline to 1 month and 3 months were 1.56 ± 1.45 and 1.75 ± 0.91, respectively, which were significant ($p < 0.05$) and when compared from 1 month to 3 months, it was 0.18 ± 1.14, which was statistically non-significant ($p>0.05$) (Table 3).

On intergroup comparison the difference in mean pocket depth at baseline between Group A and B

was 0.15 ± 1.70 which was statistically non-significant (Table 4), and at 1 month, Group A showed an additional pocket depth reductions of 0.28 ± .99 over the Group B which were statistically non-significant. And at 3 months, Group A over Group B showed an additional pocket depth reduction of 0.84 ± .98, which was statistically significant (Table 4).

Table: 4 Intergroup comparison of pocket depth at different period

	Group	Mean ± SD	Comparison	Mean ± SD	t' value	P' value
Baseline	Group A	6.18±1.20				
	Group B	6.03±1.14	Group A vs Group B	0.15±1.70	0.51^{NS}	0.608
1 Month	Group A	4.18±1.02				
	Group B	4.46±0.67	Group A vs Group B	0.28±0.99	1.60^{NS}	0.119
3 Month	Group A	3.43±0.71				
	Group B	4.28±0.80	Group A vs Group B	0.84±0.98	4.83^{S}	0.001

Charted value of 't' (from distribution table by Fisher & Yates) for $p < 0.05 = 2.042$

S= significant; NS= Non- significant

Clinical attachment level

The mean attachment gains at the Group A when compared from baseline to 1 month and 3 months were 1.81 ± 0.73 and 2.37± 1.09, respectively, which were significant ($p<0.05$) and when compared from 1 month to 3 months was 0.56± 0.71, which was significant ($p<0.05$)(Table 5) again.

Table: 5 Comparison of Mean Values of clinical attachment level at Baseline, 1 Month and 3 Months - Group A, Group B

Group	Observation Period	Mean ± SD (in mm)	Comparison	Mean ± SD	t' value	P' value
Group A	Baseline (BL)	6.18 ± 1.20				
	1 month (1M)	4.37 ± 1.03	BL Vs 1M	1.81 ± 0.73	13.89S	0.001
	3 month(3M)	3.81 ± 0.64	BL Vs 3M	2.37 ± 1.09	12.21S	0.001
			1M Vs 3M	0.56 ± 0.71	4.44S	0.001
Group B	Baseline (BL)	6.06±1.15				
	1 month (1M)	5.00±0.89	BL Vs 1M	1.06±0.68	8.71S	0.001
	3 month(3M)	4.80±0.98	BL Vs 3M	1.25±0.77	8.71S	0.001
			1M Vs 3M	0.18±0.47	0.924NS	0.365

Charted value of 't' (from distribution table by Fisher & Yates) for $p < 0.05 = 2.042$

S= significant; NS= Non- significant

The mean attachment gains at the Group B when compared from baseline to 1 month and 3 months were 1.06 ± 0.68 and 1.25 ± 0.77, respectively, which were significant ($p<0.05$) and when compared from 1 month to 3 months was 0.18±

0.47, which was statistically non-significant (p >0.05).

On intergroup comparison at baseline the difference in mean clinical attachment levels between Group A and B, was 0.45 ± 0.68 which was statistically non-significant (Table 6), and at 1 month, Group A showed more improvement in clinical attachment level over Group B, 0.67 ± 0.87 which was statistically significant. And at 3 months also, Group A over Group B showed more improvement in clinical attachment level of 0.96 ± 0.94, which was statistically significant (Table 6).

Table: 6 Intergroup comparison of clinical attachment level at different time period

	Group	Mean±SD	Comparison	Mean±SD	t' value	P'value
Baseline	Group A	6.18±1.20				
	Group B	6.06±1.15	Group A vs Group B	0.45±0.68	0.52NS	0.6
1 Month	Group A	4.37±1.03				
	Group B	5.00±0.89	Group A vs Group B	0.67±0.87	4.32S	0.001
3 Month	Group A	3.81±0.64				
	Group B	4.80±0.98	Group A vs Group B	0.96±0.94	5.68S	0.001

Charted value of 't' (from distribution table by Fisher & Yates) for $p < 0.05 = 2.042$S= significant; NS= Non- significant

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