

Clinical efficacy of sustained release chlorhexidine in collagen membrane in the non surgical management of chronic localised periodontitis

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Abstract

Background: Aim of the study is to determine the efficacy of sustained release chlorhexidine in collagen membrane in the management of chronic localised periodontitis

Materials and methods: The study was conducted using 2.5 mg of chlorhexidine incorporated in fish collagen membrane. Patients with localized periodontitis with 5-8 mm pocket depth and single rooted teeth with involvement of one or two surfaces were included for the study. After one week of initial therapy (scaling) patients who maintain oral hygiene with PPD 5-8 mm were randomly assigned to control and test group of 61 sites each (35 patients in test group and 23 patients in control group). Test groups received Scaling and Root planing (SRP) + collagen chlorhexidine chip while the control group received SRP alone. Parameters probing pocket depth (PPD), clinical attachment level (CAL) and gingival index (GI) were recorded at baseline and at 1, 3, 6 and 9 months were compared.

Results: The test groups showed a significant reduction in PPD and gain in CAL (P -value < 0.0001) 5.89 ± 0.97 at baseline to 3.30 ± 1.16 at 9 months when compared to controls (5.51 ± 0.92 , 4.86 ± 1.50) and reduction in gingival index (2.00 ± 0.00 at baseline to 0.33 ± 0.47 at 9 months) when compared to control sites (1.96 ± 0.20 at baseline to 1.20 ± 0.60 at 9 months) which is statistically significant.

Conclusion: Local drug delivery using collagen chlorhexidine chip along with SRP is a predictable treatment option for the non surgical management of chronic localized periodontitis. The need for detailed microbiological study persist to correlate with the clinical findings observed.

Key words: Chlorhexidine, collagen membrane

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I. Introduction

Periodontitis is characterized by connective tissue attachment loss between the root and supporting alveolar bone. Bacterial plaque is essential for the initiation of chronic periodontitis¹. Putative pathogens associated with periodontal disease are susceptible to a variety of antiseptics and antimicrobials. Topical administration of antibacterial agents in the form of mouthwashes has been shown to be effective in controlling supragingival plaque². Non-surgical treatment of periodontal pockets is mainly based on scaling and root planing in compliant patients and exposure to initial therapy is usually associated with resolution of marginal gingival inflammation, shrinkage of soft tissue and a reduced periodontal probing depth. The two essential components of successful non-surgical therapy are complete subgingival scaling with root debridement and effective microbial plaque control. It should also be noted that in most of the controlled release local delivery system that have been studied, the level of antimicrobial release into the periodontal pocket far exceeds levels involved in normal antimicrobial mechanism. In scenario, a biodegradable chip for the sustained delivery of chlorhexidine is used in this study to evaluate its efficacy for the management of chronic localized periodontitis.

II. Background

The clinical indications for the use of chlorhexidine are associated both with its antiplaque properties and its capacity to act as a more general, bactericidal antiseptic. Chlorhexidine has been established as the most effective plaque control compound.³⁻⁷ Professional removal of plaque is recommended before starting a chlorhexidine regimen as a plaque control substitute.⁸

Chlorhexidine has been found to be effective against subgingival bacteria when delivered through a sustained release device. The microbial effect was evident for up to 11 weeks after treatment and clinical efficacy upto 2 years in terms of reduced probing depth, gain in attachment levels and reduction of bleeding.⁹ The controlled delivery systems that have been used in periodontics may be classified as either reservoir with rate controlling system and without rate controlling system. The reservoirs without rate controlling system include hollow fibers filled with a therapeutic agent in which the agent is released simply by diffusion through the reservoir wall.¹⁰ Intra pocket devices can be divided into two broad categories – degradable and non-degradable. Degradable system has the advantage of requiring the patient to pay only a single visit to the therapist for inserting the device. This minimizes patient visits and ensures compliance in that the patient does not have to return to have the device removed. Non-degradable devices like slabs of methyl methacrylate, ethyl cellulose film etc have the advantage that the therapist controls the removal of the device and therefore has greater control over the time of exposure. The first report on a degradable intrapocket sustained-release delivery system was the study by Noguchi et al (1984) using hydroxypropylcellulose films. Different types of collagen-based membranes have also been tested for local drug delivery. A degradable controlled – release device based on a formaldehyde cross linked Byco protein matrix containing chlorhexidine has been described by Steinberg et al (1990). Using 2% glutaraldehyde cross-linked atelocollagen, Minabe et al (1989)¹¹ developed a degradable delivery system to deliver tetracycline. A collagen film containing 5% metronidazole was evaluated as an adjunct to scaling and root planing in a three-month clinical trial (Hitzig et al 1994)¹². Local delivery of 1% alendronate gel into the periodontal pocket stimulated a significant increase in PD reduction gain in clinical attachment and bone fill compared to placebo gel as an adjunct to SRP (Anuj Sharma et al 2012)^{13, 26}. The studies of chlorhexidine chip, which have been undertaken globally, show a beneficial effect of sustained release chlorhexidine in pocket depth reduction.

A sustained-release system for local delivery of chlorhexidine (Perio Chip, manufactured by Perio Products Ltd. and distributed by Astra Pharmaceuticals) was the first subgingival sustained release chlorhexidine delivery system. The chip is a small, rectangular chip (rounded at one end) that contains 2.5 milligrams of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin that is cross-linked with glutaraldehyde. It is intended to be inserted in periodontal pockets that have a probing depth of 5 millimeters or greater as an adjunct to scaling or root planning (SRP), in patients who have adult periodontitis. When in situ, there is an initial peak concentration of 2000 µg/ml chlorhexidine in crevicular fluid¹³. Concentration of the drug remain above the MIC for more than 99% of per pocket flora for up to 9 days¹⁴.

Collagen is the most abundant protein in the body and is a main constituent of periodontal connective tissue. Collagen membranes used for regenerative therapy are well tolerated by the body and possess hemostatic properties that enhance wound healing. It is a weak immunogen and does not elicit an antibody response and is absorbed naturally.

III. Materials and methods

The present study was a randomized controlled clinical trial and the study protocol was approved by the Ethical Committee, Govt Medical College, Trivandrum. The study was conducted in the Department of Periodontics, Govt. Dental College, Trivandrum in collaboration with Sri Chitra Thirunal Institute of Medical Research, Poojappura. Collagen-Chlorhexidine chip was developed by Eucare Pharmaceuticals, Chennai, by incorporating 2.5 mg chlorhexidine from a 20% chlorhexidine solution in fish collagen membrane. Size of the chip is 4x5 mm. Thickness of the membrane is 0.23 – 0.32 mm and weighs about 10 mg.

Intervention

Fish Collagen is derived from tissues of fresh water edible fish species. The tissue is purified by a series of chemical and bio-chemical processes to remove undesirable impurities to make it a pure collagen material, which is non-immunogenic in nature. The above collagen stock is mixed with chlorhexidine gluconate at a desired concentration so as to ensure 2.5mg of the drug in each chip after the drying process under laminar airflow. The entire operation is performed under aseptic conditions in a clean room environment using current good manufacturing product (cGMP) facilities. The collagen -chlorhexidine chip is cross-linked with suitable cross-linking agent glutaraldehyde to increase the in-vivo persistence. The chip is individually packed in a medical grade pouch and sterilised by Gamma irradiation at 2.5 megarads. The absorption peak of chlorhexidine incorporated in the collagen membrane was observed by dissolving it in distilled water. This was also found to be 255 nm. Thus it could be inferred that no chemical change occurred to the chlorhexidine when it was incorporated in the collagen membrane.

Inclusion criteria:

Age group – 20-50 yrs

Probing pocket depth – 5-8mm

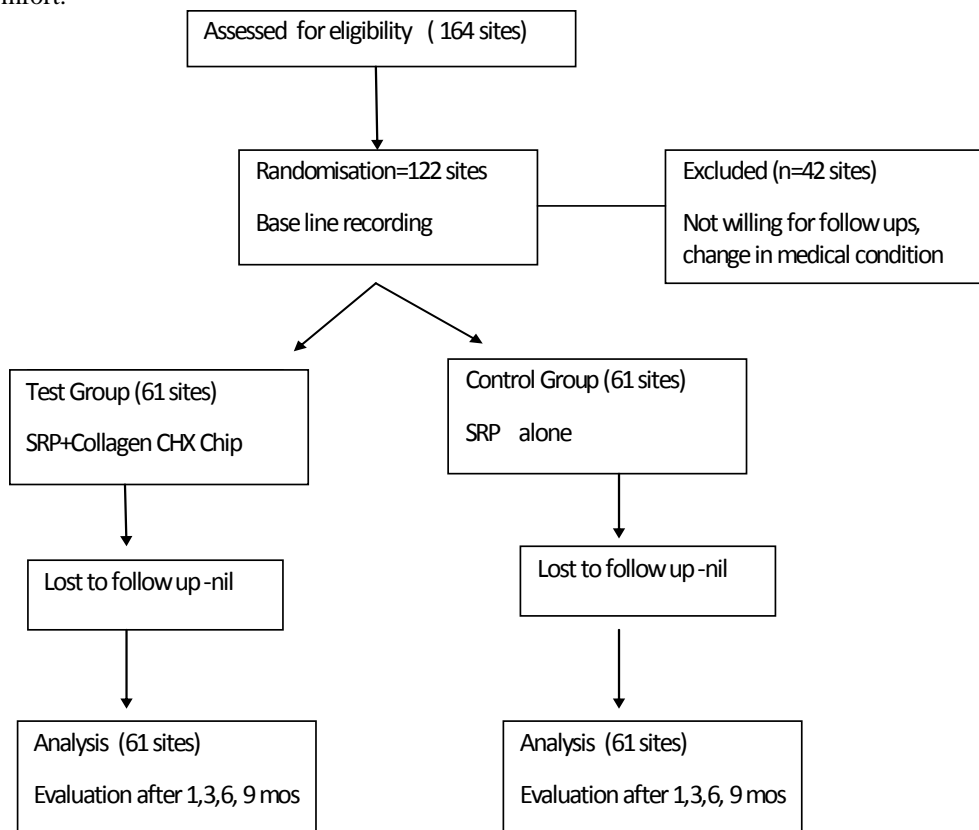
Single rooted tooth with involvement of one or two surfaces
No relevant medical conditions that could interfere with periodontal health

Exclusion criteria :

- Patients who are allergic to chlorhexidine
- Pregnant and lactating mothers
- Tooth with recession
- Habitual smokers
- Prior antibiotic therapy for any illness during the past 3 months
- Tooth with mobility

Procedure

After obtaining informed consent patients with chronic localized periodontitis were given supragingival scaling and oral hygiene instructions using flip charts. After one week of initial therapy (scaling) patients who maintain oral hygiene are randomly assigned to test and control groups and base line clinical parameters like probing pocket depth (PPD), clinical attachment level (CAL), Loe & Silness gingival Index (GI) were recorded in the proforma after selection of the appropriate sites.(PPD 5-8mm) For standardization of clinical measurements, customized acrylic stents were prepared and the base of the stent served as the reference point for measurement like PPD and CAL. A thorough subgingival scaling and root planing was done using hand instruments under topical analgesia for both test and control sites. Along with SRP, test group receives collagen - chlorhexidine chip. The chip is inserted into periodontal pocket subgingivally with a tweezer after drying the area. To avoid dislodgement of the chip, periodontal dressing was placed and patients were instructed to refrain from brushing and flossing those sites for 1 week. Patients were asked to return if they experience any untoward effects like pain, burning sensation etc. After 1 week, they were recalled for pack removal and evaluation of any inflammatory response. Patients were reevaluated at 1, 3, 6 and 9 months. In both groups, if there was no reduction in any of the clinical parameters selected for two subsequent recalls, surgical therapy was given. In the test group, chip placement was repeated where the pocket depth remain > 5mm at recall visit. A second chip was placed in 25 sites in 5 patients at the third visit (ie 6 months). No untoward reaction to this formulation was observed in any patient and no patient requested removal of the film due to discomfort.



IV. Statistical Analysis

61 sites were treated in the test and control group and tooth was taken as the randomization unit. Either labial, lingual, mesial or distal surfaces were taken. If a tooth is having more than one site both sites were given the same treatment and the deepest site was taken for analysis. If more than two sites are involved, it was not taken for the study. Statistical analysis was done using SPSS statistical package. Mann-Whitney test was used to assess the statistical significance of each variable reduction for the test and control group at 1, 3, 6 and 9 months compared to baseline values. Statistical significance was declared if 'P' value was found less than or equal to 0.05. For the test group, the baseline PPD (5.89 ± 0.97) at 1 month (3.93 ± 1.09) 3 months (4.16 ± 1.25) 6 months (3.49 ± 1.39) and at 9 months (3.30 ± 1.16). The baseline clinical attachment level (5.89 ± 0.97) at 1 month (3.93 ± 1.09) 3 months (4.16 ± 1.25) 6 months (3.49 ± 1.39) and at 9 months (3.30 ± 1.16). The baseline gingival index (2.00 ± 0.00) at 1 month (0.57 ± 0.53) 3 months (0.87 ± 0.81) 6 months (0.46 ± 0.56) and at 9 months (0.33 ± 0.47). For the control group, the baseline PPD (5.51 ± 0.92) at 1 month (4.67 ± 0.86) 3 months (4.76 ± 1.39) 6 months (4.63 ± 1.47) and at 9 months (4.86 ± 1.50). The baseline clinical attachment level (5.51 ± 0.92) at 1 month (4.67 ± 0.86) 3 months (4.76 ± 1.39) 6 months (4.63 ± 1.47) and at 9 months (4.86 ± 1.50). The baseline gingival index (1.96 ± 0.20) at 1 month (1.12 ± 0.48) 3 months (1.33 ± 0.62) 6 months (1.06 ± 0.65) and at 9 months (1.20 ± 0.60). (Table 2)

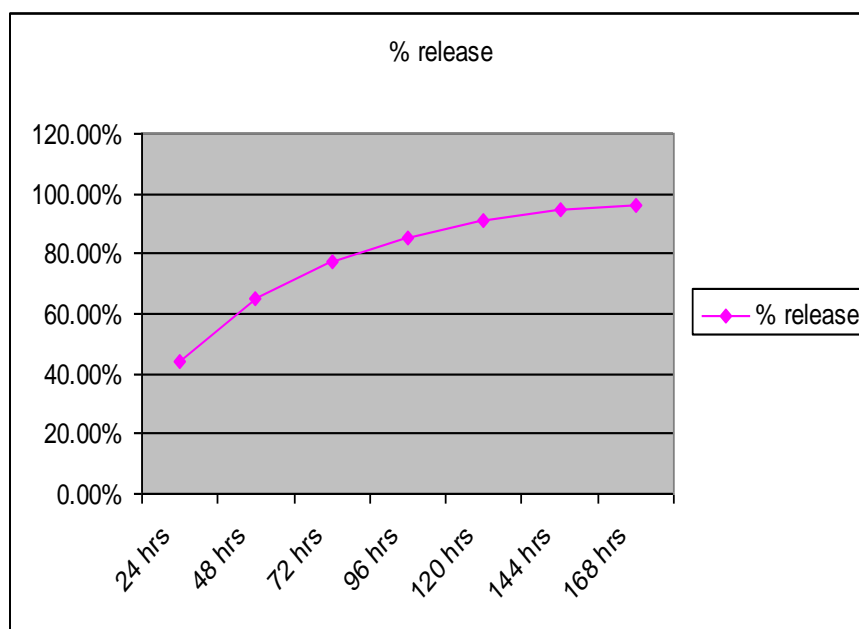
V. Discussion

The present concept of management for localized periodontitis is focusing on non-invasive methods. Based on this principle local drug delivery using chlorhexidine was used in the study. As this was a study of efficacy of therapeutic intervention, randomized controlled design was selected as the appropriate design. Chlorhexidine was selected for evaluation because of its antiplaque effect, which was proved as early as 1969.^{14,15} and Victor Quintas 2015¹⁶ Goodson 1989 demonstrated that for patients with periodontitis the mean amount of chlorhexidine that is required in the gingival crevicular fluid (GCF) is between 2.3 – 3.9 mg. So in the present study 2.5mg of chlorhexidine was incorporated in the membrane.

Table 1: Invitro release pattern of the Collagen-Chlorhexidine Chip used in the test Group

Time in hrs	Release rate in μg	Release rate in %
24 hrs	1105 μg	44.2%
48 hrs	525 μg	65.2%
72 hrs	300 μg	77.2%
96 hrs	195 μg	85%
120 hrs	150 μg	91%
144 hrs	85 μg	94.4%
168 hrs	40 μg	96%

Graph – 1: Invitro release rate of chlorhexidine from Chlorhexidine Collagen Membrane Chip



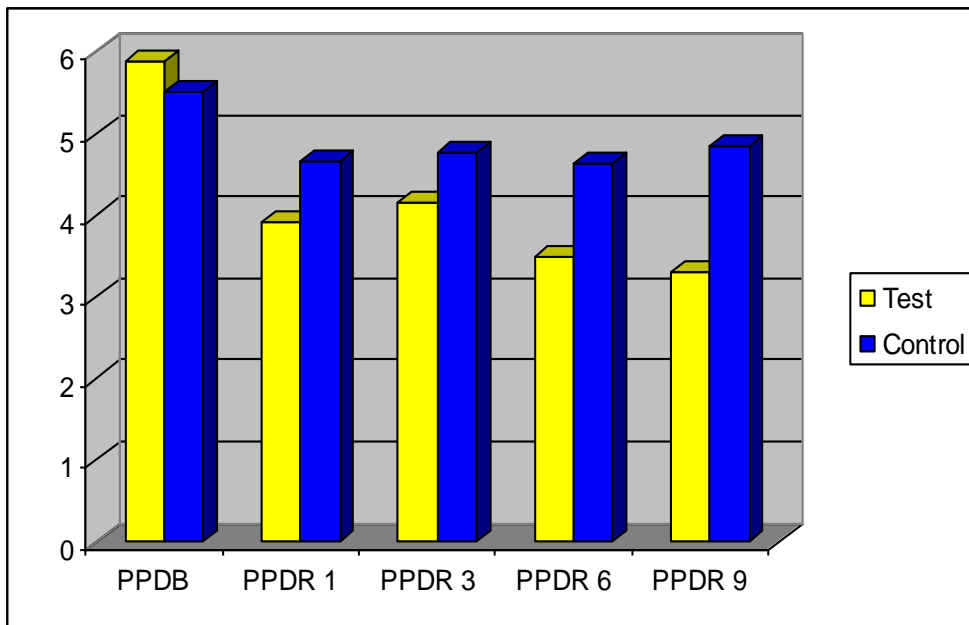
In the present study the release pattern showed an average concentration of chlorhexidine >125 µg/ml for 5 days (Table1) and this concentration is above the minimum inhibitory concentration for more than 99% of the periodontal pocket flora¹⁴. Chlorhexidine chip was used as an adjunct to scaling and root planing with repeated administration every three months in pockets with probing pocket depth >5mm¹⁷. As contrary to the above study a second chip was placed at 6 months review where PPD remained > 5mm at recall visit. Probing pocket depth of 5-8mm was selected in accordance with the study conducted by Jeffcoat et al 2000^{18,19}. The results indicate that the chlorhexidine chip can maintain clinically effective levels of chlorhexidine in GCF of periodontal pockets for over 1 week with no detectable systemic absorption. (AhmedY.Garnal 2011)^{20,21} The percentage of periodontal pocket sites that evidenced a reduction of 2 mm or more from baseline increased in the collagen- chlorhexidine chip + SRP group. This is in accordance with the study conducted by Jeffcoat et al 1998 and Komal Puri (2013)^{17,28} Three months had been selected as the treatment interval for chlorhexidine chip placement because effects of locally delivered controlled release chlorhexidine have been shown to be evident for upto 11 weeks after administration (Navjot Jhinger 2015).^{24,29} Clinical assessment of local delivery systems is by the evaluation of reduction of probing pocket depth, gain in clinical attachment level and assessing the gingival index (Nezih Azmak 2002)^{17,25}. At 9 months significant reductions from baseline favoring the collagen-chlorhexidine chip compared with controls were observed with respect to probing pocket depth, clinical attachment level and gingival index.¹⁷ (Table2)

Several local drug delivery systems employed as monotherapies improved periodontal health and provided significant enhancement of parameters used to monitor periodontal status. (Anuj Sharma 2012, Nezih Azmak 2002, Greenstein 2006)^{25,26,27} The improved efficacy of collagen - chlorhexidine chip compared to SRP alone throughout the period may at least in part, to the fact that some of the pockets received a second application of the chip. This is accordance with the study by Soskolne²⁹ who demonstrated that a second application of the chlorhexidine chip at three months showed a continued improved efficacy of probing pocket depth reduction and gain in clinical attachment level. It is indicated as an adjunct to SRP procedures for the reduction in pocket depth in patients with chronic periodontitis and may be used as a part of periodontal maintenance program, which includes good oral hygiene and SRP (Heasman 2001)^{22,23}

Table 2: Comparison of PPD Reduction, Gain in Clinical Attachment Level and GI Reduction for Test and Control Groups at 1,3,6 and 9 Months to Mean Baseline

VARIABLE	BASELINE	1 MONTH	3 MONTHS	6 MONTHS	9 MONTHS
PPD- test	5.89 ± 0.97	3.93±1.09	4.16 ±1.25	3.49±1.39	3.30 ±1.16
PPD -con	5.51± 0.92	4.67±0.86	4.76±1.39	4.63±1.47	4.86±1.50
CAL -test	5.89 ± 0.97	3.93±1.09	4.16 ±1.25	3.49±1.39	3.30 ±1.16
CAL -con	5.51± 0.92	4.67±0.86	4.76±1.39	4.63±1.47	4.86±1.50
GI -test	2.00± 0.00	0.57± 0.53	0.87 ± 0.81	0.46 ± 0.56	0.33 ± 0.47
GI -con	1.96± 0.20	1.12 ± 0.48	1.33 ± 0.62	1.06 ± 0.65	1.20 ± 0.60
MANN-WHITNEY (PPD) P value Significance		996.500 0.0001 S	1122.00 0.006 HS	781.00 0.0001 HS	589.500 0.0001 HS
MANN-WHITNEY (CAL) P value Significance		996.500 0.0001 S	1122.00 0.006 HS	781.00 0.0001 HS	589.500 0.0001 HS
MANN-WHITNEY (GI) P value Significance		829.500 0.0001 HS	1053.00 0.002 HS	823.500 0.0001 HS	512.500 0.0001 HS

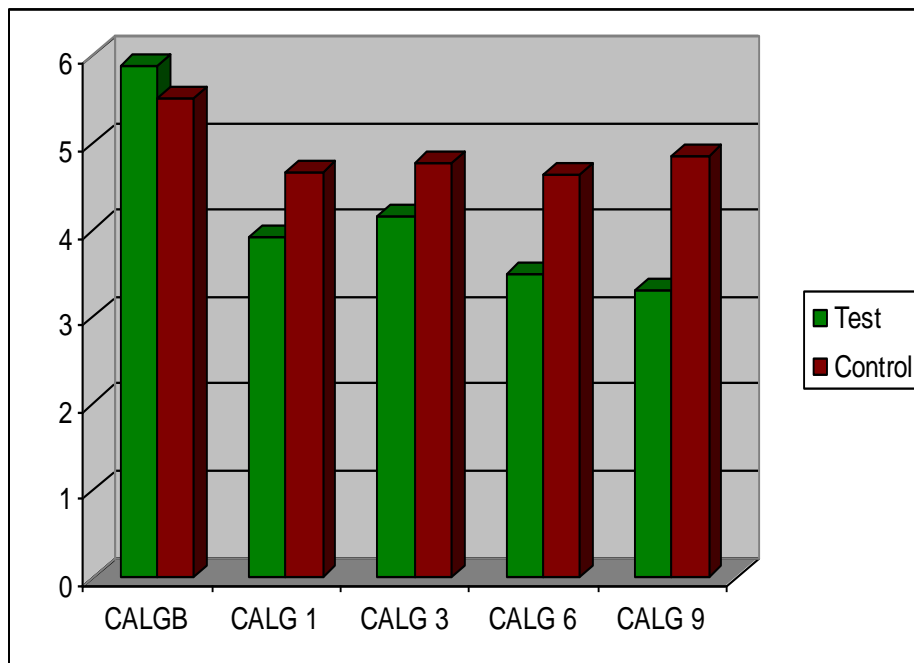
Graph – 2: Baseline PPD & PPD reduction at 1,3,6 & 9 months in test and control groups



PPD B- Probing pocket depth at base line

PPDR 1 , PPDR 3, PPDR 6, PPDR 9 - Probing pocket depth reduction at one month, 3 months, 6 months, 9 months

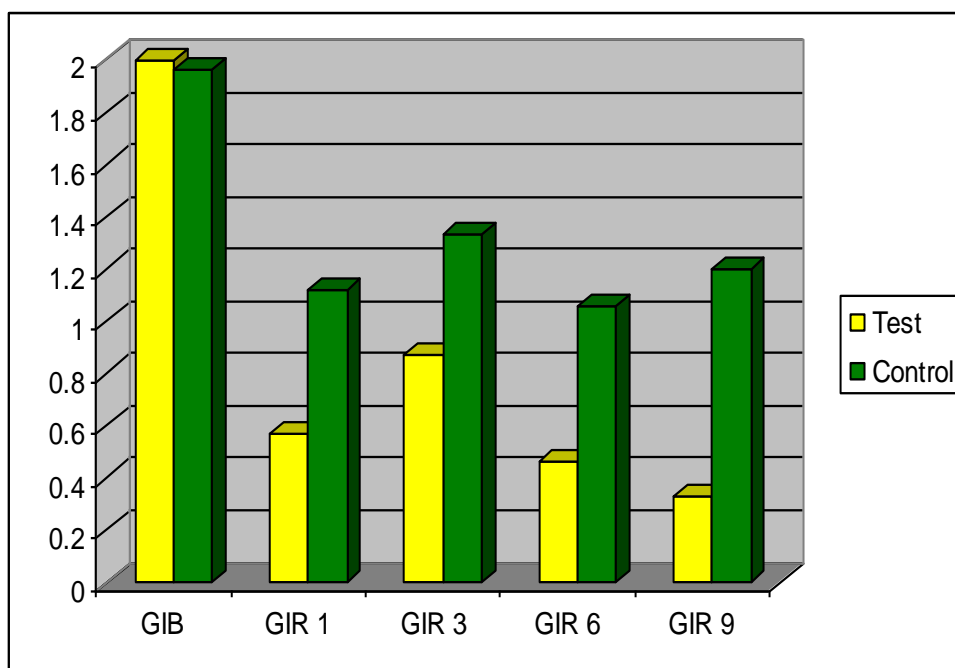
GRAPH – 3: Baseline CAL & Gain in CAL at 1,3,6 & 9 months in test and control groups



CALG B- Clinical attachment level at base line

CALG 1, 3 , 6, 9 - Gain in clinical attachment level at one month, 3 months, 6 months, 9 months

GRAPH – 4: Baseline GI & Gingival Index Reduction 1,3,6 & 9 Months In test and control groups



GI B- Gingival index at base line

GIR 1,3 6, 9 - Gingival index reduction at one month,3 months, 6 months, 9 months

VI. Conclusion

The results showed that both SRP and local drug delivery devices are effective for treating chronic localized periodontitis. However SRP in combination with local drug delivery using collagen- chlorhexidine chip is a simple and non invasive technique that consists of sufficient quantity of the drug to provide adequate therapeutic level, as a beneficial adjunctive treatment modality to enhance periodontal health. Hence this therapy can be extended to multiple sites, patients who are not willing for surgery, as well as compromised patients. Mean pocket depth reduction of 2 mm with collagen -chlorhexidine chip shows a reduction of periodontal disease and this treatment modality is a definite treatment alternative to manage periodontal disease. The use of this technique in acute periodontal conditions has to be studied in future.

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