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Chlorhexidine chip and tetracycline fibers as adjunct to scaling and root planing – A clinical study

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Abstract

Aim: Prevention of periodontal disease progression is the primary goal of periodontal therapy. When conventional therapy is found inadequate to attain periodontal health in chronic periodontitis, local antimicrobial agents have been used as adjunct to scaling and root planing, producing encouraging results. Hence, a study was undertaken to evaluate clinically, the newly released sustained drugs, PerioCol™-CG (Chlorhexidine - CHX- chip) with Periodontal Plus AB™ (Tetracycline fibers). **Methods:** Patients were allocated in 3 experimental treatment groups, Group A- SRP + CHX Chip, Group B- SRP + Tetracycline fibers, and Group C- SRP alone (control group). Forty-five sites in 14 patients (9 females and 5 males) with chronic periodontitis (5-8mm probing depth), were evaluated clinically for probing depth (PD) and relative attachment level (RAL). **Results:** All the treatment groups were found to be efficacious in the treatment of periodontal disease as demonstrated by improvement in PD and RAL. **Conclusion:** Combination of SRP + CHX chip (Group A) resulted in added benefits compared to the other two treatment groups.

Keywords: Chlorhexidine chip, chronic periodontitis, tetracycline fibers.

Introduction

Chronic periodontitis results in a progressive loss of attachment and formation of periodontal pocket. The process of periodontal pocket formation represents the pathologic sequela of microbial and inflammatory mediated degradation of collagenous connective tissue and alveolar bone[1].

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]. Hence the use of several antimicrobial agents started gaining prominence as chemical aids would compensate for technical limitations and prevent early microbial recolonization, to ultimately ensure, the best chance for clinical improvements. These chemical agents may gain access into the periodontal pocket through both a systemic and local route of delivery. Since systemic use of antibiotics may cause several side effects (sensitivity, resistant strains and superinfections), contemporary research is now focused on the role of topical antimicrobial agents in the treatment of periodontitis.

Various agents have been used to prevent further progression of periodontal disease

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either as monotherapy or as an adjunct to scaling and root planing (SRP) procedure. These include tetracycline, doxycycline, minocycline, chlorhexidine[3], metronidazole[4], enzymes and quaternary ammonium compounds, which have been administered topically in pure forms by their incorporation in chewing gums, dentifrices, acrylic strips, hollow fibers, films, ointments, gels etc. It is clear that for local antimicrobial therapy to be clinically effective, successful mechanisms to deliver sustained and adequate concentration of the active agent to the periodontal pocket are required[5].

Topical antiseptics have been successfully used for treating plaque-related gingivitis, among which chlorhexidine (CHX) remains one of the most effective antimicrobials reported till now and is not known for any appreciable resistance to oral microorganisms. However, subgingival irrigation using CHX solution or CHX gels turned out to be poorly effective in the treatment of periodontitis, due to the inability to retain biologically significant concentrations of the drug for sufficient lengths of time within the confines of the periodontal pocket. However, it is difficult to maintain the effective antibacterial concentrations, for a sufficient period in periodontal pockets for a variety of reasons like poor penetration by mouth rinses, rapid dissipation of irrigation solutions, relatively low localized concentrations achievable with high systemic dose of antibiotics.

Hence, slow-release devices have been developed. There are two subtypes: "sustained release devices", delivering the drug for less than 24 h, and "controlled delivery devices" (CDDs), releasing the agent over an extended period of time.

Goodson (1989)[6] pointed out that; successful control of periodontal microflora requires a delivery of an intrinsically effective antimicrobial agent, according to the fundamental pharmacokinetic principles. These agents reach the site of action, *i.e.* the periodontal pocket, and maintain minimum effective concentration for a sufficient duration to produce the desired specific therapeutic effect.

Among the tested antibiotics, tetracyclines were the first and had their efficacy evaluated in a number of periodontal clinical studies. Tetracyclines have been incorporated into a variety of delivery systems for insertion into periodontal pockets. These include hollow fibers[7], ethylene vinyl acetate copolymer fibers[8], ethyl cellulose fibers[9], acrylic strips[5], collagen preparations[10].

Recently, a new local drug delivery system, PerioCol™-CG, which contains fibrilar collagen of fish origin with 2.5 mg (approximately) of CHX (Eucare Pharmaceuticals, Chennai, India), and another local drug, 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.

Since research with drug delivery systems is limited, the present clinical study evaluated comparatively the efficacy of two commercially available new controlled-release drugs - CHX chip (PerioCol™ -CG) and Tetracycline fibers (Periodontal Plus AB)™ - as adjunct to SRP in the treatment of chronic periodontitis.

Material and methods

Forty-five bleeding sites, with a probing depth 5-8mm, were selected in 14 patients of both genders (9 females and 5 males) aged between 20 to 50 years from the Outpatient Department of Periodontics at Sardar Patel Postgraduate Institute of Dental and Medical Sciences, Lucknow, Uttar Pradesh, India.

The Ethical committee of Sardar Patel Postgraduate Institute of Dental and Medical Sciences, Lucknow, Uttar Pradesh, India, approved the study and written informed consent was obtained from all patients. Patients with good systemic health, patients who had not received any surgical or non-surgical periodontal therapy in the past 6 months, who had not received antibiotic therapy in the past 6 months, who were diagnosed as suffering from chronic generalized periodontitis, and patients who had periodontal pocket measuring 5-8mm in different quadrants were enrolled. Individuals with history of using anti-microbial mouthrinses within 2 months of the baseline visit or on routine basis or patients having a history of allergy to tetracycline; CHX or lidocaine, were excluded from the study.

The selected sites were randomly divided into 3 groups: Test Group A (SRP + CHX Chip) – Included 15 sites treated by SRP with chlorhexidine chip. Test Group B (SRP + Tetracycline Fibers) - Included 15 sites treated by SRP with tetracycline fibers. Test Group C (SRP alone) - Included 15 sites treated with SRP alone.

The clinical parameters recorded are the probing depth (PD) using UNC-15 periodontal probe and relative attachment level (RAL) using customized acrylic stent (Figure 1). After recording clinical parameters from each site at baseline, a thorough SRP was done, in all the 3 groups. The clinical parameters were assessed at baseline, after 1 month and 3 months after receiving all the 3 treatments in a same patient; as it is a split-mouth study.

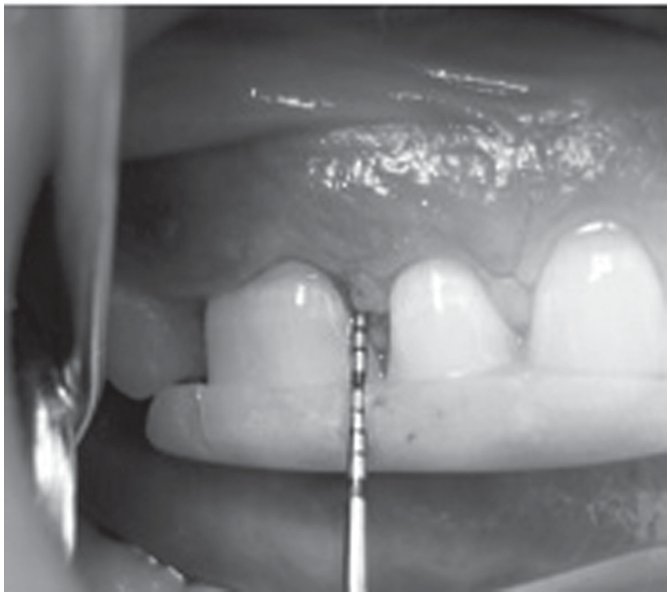

Fig.1. Measurement of probing depth and relative attachment level.

Chlorhexidine chip (PerioCol™- CG) (Figure 2)

PerioCol – CG is a small, orange-brown in a rectangular chip form (rounded at one end) for easy insertion into periodontal pockets. Size of the chip is 4 x 5mm and thickness is 0.25-0.32mm and 10 mg weight. Each chip contains approximately 2.5 mg of CHX in a biodegradable matrix of fibrilar collagen of fish origin (Eucare Pharmaceuticals, Chennai, India).

Tetracycline fibers (Periodontal Plus AB™) (Figure 3)

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.

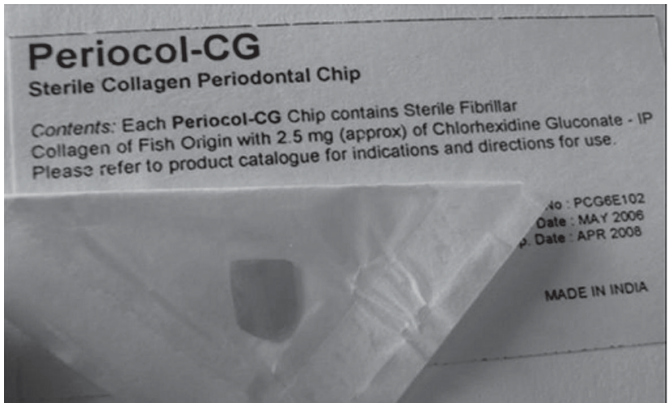

Fig. 2. Chlorhexidine chip (PerioCol™- CG).

Fig. 3. Tetracycline fibers (Periodontal AB Plus™).

Administration (Figures 4 and 5)

Subgingival administration of chlorhexidine chip was accomplished by inserting the round end of the chip directly into the base of the pocket. Chip was pressed apically so that it rest subgingivally at the base of the pocket. Whereas, soaked Tetracycline fibers were inserted into the base of the periodontal pocket. Gentle force was used with straight probe, so that the material fills the depths and curves of the pocket.

The gingiva was subsequently and carefully adapted to close the entrance of the gingival margin and hand pressure was applied for just a few minutes to encourage hemostasis and initial setting of the material inside the pocket. The gingival margin was sealed with Coe-pak to prevent the dislodgement of the drug and to prevent the ingress of oral fluids.

Both these drugs degrade within 7-10 days after insertion. Patients were recalled after 7 days for Coe-pak removal and were evaluated for any inflammatory response.

Patients were instructed not to chew any hard, crunchy or sticky food for at least 1 week, postpone brushing and flossing on the treated site for 1weeek, not to disturb the area with tongue, finger or tooth pick, and to report immediately if the material is dislodged before the scheduled recall visit or if pain, swelling or any other problem occurs.

The results were averaged out for each parameter. Values are depicted as mean ± SD. For comparisons between different time intervals paired t-test were used. T test for independent samples were used for intergroup comparisons at the different time intervals, The confidence level of the study was kept at 95% and hence a 'p' value <0.05 was considered as significant. Paired t-test and Student's t-test were used to evaluate and establish differences between baseline, 1 month and 3 months values.

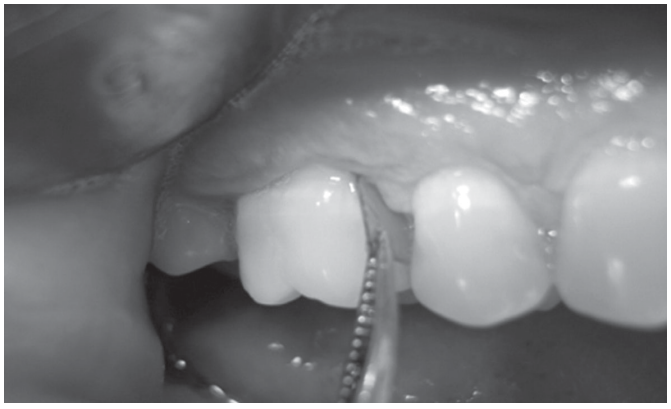

Fig. 4. Placement of chlorhexidine chip

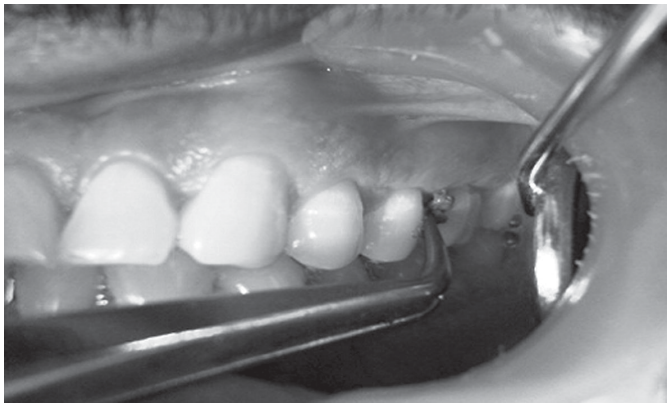

Fig. 5. Placement of tetracycline fibers

Results

Results are presented in Tables 1 to 3. The recording of all the clinical parameters was done at baseline and after 1 month and 3 months. Finally, the complete data were statistically analyzed.

None of the subjects reported any oral symptoms at any time during the trial such as toothache (including dental or gingival), painful symptomatology (including oral pain, tenderness, soreness, discomfort or sensitivity), inflammation, allergy, abscess, altered taste or increased salivation, etc.

Probing Depth

From baseline to 3 months, Group A (SRP +CHX Chip) had significantly higher mean percentage reduction as compared to Group B (p=0.007) as well as Group C (p<0.001). These findings were similar to that of previous studies[11-15].

Relative Attachment Level

From baseline to 3 months Group A (SRP +CHX chip) had significantly higher mean percentage gain as compared to Group B (p=0.046) as well as Group C (p=0.001). These findings were similar to that of other authors[16-20], who studied the changes in probing depth following 2 years of periodontal maintenance therapy including adjunctive controlled release of biodegradable CHX chip.

Table 1. Probing depth values (in mm).

Group A (CHX Chip + SRP)			Group B (TTC Fibers + SRP)			Group C (SRP alone)		
Baseline	1 month	3 months	Baseline	1 month	3 months	Baseline	1 month	3 months
8.00	6.00	3.00	7.00	5.00	4.00	7.00	6.00	5.00
7.00	5.00	3.00	8.00	6.00	4.00	6.00	5.00	5.00
7.00	6.00	4.00	7.00	6.00	6.00	5.00	4.00	4.00
6.00	6.00	5.00	8.00	7.00	5.00	6.00	5.00	5.00
6.00	4.00	3.00	8.00	5.00	4.00	6.00	4.00	4.00
7.00	4.00	3.00	7.00	4.00	3.00	7.00	6.00	5.00
8.00	5.00	3.00	8.00	6.00	4.00	7.00	5.00	5.00
8.00	5.00	4.00	8.00	5.00	4.00	7.00	5.00	4.00
8.00	6.00	5.00	6.00	5.00	4.00	5.00	4.00	4.00
6.00	4.00	3.00	7.00	5.00	5.00	5.00	4.00	5.00
8.00	6.00	4.00	5.00	4.00	4.00	6.00	4.00	5.00
5.00	4.00	3.00	6.00	5.00	5.00	6.00	5.00	5.00
6.00	4.00	3.00	7.00	6.00	6.00	5.00	4.00	3.00
8.00	6.00	5.00	8.00	6.00	4.00	6.00	5.00	5.00
8.00	5.00	4.00	7.00	5.00	3.00	6.00	4.00	5.00

Table 2. Relative attachment level values (in mmm).

Group A (CHX Chip + SRP)			Group B (TTC Fibers +SRP)			Group C (SRP alone)		
Baseline	1 month	3 months	Baseline	1 month	3 months	Baseline	1 month	3 months
12.00	8.00	6.00	11.00	8.00	8.00	10.00	7.00	7.00
11.00	7.00	6.00	12.00	8.00	7.00	9.00	7.00	6.00
11.00	7.00	7.00	10.00	8.00	7.00	8.00	6.00	7.00
10.00	7.00	5.00	11.00	8.00	8.00	9.00	7.00	6.00
10.00	9.00	8.00	11.00	9.00	8.00	10.00	8.00	8.00
11.00	8.00	8.00	12.00	9.00	8.00	11.00	9.00	9.00
11.00	6.00	6.00	11.00	7.00	7.00	10.00	7.00	7.00
11.00	7.00	6.00	11.00	7.00	6.00	9.00	6.00	6.00
12.00	7.00	7.00	8.00	6.00	6.00	7.00	6.00	5.00
10.00	8.00	7.00	9.00	7.00	7.00	8.00	6.00	6.00
12.00	9.00	8.00	9.00	7.00	6.00	8.00	6.00	6.00
9.00	7.00	6.00	10.00	7.00	7.00	9.00	8.00	8.00
10.00	8.00	6.00	10.00	8.00	8.00	8.00	7.00	7.00
11.00	8.00	7.00	11.00	7.00	7.00	9.00	7.00	6.00
11.00	8.00	6.00	11.00	8.00	7.00	10.00	8.00	6.00

Table 3. Post treatment clinical changes and comparison between the 3 groups

Measurement	Groups	0-1 month	0-3 months
Probing depth(in mm)	Group A	2.000±0.795	3.400±0.995
	Group B	1.803±0.716	2.803±1.231
	Group C	1.340±0.489	1.400±0.754
Significance		p < 0.01 Sig.	p < 0.01 Sig.
Relative attachmentlevel	Group A	3.200±1.099	4.200±1.214
(Gain) (in mm)	Group B	2.866±0.788	3.333±0.821
	Group C	2.000±0.605	2.334±1.000
Significance		p < 0.01 Sig.	p < 0.01 Sig.

Discussion

A periodontal disease essentially comprises of a group of oral infections, whose primary etiological factor is dental plaque, which results in an inflammatory lesion in the supporting tissues. Removal of the cause (and its effects) is the primary aim of both non-surgical and surgical treatment regimens. The major non-surgical therapeutic approach involves mechanical SRP. The infective nature of the disease has lead to the widespread use of antimicrobials, as an adjunct to SRP.

Local delivery of controlled release antimicrobials has some advantages over the systemic route, including the high local drug levels in the periodontal pockets and avoidance of drug compliance issues. In the present study, an attempt was made to evaluate effectiveness of CHX chip (PerioCol™- CG) and tetracycline fibers (Periodontal AB Plus™), in the treatment of chronic periodontitis, as an adjunct to SRP. CHX and tetracycline were chosen in the present study, because of their proven efficacy in the management of periodontal diseases. Tetracycline is known for its antibacterial actions and also due to number of additional properties that have been recently identified. These include colagenase inhibition, anti-inflammatory actions and inhibition of bone resorption.

CHX is a widely used broad-spectrum antimicrobial agent, encompassing gram-positive and gram-negative bacteria, yeasts,

dermatophytes and some lipophilic viruses. The antibacterial mode of action is explained by the fact that the cationic CHX molecule is rapidly attracted by the negatively charged bacterial cell surface. After adsorption, the integrity of the bacterial cell membrane is altered, which results in a reversible leakage of bacterial low molecular-weight components at low dosage or more severe membrane damage at higher doses (bactericidal). Tetracycline-HCl is a bacteriostatic agent that inhibits bacterial protein synthesis and, as such, requires a significantly longer exposure time for bacterial damage than, for example, metronidazole or CHX. It however, has the ability to bind to the hard tissue walls of pockets to establish a drug reservoir.

The crux of the present study clearly shows that, the locally delivered CHX chip (PerioCol™-CG) along with mechanical debridement resulted in a clinically meaningful improvement of all clinical parameters, which was maintained significant throughout the study duration.

In order to be effective, a pharmaceutical agent should reach the entire periodontal pocket up to the bottom and should be maintained long enough at a sufficient concentration for the intended pharmaceutical effect to occur. Periodontal pockets, however, possess complicating anatomic characteristics. Furthermore, periodontal pathogens in the subgingival environment reside in a biofilm adhering to the exposed root cementum or to the soft tissue, or even invading the pocket epithelium, the underlying connective tissue or the root dentin. The aggregation of bacteria in a biofilm impairs the diffusion or may even inactivate antimicrobial agents. Thus, high concentrations of antimicrobial agents are needed before a beneficial effect can be expected. Various biofilm experiments indicate that the necessary minimum inhibitory concentrations (MIC) of antimicrobial agents, are at least 50 times higher (or even 210,000 times), than for bacteria growing under planktonic conditions[21-23].

Moreover, the minimum contact time for an antimicrobial agent to be active depends on the mechanism by which the agent inhibits or destroys target bacteria. CHX (which kills microorganisms by compromising the integrity of the cell membrane) and povidone-iodine (which kills bacteria on contact) require a shorter exposure time than, for example, a bacteriostatic agent, such as tetracycline, which inhibits protein synthesis[23].

However, the substantivity of a topically applied agent is increased spontaneously, if it binds to the soft and/or hard tissue surfaces within the pocket. CHX has the advantage of prolonged supragingival substantivity, because it can bind to the intraoral soft and hard tissues[24]. Ciancio et al.[25], reported that tetracycline applied via TTC-fibers does not penetrate into the gingiva a significant distance to kill or suppress tissue invasive organisms, such as A. actinomycetemcomitans.

Besides the pharmacokinetics, the patient's comfort, ease of placement of the drug into the periodontal pocket and the cost-benefit ratio are key elements for determining the selection and efficacy of a product.

The results from the present study suggest that the application of CHX chip combined with SRP is beneficial in the treatment of chronic periodontitis and improving periodontal parameters for 3 months duration. In spite of the proven additive benefits, the availability and costs associated with controlled delivery devices have so far limited their application. However, as this material i.e. PerioCol™- CG (CHX chip) is of Indian origin, easy to place in periodontal pocket, less time consuming and is relatively cost effective, its use can be expanded easily in Indian population.

References

1. Drisko CL, Cobb CM, Killoy WJ, Michalowicz BS, Pihlstrom BL, Lowenguth RA et al. Evaluation of periodontal treatment using controlled release tetracycline fibers: clinical response. J Periodontol. 1995; 66: 692-9.
2. Slots J, Rams TE. Antibiotics in periodontal therapy: Advantages and disadvantages. J Clin Periodontol. 1990; 17: 479-95
3. Cetin EO, Buduneli N, Atlihan E, Kirilmaz L. In vitro studies on controlled-release cellulose acetate films for local delivery of chlorhexidine, indomethacin, and meloxicam. J Clin Periodontol. 2004; 31: 1117-21.
4. Kaner D, Bernimoulin J-P, Hopfenmuller W, Kleber B-M, Friedmann A. Controlled-delivery chlorhexidine chip versus amoxicillin/ metronidazole as adjunctive antimicrobial therapy for generalized aggressive periodontitis: a randomized controlled clinical trial. J Clin Periodontol. 2007; 34: 880-91.
5. Addy M, Rawle L, Handley R, Newman HN, Coventry JF. The development and in-vitro evaluation of acrylic strips and dialysis tubing for local drug delivery. J Periodontol. 1982; 53: 693-9.
6. Goodson JM. Pharmacokinetic principles controlling efficacy of oral therapy. J Dent Res.. 1989; 68: 1625-32.
7. Goodson JM, Haffajee A, Socransky SS. Periodontal therapy by local delivery of tetracycline. J Clin Periodontol. 1979; 6: 83-92.
8. Goodson JM, Holborow D, Dunn RL, Hogan P, Dunham S. Monolithic tetracycline containing fibers for controlled delivery to periodontal pockets. J Periodontol. 1983; 54: 575-9.
9. Friedman M, Golomb G. New sustained release dosage form of chlorhexidine for dental use. 1. Development and kinetics of release. J Periodont Res. 1982; 17: 323-8.
10. Minabe M, Takeuchi K, Tamura T, Hori T, Umemoto T. Subgingival administration of tetracycline on a collagen film. J Periodontol. 1989; 60: 552-6.
11. Jeffcoat MK, Bray KS, Ciancio SG, Dentino AR, Fine DH, Gordon JM et al. Adjunctive use of a subgingival controlled-release chlorhexidine chip reduces probing depth and improves attachment level compared with scaling and root planing alone. J Periodontol. 1998; 69: 989-97.
12. Killoy WJ. Assessing the effectiveness of locally delivered chlorhexidine in the treatment of periodontits. J Am Dent Assoc. 1999; 130: 567-90.
13. Heasman PA, Heasman L, Stacey F, McCracken GI. Local delivery of chlorhexidine gluconate (PerioChipTM) in periodontal maintenance patients. J Clini Periodontol. 2001; 28: 90-5.
14. R. Mythili, T. Ramakrishnan, Biju Mammen. Effect of controlled-release device containing chlorhexidine gluconate in the treatment of adult periodontitis – A clinical and microbiological study. J Ind Soc Periodontol. 2006; 10: 321-4.
15. Ronald HW Cheng, W. Keung Leung, Esmonde F. Corbet. Non-surgical periodontal therapy with adjunctive chlorhexidine use in adults with Down Syndrome. A prospective case series. J Periodontol. 2008; 79: 379-85.
16. Soskolne WA, Proskin HM, Stabholz A. Probing depth changes following 2 years of periodontal maintenance therapy including adjunctive controlled release of chlorhexidine. J Periodontol. 2003; 74: 420-7.
17. Chen YT, Hung SL, Lin LW, Chi LY, Ling LJ. Attachment of periodontal ligament cells to Chlorhexidine loaded guided tissue regeneration membranes. J Periodontol. 2003; 74: 1652-59.
18. Juliana Carvalho, M. John Novak, LF Mota. Evaluation of the effect of subgingival placement of chlorhexidine chips as an adjunct to scaling and root planing. J Periodontol. 2007; 78: 997-1001.
19. Paolantonio M, D'Angelo M, Grassi RF, Perinetti G, Piccolomini R, Pizzo G et al. Clinical and microbiologic effects of subgingival controlled release delivery of chlorhexidine chip in the treatment of periodontitis : a multicenter study. J Periodontol. 2008; 79: 271-82.
20. Mizrak T, Guncu GN, Caglayan F, Balci TA, Aktar GS, Ipek F. Effect of a controlled release chlorhexidine chip on clinical and microbiological parameters and prostaglandin E2 levels in gingival crevicular fluid. J Periodontol. 2006; 77: 437-43.
21. Rodrigues IF, Machion L, Casati MZ, Nociti FH Jr, de Toledo S, Sallum AW, Sallum EA. Clinical evaluation of the use of locally delivered chlorhexidine in periodontal maintenance therapy. J Periodontol. 2007; 78: 624-8.
22. Iyad Hussein, Meena Ranka, Angela Gilbert and Kevin Davey. Locally delivered antimicrobials in the management of periodontitis: a critical review of the evidence for their use in practice. Dent Update. 2007; 34: 494-506.
23. Quirynen M, Teughels W, De Soete M, van Steenberghe D. Topical antiseptics and antibiotics in the initial therapy of chronic adult periodontitis: microbiological aspects. Periodontol 2000. 2002; 28: 72-90.
24. Bonesvoll P, Gjermo P. A comparison between chlorhexidine & some quaternary ammonium compounds with regard to retention, salivary concentration & plaque inhibiting effect in human mouth after mouth rinses. Arch Oral Biol. 1978; 23: 289-94.
25. Ciancio SG, Cobb CM, Leung M. Tissue concentration and localization of tetracycline following site specific tetracycline fiber therapy. J Periodontol. 1992; 63: 849-53.