International Journal of Enhanced Research in Medicines & Dental Care, ISSN: 2349-1590
Vol. 3 Issue 7, July-2016, Impact Factor: 1.102

Clinical Evaluation of Locally Delivered Tetracycline Fibers (Periodontal Plus AB^{tm}) As an Adjunct to Non Surgical Periodontal Treatment in Patients with Chronic Periodontitis and Type Ii Diabetes

Dr. Sonia[1], Dr. (Mrs.) Vipin Bharti[2], Dr. Manoj Kumar[3], Dr. Ginnia Bhayana[4], Dr. Sonam khurana[5]

[1]MDS, Department of Periodontics
[2]Principal and Head of Department of Periodontics, Government Dental College & Hospital, Patiala-147001, (Punjab) India
[3] MBBS, Medical officer, Safidon, Jind, Haryana.
[4]MDS, Department of Prosthodontics, PGIMS Rohtak
[5]MDS, Department of oral medicine and radiology

ABSTRACT

Objective: The aims and objectives of the present study wereTo clinically evaluate efficacy of non-surgical periodontal treatment alone in type II diabetic patients with chronic periodontitis and To clinically evaluate efficacy of locally delivered tetracycline fibers (periodontal plus AB^{TM}) as an adjunct to non-surgical periodontal treatment in type II diabetic patients with chronic periodontitis.

Materials and Methods: A total of 50 patients in the age of group of 35-60 years (both male and female) with type II diabetes and suffering from chronic periodontitis with pocket depth of ≥5mm in teeth of posterior segment were selected for this randomized study design based on various inclusion and exclusion criteria. The selected subjects were randomly divided into Group I and Group II according to randomized study design.Group I- selected site treated with scaling and root planing alone. Group II - selected site treated with scaling and root planing followed by local delivery of tetracycline fibers (periodontal plus AB^{TM}). Periodontal dressing were applied on selected site in both the groups.All clinical parameters were assessed at baseline and at the end of 3 and 6 months.

Results: There was statistically significant reductions found in the plaque index score and papillary bleeding score in group I and group II from baseline to the end of 3 months and baseline to the end of 6 months. On comparison, difference in reduction of plaque index score and papillary bleeding score between group I and group II were statistically non-significant at all time intervals. There was statistically significant probing pocket depth reduction and clinical attachment gain found in group I and group II from baseline to the end of 3 months and baseline to the end of 6 months. On comparison, probing pocket depth reductionand clinical attachment gain between group I and group II, Group II showed statistically significant more probing pocket depth reduction than Group I from baseline to the end of 3 months and from baseline to the end of 6 months.

Conclusion: Within limits of the study, it may be concluded that the non-surgical periodontal therapy is effective in the management of periodontal pockets in type II diabetes patients which led to a significant reduction in plaque score, papillary bleeding score, pocket depth and gain in clinical attachment level, and adjunctive use of locally deliveredtetracycline fibers (periodontal plus AB) with non-surgical periodontal treatment demonstrated significantly better results in terms of probing pocket depth reduction and gain in clinical attachment level as compared to non-surgical periodontal treatment alone.

INTRODUCTION

Chronic periodontitis is defined as an inflammatory disease of the tooth supporting tissues that provoke progressive destruction of the periodontal ligament and alveolar bone, resulting in pocket formation, gingival recession or both. Periodontitis is a multifactorial disease, but it is an infection and bacterial species are the primary aetiologic agents. So, therapy is necessarily directed at controlling the bacterial flora associated with the periodontal disease.[1]

Diabetes mellitus (DM) is a hormonal disease characterized by changes in carbohydrate, protein, and lipid metabolisms and associated with hyperglycemia, hyperlipidemia, and associated complications. The five "classic" major complications of diabetes includesmicroangiopathy, nephropathy, neuropathy, macrovascular disease, anddelayed wound healing. Periodontitis has been recognized as the sixth complication associated with diabetes.[2]

Both diabetes and periodontitis are chronic diseases. Diabetic complications result from microvascular and macrovascular disturbances. There is a potential differences in the immunomodulatory responses to bacteria between diabetic and non- diabetic subjects. Hyperglycemia progressively leads to glycation of body proteins, forming advanced glycationend products (AGE). These AGEs, may stimulate phagocytes to release inflammatory cytokines such as TNF and IL-6 that play a central role in diabetic complications and impair the normal formation of extracellular matrix components. These alterations in diabetics have an adverse effect on periodontal tissues, especially collagen stability and vascular integrity and increasing susceptibility to tissue destruction.[3]

In Chronic Periodontitis theconventional therapy is directed towards the suppression of subgingival infections foci by mechanical debridement, such as scaling and root planing (SRP), or surgical procedures. However, with the recognition that periodontal diseases are associated with specific pathogens, interest has grown in the use of antimicrobial drugs for inhibition of these microorganisms.Antibiotics may enhance the effect of mechanical debridement procedures by reducing the recurrence rate of periodontal infection, preventing the systemic extension of infection during the acute phases of periodontitis, and restoring the equilibrium among different bacterial species harbored in the oral cavity.

The long-term use of systemic antibiotics repeatedly is filled with potential dangers, including development of resistant strains and superimposed infections, and problems such as lack of patient compliance. Therefore, the local administration of antimicrobials is a useful solution to these complications.It offers the advantages of high concentrations at the target site with reduced dosage, fewer applications, and high patient acceptability.Thus, adjunctive use of LDD may provide a beneficial response, especially in specific areas where conventional forms of therapy might fail. The local drug delivery systems are especially indicated for patients in maintenance phase, medically compromised patients who cannot undergo surgical therapy, institutionalized patients, localized refractory sites, and also in failing implants. They are also indicated prior to regenerative surgery to improve the predictability by reducing the bacterial load.[4]

The tetracyclines comprise a group of broad-spectrum antimicrobial agents that were introduced into clinical practice in the late 1940s. The proven efficacy of tetracycline group of drugs in the management of periodontitis may be related to their antibacterial action along with other additional properties which include anti-collagenase activity, inhibition of bone resorption, anti-inflammatory action and the ability of tetracyclines to promote the attachment of fibroblasts and connective tissue to root surfaces.[5] Local administration of tetracycline also helps in deposition of a layer of tetracycline on or within the epithelium of pocket walls which serve as ''barrier'' to the entry of pathogenic bacteria in the pocket wall.[6] The local drug delivery product used earlier by Goodsonwas non-resorbable ethylene/vinyl acetate copolymer fibre.[7] Recently, it is being used in the form of resorbable tetracycline fibers available as PERIODONTAL PLUS AB^{TM} (Group Pharmaceuticals Ltd, Mumbai, India. 25mg collagen fibre impregnated with 2mg Tetracycline).

Although many studies have shown advantages for using tetracycline as local drug delivery in chronic periodontitis .The use of a local delivery system as an adjunct to periodontal therapy in individuals who have a systemic disease, such as diabetes, and, who would be more susceptible to progressive periodontitis, has not been addressed much in clinical investigations. The introduction of local delivery antibiotic therapy to improve the healing response and clinical results after conservative periodontal therapy may be of great value in the treatment of diabetic patients with periodontitis.To the best of our knowledge there is no reported study on the use of locally delivered tetracycline fibers (periodontal plus AB^{TM}) in diabetic patients with chronic periodontitis.

Therefore, the purpose of present study was the clinical evaluation of locally delivered tetracycline fibers (periodontal plus AB^{TM}) as an adjunct to non-surgical periodontal treatment in patients with chronic periodontitis and type II diabetes.

MATERIALS AND METHODS

Total of 50 patients in the age group of 35-60 years (both male and female) with type II diabetes and suffering from chronic periodontitis visiting the Department of Periodontology of Govt. Dental College and Hospital, Patiala (Punjab) were selected for this randomized study design based on the following criteria.

Inclusion Criteria:

1. Well controlled type II diabetic patients based on the criterion of American diabetic association 2013 and glycated haemoglobin levels with probing depth (PD) ≥ 5 mm in teeth of posterior segment.
2. Patients without history of periodontal therapy or use of antibiotics in the preceding 6 months.
3. Patients showing cooperation for the treatment

Exclusion criteria

1. Patients with any other known systemic disease
2. Patients with known or suspected allergy to the tetracycline group or any related antimicrobials
3. Patient using any medicated toothpaste or antibacterial mouthwash
4. Patients with aggressive periodontitis, smokers and alcoholics
5. Immunocompromised patients
6. Pregnant or lactating females

All selected subjects received verbal information regarding participation, and written informed consent was obtained for participation in the study.

Material used in study:
Tetracycline:

Resorbable pure fibrillar collagen fibers 25 mg, impregnated with tetracycline hydrochloride 2 mg (Periodontal plus AB^{TM}) were used.

METHODOLOGY

All subjects selected were instructed regarding home care oral hygiene measures. These included use of soft toothbrush with conventional tooth paste by employing Modified Stillman method of tooth brushing twice daily.Only one site per selected subject i.e. the site/surface of tooth with maximum pocket depth and presence of bleeding and probing was enrolled for study. At baseline clinical parameters recorded were probing pocket depth, clinical attachment level, plaque index andpapillary bleeding index.

Study design

Full mouth supra-gingival scaling and polishing of teeth of each selected subject was done and plaque score was brought to zero. Root planing of selected site was done. The selected subjects were randomly divided into two groups:

Group 1- selected site treated with scaling and root planing alone
Group II- selected site treated with scaling and root planing followed by local delivery of tetracycline fibers (periodontal plus AB^{TM})
Periodontal dressing were applied on selected site in both the groups.

Recording and recall visits

All clinical parameters were assessed at baseline and at the end of 3 and 6 months.
The data thus collected was compiled and put to statistical analysis to arrive at the results.

RESULTS

There was statistically significant reductions found in the plaque index score and papillary bleeding score in group I and group II from baseline to the end of 3 months and baseline to the end of 6 months, while reduction in plaque index score

and papillary bleeding score from 3 months to the end of 6 months were found to be statistically non-significant. On comparison, difference in reduction of plaque index score and papillary bleeding score between group I and group II were statistically non-significant at all time intervals.[Table 1-6][Figure 1,2]

Table –1: Plaque Score (Group I)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	1.50 – 5.00	2.70±0.80
2.	3 Months	25	1.00 – 3.50	2.00±0.74
3.	6 Months	25	0.50 – 3.00	1.72±0.65

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	3.21	0.002 (<0.05)	S
Baseline to 6 Months	4.75	0.000 (<0.05)	S
3 Months to 6 Months	1.42	0.161 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table –2: Plaque Score (Group Ii)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	2.00 – 4.50	2.74±0.75
2.	3 Months	25	1.00 – 4.00	2.06±0.67
3.	6 Months	25	1.00 – 2.50	1.76±0.50

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	3.38	0.001 (<0.05)	S
Baseline to 6 Months	5.43	0.000 (<0.05)	S
3 Months to 6 Months	1.79	0.079 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 3: Comparison of Mean Change of Plaque Score between Group I and Group Ii at Different Time Intervals

Time	Group	N	Mean Change	t value	p value	Sig.
Baseline to 3 Months	I	25	0.70±0.54	0.16	0.874 (>0.05)	NS
	II	25	0.68±0.32			
Baseline to 6 Months	I	25	0.98±0.59	0.00	1.000 (>0.05)	NS
	II	25	0.98±0.49			
3 Months to 6 Months	I	25	0.28±0.25	0.23	0.817 (>0.05)	NS
	II	25	0.30±0.35			

(NS = NON-SIGNIFICANT)

Table – 4: Papillary Bleeding Index (Group I)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	0.50 – 3.50	1.99±0.81
2.	3 Months	25	0.25 – 3.25	1.44±0.81
3.	6 Months	25	0.25 – 2.75	1.23±0.71

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	2.40	0.020 (<0.05)	S
Baseline to 6 Months	3.53	0.000 (<0.05)	S
3 Months to 6 Months	0.97	0.334 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 5: Papillary Bleeding Index (Group II)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	1.00 – 3.00	2.38±0.58
2.	3 Months	25	0.25 – 2.75	1.64±0.68
3.	6 Months	25	0.50 – 2.75	1.40±0.65

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	4.14	0.000 (<0.05)	S
Baseline to 6 Months	5.62	0.000 (<0.05)	S
3 Months to 6 Months	1.27	0.208 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 6: Comparison of Mean Change of Papillary Bleeding Score between Group I and Group Ii at Different Time Intervals

Time	Group	N	Mean Change	t value	p value	Sig.
Baseline to 3 Months	I	25	0.55±0.54	1.32	0.190 (>0.05)	NS
	II	25	0.74±0.47			
Baseline to 6 Months	I	25	0.76±0.55	1.49	0.141 (>0.05)	NS
	II	25	0.98±0.49			
3 Months to 6 Months	I	25	0.21±0.20	0.49	0.624 (>0.05)	NS
	II	25	0.24±0.23			

(NS = NON-SIGNIFICANT)

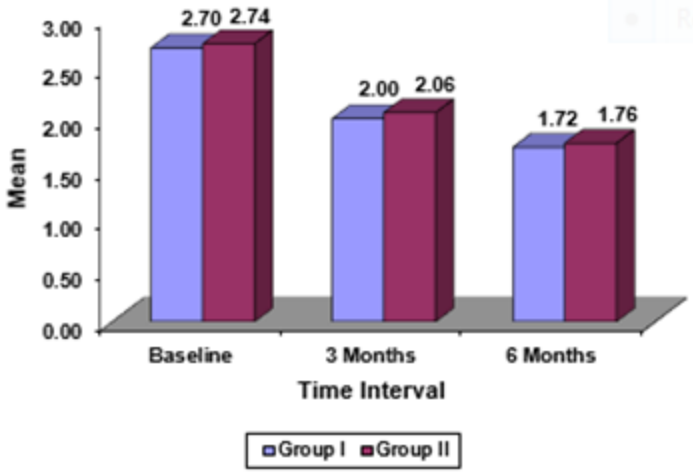

Figure-1: Mean plaque score between group I and group II at Different time Intervals

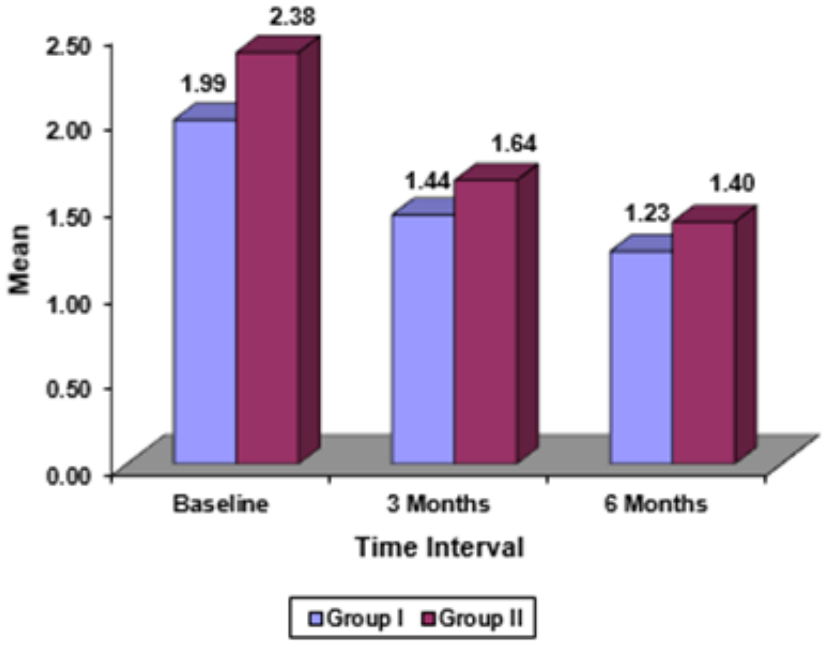

Figure-2: Mean papillary bleeding index between group I and group II at Different time Intervals

There was statistically significant probing pocket depth reduction found in group I and group II from baseline to the end of 3 months and baseline to the end of 6 months, while probing pocket depth reduction from 3 months to the end of 6 months was found to be statistically non-significant. On comparison, probing pocket depth reduction between group I and group II, Group II showed statistically significant more probing pocket depth reduction than Group I from baseline to the end of 3 months and from baseline to the end of 6 months, while probing pocket depth reduction from 3 months to the end of 6 months was found to be statistically non-significant. [Table 7-9][Figure 3]

Table – 7: Probing Pocket Depth (Group I)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	5.00 – 8.00	5.56±0.92
2.	3 Months	25	3.00 – 7.00	4.76±1.05
3.	6 Months	25	3.00 – 7.00	4.60±1.04

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	2.86	0.006 (<0.05)	S
Baseline to 6 Months	3.45	0.001 (<0.05)	S
3 Months to 6 Months	0.54	0.590 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 8: Probing Pocket Depth (Group Ii)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	5.00 – 9.00	5.96±1.06
2.	3 Months	25	3.00 – 8.00	4.44±1.00
3.	6 Months	25	3.00 – 6.00	4.12±0.73

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	5.21	0.000 (<0.05)	S
Baseline to 6 Months	7.15	0.000 (<0.05)	S
3 Months to 6 Months	1.29	0.202 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 9: Comparison of Mean Change of Probing Pocket Depth between Group I and Group Ii at Different Time Intervals

Time	Group	N	Mean Change	t value	p value	Sig.
Baseline to 3 Months	I	25	0.80±0.71	3.58	0.000 (<0.05)	S
	II	25	1.52±0.71			
Baseline to 6 Months	I	25	0.96±0.84	3.49	0.001 (<0.05)	S
	II	25	1.84±0.94			
3 Months to 6 Months	I	25	0.16±0.37	1.19	0.239 (>0.05)	NS
	II	25	0.32±0.56			

(S = SIGNIFICANT, NS = NON-SIGNIFICANT)

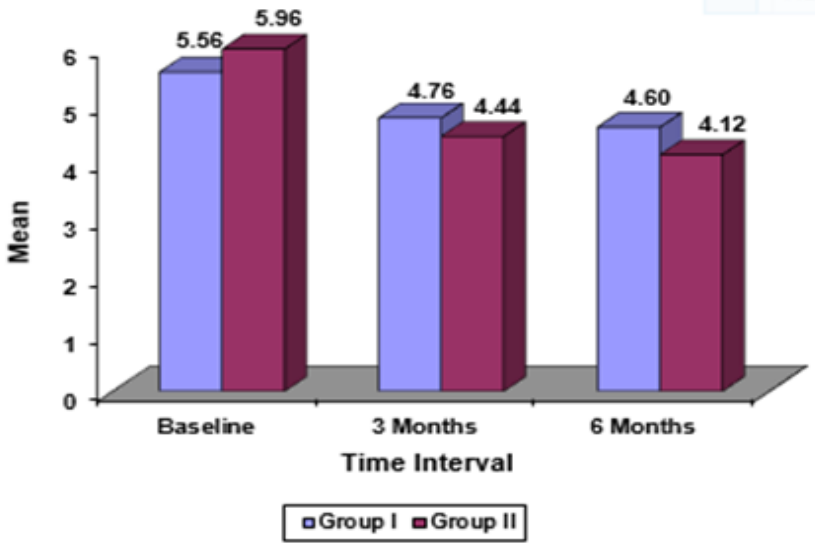

Figure-3: Mean probing pocket depth between group I and group II at different time intervals

There was statistically significant clinical attachment level gain found in group I and group II from baseline to the end of 3 months and baseline to the end of 6 months, while clinical attachment level gain from 3 months to the end of 6 months was found to be statistically non-significant. On comparison, clinical attachment level gain between group I and group II, Group II showed statistically significant more clinical attachment level gain than Group I from baseline to the end of 3 months and baseline to the end of 6 months, while clinical attachment level gain from 3 months to the end of 6 months was found to be statistically non-significant. [Table 10-12][Figure 4]

Table – 10: Clinical Attachment Level (Group I)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	4.00 – 7.00	5.32±0.99
2.	3 Months	25	2.00 – 6.00	4.64±1.04
3.	6 Months	25	2.00 – 6.00	4.56±0.96

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	2.37	0.022 (<0.05)	S
Baseline to 6 Months	2.75	0.008 (<0.05)	S
3 Months to 6 Months	0.28	0.778 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 11: Clinical Attachment Level (Group II)

S. No.	Time Interval	No. of Subjects	Range	Mean±SD
1.	Baseline	25	4.00 – 9.00	5.84±1.28
2.	3 Months	25	3.00 – 8.00	4.32±1.22
3.	6 Months	25	3.00 – 7.00	4.12±1.13

Statistical Analysis

Comparison	t value	p value	Significance
Baseline to 3 Months	4.29	0.000 (<0.05)	S
Baseline to 6 Months	5.03	0.000 (<0.05)	S
3 Months to 6 Months	0.60	0.550 (>0.05)	NS

(S – SIGNIFICANT, NS – NON SIGNIFICANT)

Table – 12: Comparison of Mean Change of Clinical Attachment Level between Group I and Group Ii at Different Time Intervals

Time	Group	N	Mean Change	t value	p value	Sig.
Baseline to 3 Months	I	25	0.68±0.63	4.42	0.000 (<0.05)	S
	II	25	1.52±0.71			
Baseline to 6 Months	I	25	0.76±0.72	4.49	0.000 (<0.05)	S
	II	25	1.72±0.79			
3 Months to 6 Months	I	25	0.08±0.28	1.20	0.232 (>0.05)	NS
	II	25	0.20±0.41			

(S = SIGNIFICANT, NS = NON-SIGNIFICANT)

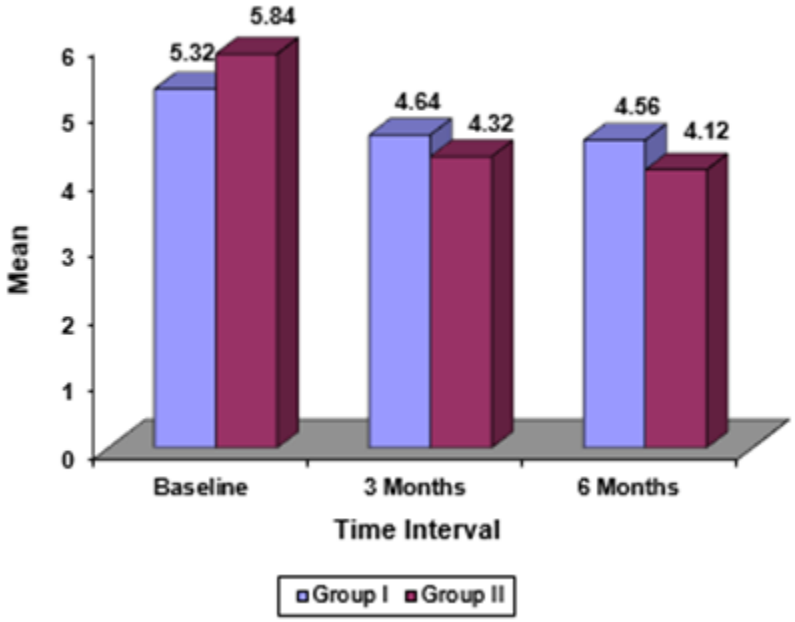

Figure-4: Mean clinical attachment level between group I and group II different time intervals

It was also observed that tetracycline fibers were well tolerated by all subjects as no unusual findings with regard to the post-operative healing as well as no sign or symptom of any adverse manifestation was elicited.

DISCUSSION

Periodontitis is an inflammatory disease of supporting tissues of the teeth caused by presence of subgingival pathogenic bacteria that co-exist in a highly organized plaque biofilm.[8] This bacterial plaque is considered to be primary etiological factor in the initiation and progression of gingival and periodontal diseases. [9]Therefore one of the key elements of periodontal therapy includes the alteration of plaque biofilm and subsequent eradication of suspected periodontal pathogens.

Diabetes is a metabolic disease that, due to disturbances in insulin production, leads to abnormal fat, sugar, and protein metabolism and resultant hyperglycemia that can ultimately induce diverse multiple system pathologies. The relationship between periodontitis and diabetes is widely accepted.[10]

Periodontitis has been identified as the sixth complication of diabetes[11]and its prevalence in type 2 diabetic patients is more than twice that of non-diabetic patients[12]. Diabetic patients display an increased severity of periodontal disease with severity being related to diabetic control but unrelated to diabetic duration[13].Both diabetes and periodontitis are chronic diseases. diabetes alters the host immuno-inflammatory responses, such as upregulation of inflammatory cell phenotype, elevation of proinflammatory cytokines, increased collagenase activity, and production of reactive oxygen species, thus enhancing the possibility of risk and prevalence of periodontitis[14].

The greatest therapeutic challenge associated with the successful treatment of periodontitis is the ability to alter or eliminate the bacteria that cause the infection. Recent research has focused on the role of topical antimicrobials in the treatment of periodontitis. By delivering the antimicrobial agent directly into the periodontal pocket, high intrasulcular drug levels can be achieved with minimum systemic exposure[7]. Compared to a systemic regimen, local delivery may offer important benefits in terms of adverse reactions and patient compliance[15]. Because of these factors, a number of local delivery systems are being developed and various active ingredients have been explored in an attempt to provide therapeutic drug levels within the periodontal pocket[16].

Various locally delivered antimicrobials have been succesfully tried in treatment of chronic periodontitis including tetracycline, metronidazole, minocycline, azithromycin etc. either on their own or in combination with scaling and root planning.

Among the number of antibiotics available for use as local drug delivery, tetracyclines have long been described as useful adjuncts in the treatment of periodontal patients, an approach based on its three perceived advantages (1) as antibiotics, tetracyclines are effective in suppressing gram negative periodontopathogenic organisms in the subgingival plaque. (2) Tetracycline fibers have been found to maintain a high concentration of tetracycline in the GCF (1300µg/ml) for 10 days (3) this antibiotic can bind to the tooth surface and then be slowly released as a still active antimicrobial. In addition tetracycline possesses a number of non- antimicrobial properties i.e. the ability to promote fibroblast and connective tissue attachment to the tooth surface which is relevant to regeneration of periodontal tissue lost during disease, anti-inflammatory property, and potential to counteract collagenolytic enzymes such as collagenase, MMP8 and elastase[17].

Although many studies have shown advantages for using local drug delivery in management of chronic periodontitis. However, the use of a local delivery system as an adjunct to periodontal therapy in individuals who have a systemic disease, such as diabetes, and, who would be more susceptible to progressive periodontitis, has not been addressed much in clinical investigations. The introduction of local delivery antibiotic therapy to improve the healing response and clinical results after conservative periodontal therapy may be of great value in the treatment of diabetic patients with periodontitis. To the best of our knowledge there is no reported study on the use of locally delivered tetracycline fibers (periodontal plus AB^{TM}) in diabetic patients with chronic periodontitis.

Therefore, the purpose of present study was the clinical evaluation of locally delivered tetracycline fibers (periodontal plus AB^{TM}) as an adjunct to non-surgical periodontal treatment in patients with chronic periodontitis and type II diabetes.

CONCLUSION

Within limits of the study, it may be concluded that the non-surgical periodontal therapy is effective in the management of periodontal pockets in type II diabetes patients which led to a significant reduction in plaque score, papillary bleeding score, pocket depth and gain in clinical attachment level, and adjunctive use of locally deliveredtetracycline fibers (periodontal plus AB) with non-surgical periodontal treatment demonstrated significantly better results in terms of probing pocket depth reduction and gain in clinical attachment level as compared to non-surgical periodontal treatment alone. This can provide a new direction in the field of periodontal treatment in this special group of patients who are at greater risk for periodontal destruction. However, long term, multicenter randomized, controlled clinical trial should be carried out to affirm the observations of our study.

REFERENCES

[1] **Pradeep AR, Bajaj P, Agarwal E, Rao NS, Naik S, Kalra N, Priyanka N:**Local drug delivery of 0.5% azithromycin in the treatment of chronic periodontitis among smokers. Australian Dental Journal 2013; 58: 34-40
[2] **Grover H, Luthra S:**Molecular mechanisms involved in the bidirectional relationship between diabetes mellitus and periodontal disease.Journal of Indian Society of Periodontology - Vol 17, Issue 3, May-Jun 2013
[3] **Martorelli de Lima AF et al:** Therapy with adjunctive doxycycline local delivery in patients with type 1 diabetes mellitus and periodontitis. J Clin Periodontal 2004; 31: 648–653 doi: 10.1111/j.1600-051X.2004.00576.x
[4] **Agarwal E et al:** Locally Delivered 0.5% Azithromycin, as an Adjunct to Non Surgical Treatment in Chronic Periodontitis With Type II Diabetes: A Randomized Controlled Clinical Trial. Journal of Periodontology; Copyright 2012 DOI: 10.1902/jop.2012.120172
[5] **Gordon JM, Walker CB, Murphy JC, Goodson JM, Socransky SS:** concentration of tetracycline in human gingival fluid after single doses. J Clinical Periodontol: 1981;8:117-121
[6] **Ciancio SG, Cobb CM, Leung M:** Tissue concentration and localization of tetracycline following site-specific tetracycline fiber therapy: J Periodontol 1992;63:849-853
[7] Goodson JM, Hogan PE, DunhamSL. Clinical responses following periodontaltreatment by local drug delivery.J Periodontol 1985; 56: 81–7.
[8] **Williams R.C., Paquette W.D., Offernbacher S, Adams F.D., Armitage C.G., Bray K:** Treatment of periodontitis by local administration of Minocycline microspheres: A controlled trial. J Periodontol 2001; 72(11): 1535-1544
[9] **Wade WG, Addy M:** In- vitro activity of Chlorhexidine containing mouth wash against subgingival bacteria. J Periodontol 1989; 60: 521-525.
[10] **Bajaj P et al:** Locally delivered 0.5% clarithromycin, as an adjunct to nonsurgical treatment in chronic periodontitis with well-controlled type 2 diabetes: a randomized controlled clinical trial .Journal of Investigative and Clinical Dentistry +--2012, 3, 276–283
[11] **Shah NH, Railkar AS, Chen FC, Tarantino R, Kumar S, Murjani M**: A biodegradable injectable implant for delivering micro and macromolecules using poly (lacticcoglycolic) acid (PLGA) copolymers. J Control Release 1993;27:139-147.
[12] **Mealey BL, Oates TW:** Diabetes mellitus and periodontal diseases. J Periodontol2006; 77: 1289-1303
[13] **Loe H:** Periodontal Disease. The sixth complication of diabetes mellitus. Diabetes Care 1993; 16: 329-3
[14] **Gadagi JS, Chava VK, Reddy VR:** Green tea extract as a local drug therapy on periodontitis patients with diabetes mellitus: A randomized case–control study Journal of Indian Society of Periodontology-vol 17,Issue 2, Mar-Apr 2013
[15] Needleman IG, Pandya NV, SmithSR, Foyle DM. The role of antibioticsin the treatment of periodontitis (Part2 – Controlled drug delivery). Eur JProsthodontRestor Dent 1995; 3:111–17.
[16] Kornman KS. Controlled release oflocal delivery of antimicrobials in periodontics – Prospects for thefuture. J Periodontol 1993; 64: 782–91.
[17] **Golub ML, Ramamurthy NS, and McNamara TF:**Tetracyclines Inhibit Connective Tissue Breakdown: New Therapeutic Implications foran Old Family of Drugs. Critical Reviews in Oral Biology and Medicine1991, 2(2):297-322