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 corelate with the clinical findings observed.

Key words: Chlorhexidine, collagen membrane

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 periodontitis. 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 plaque. 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. Professional removal of plaque is recommended before starting a chlorhexidine regimen as a plaque control substitute.
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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 up to 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. 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 fluid. The drug remain above the MIC for more than 99% of per pocket flora for up to 9 days.14 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 posses hemostatic properties that enhances wound healing. It is a weak immunogen and do 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 Eucares 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.

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**Assessed for eligibility (164 sites)**

- **Randomisation** = 122 sites  
  - Base line recording  
  - Excluded (n=42 sites)  
    - Not willing for follow ups, change in medical condition

- **Test Group (61 sites)**  
  - SRP + Collagen CHX Chip
  - Lost to follow up-nil
  - Analysis (61 sites)  
    - Evaluation after 1, 3, 6, 9 mos

- **Control Group (61 sites)**  
  - SRP alone
  - Lost to follow up-nil
  - Analysis (61 sites)  
    - Evaluation after 1, 3, 6, 9 mos
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 2015,16 Goodson1989 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

<table>
<thead>
<tr>
<th>Time in hrs</th>
<th>Release rate in μg</th>
<th>Release rate in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs</td>
<td>1105 μg</td>
<td>44.2%</td>
</tr>
<tr>
<td>48 hrs</td>
<td>525 μg</td>
<td>65.2%</td>
</tr>
<tr>
<td>72 hrs</td>
<td>300 μg</td>
<td>77.2%</td>
</tr>
<tr>
<td>96 hrs</td>
<td>195 μg</td>
<td>85%</td>
</tr>
<tr>
<td>120 hrs</td>
<td>150 μg</td>
<td>91%</td>
</tr>
<tr>
<td>144 hrs</td>
<td>85 μg</td>
<td>94.4%</td>
</tr>
<tr>
<td>168 hrs</td>
<td>40 μg</td>
<td>96%</td>
</tr>
</tbody>
</table>

Graph – 1: Invitro release rate of chlorhexidine from Chlorhexidine Collagen Membrane Chip
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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 flora. Chlorhexidine chip was used as an adjunct to scaling and root planing with repeated administration every three months in pockets with probing pocket depth >5mm. 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 etal 1998. 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). Several local drug delivery systems employed as monotherapies improved periodontal health and provided significant enhancement of parameters used to monitor periodontal status. 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 Soskolne 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 maintainance program, which includes good oral hygiene and SRP (Heasman 2001)

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

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BASELINE</th>
<th>1 MONTH</th>
<th>3 MONTHS</th>
<th>6 MONTHS</th>
<th>9 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD-test</td>
<td>5.89 ± 0.97</td>
<td>3.93±1.09</td>
<td>4.16±1.25</td>
<td>3.49±1.39</td>
<td>3.30±1.16</td>
</tr>
<tr>
<td>PPD-con</td>
<td>5.51± 0.92</td>
<td>4.67±0.86</td>
<td>4.76±1.39</td>
<td>4.63±1.47</td>
<td>4.86±1.50</td>
</tr>
<tr>
<td>CAL-test</td>
<td>5.89 ± 0.97</td>
<td>3.94±1.09</td>
<td>4.16±1.25</td>
<td>3.49±1.39</td>
<td>3.30±1.16</td>
</tr>
<tr>
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<td>5.51± 0.92</td>
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<td>4.63±1.47</td>
<td>4.86±1.50</td>
</tr>
<tr>
<td>GI-test</td>
<td>2.00± 0.00</td>
<td>0.57± 0.53</td>
<td>0.87 ± 0.81</td>
<td>0.46 ± 0.56</td>
<td>0.33 ± 0.47</td>
</tr>
<tr>
<td>GI-con</td>
<td>1.96±0.20</td>
<td>1.12 ± 0.48</td>
<td>1.33 ± 0.62</td>
<td>1.06 ± 0.65</td>
<td>1.20 ± 0.60</td>
</tr>
</tbody>
</table>

MANN-WHITNEY (PPD) P value Significance

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BASELINE</th>
<th>1 MONTH</th>
<th>3 MONTHS</th>
<th>6 MONTHS</th>
<th>9 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD-test</td>
<td>996.500</td>
<td>1122.00</td>
<td>781.000</td>
<td>589.500</td>
<td>0.0001</td>
</tr>
<tr>
<td>PPD-con</td>
<td>996.500</td>
<td>1122.00</td>
<td>781.000</td>
<td>589.500</td>
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<td>CAL-con</td>
<td>996.500</td>
<td>1122.00</td>
<td>781.000</td>
<td>589.500</td>
<td>0.0001</td>
</tr>
<tr>
<td>GI-test</td>
<td>829.500</td>
<td>1053.000</td>
<td>823.500</td>
<td>512.500</td>
<td>0.0001</td>
</tr>
<tr>
<td>GI-con</td>
<td>829.500</td>
<td>1053.000</td>
<td>823.500</td>
<td>512.500</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

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**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
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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GI B- Gingival index at base line
GIR 1,3,6, 9 - Gingival index reduction at one month, 3 months, 6 months, 9 months
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