"Local Drug Delivery---Periocol" In Periodontics

Divya P.V, K. Nandakumar

Govt.Dental College, Thiruvananthapuram

Introduction
Recent development of science and technology has revolutionized the basic outlook and approach to the problems of periodontal disease. Earlier it has been assumed that periodontal problems were invariably progressive and the morbid effects increase with passage of time. A thorough understanding of the etiopathogenesis of periodontal disease has provided the clinicians and researchers with a number of diagnostic tools and technique that has widened the treatment options.

Periodontitis describes a group of related inflammatory disease resulting in destruction of the tissues that support the tooth. It results from extension of the inflammatory process initiated in the gingiva to the supporting periodontal tissues. Clinical features of periodontitis include bleeding, pus discharge, halitosis, tooth mobility, functional impairment and ultimately tooth loss. The standard clinical measures for periodontitis are bleeding on probing, clinical attachment level and pocket depth. Tooth loss especially in the anterior region can cause psychological trauma to the patient. 5-20% of population suffer from severe generalized periodontitis, though mild to moderate periodontitis affects a majority of adults. The immediate goal is to prevent, arrest, control or eliminate periodontitis and to restore the lost, form, function, esthetics and comfort. Periodontal disease therapy has been directed at altering the periodontal environment to one, which is less conducive to the retention of bacterial plaque in the vicinity of gingival tissue. Active phase of the disease can be reversed dramatically by reducing the plaque levels. Classic regimens to achieve this aim include
(1) Instructions in oral hygiene
(2) Scaling
(3) Correction of inadequate restorative dentistry
(4) Root planing
(5) Surgical elimination of pockets etc.

Topical administration of antibacterial agents in the form of mouth washes, dentifrice or gels can be used effectively in controlling supragingival plaque. Irrigation systems or devices can deliver agents into deep pockets but clinically not effective in halting the progression of periodontal attachment loss.

Local Drug Delivery
Recently a new approach using local delivery systems containing antimicrobial has been introduced. This produces more constant and prolonged concentration profiles. Both topical delivery system and controlled release system have been termed as local delivery. The term local delivery and site-specific delivery are sometimes used synonymously. The potential therapeutic advantage of local delivery approach has been claimed to be several fold. Local delivery devices are systems designed to deliver agents locally into periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. The periodic use of local delivery systems in reducing probing depths, stabilizing attachment levels and minimizing bleeding would allow better control of the disease. Goodson et al in
1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The effectiveness of this form of therapy is that, it reaches the base of periodontal pocket and is maintained for an adequate time for the antimicrobial effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device. Controlled release delivery of antimicrobials directly into periodontal pocket has received great interest and appears to hold some promise in periodontal therapy. Some techniques for applying antimicrobial subgingivally, such as subgingival irrigation, involve local delivery but not controlled release. Controlled release local delivery systems, in which the antimicrobial is available at therapeutic levels for several days, have been evaluated in several forms and using different antimicrobials.

Controlled delivery systems are designed to release drug slowly for more prolonged drug availability and sustained drug action. These delivery systems are also called sustained release, controlled - release, prolonged release, timed release, slow release, sustained action, prolonged action or extended action. There are distinct phases in a periodontal treatment plan where a dental practitioner can use this sustained release device

1. As an adjunct to Scaling and Rootplaning
2. Periodontal maintenance therapy: Recurrent periodontitis usually involves only a few teeth. These sites are ideal for the treatment with this device.
3. For whom surgery is not an option or those who refuse surgical treatment.
4. Sustained release device is a less invasive treatment option and it requires less time compared to surgical treatment.

So patients with moderate periodontitis should receive non-surgical therapy to halt periodontal disease and limit the extent of surgical intervention needed in the future.

Intra pocket devices can be divided in two broad categories depending on degradability. Non-degradable devices (first generation) and degradable devices (second generation)

Non degradable devices have the advantage that the therapist controls the removal of the device and therefore has greater control over the time of exposure of the pocket environment to the drug. The degradable device has the advantage of requiring the patient pay only a single visit to therapist for the insertion of the device. This minimizes the patient visits and ensures compliance. Patient revisit for the removal of the device can be avoided. Devices that have been developed include fibers, films, slabs and injectable systems.

First sustained release dosage from of chlorhexidine diacetate for topical use was developed by Friedman and Golomb in1982. Release rate of chlorhexidine was measured by means of ultraviolet spectrophotometer. The release of chlorhexidine from this device and its dissolution in vitro were shown to be dependent on the degree of protein cross-linking. Nature of chlorhexidine salt used also affected the release rate. When the chlorhexidine-incorporated chip is placed subgingivally, it releases chlorhexidine content and degrades. It is released into periodontal pocket over a period of 7 days at an effective and constant rate, resulting in killing of 90% of bacteria in the pocket. On the other hand, it is a bactericidal antiseptic. 40% of chlorhexidine is released within 24 hrs and the remainder in 7-10 days. The mean concentration of chlorhexidine in gingival crevicular fluid was ±1000 mg/ml at 4hrs. and ± 480 mg/ ml within 24 hrs. and the remainder in 7-10 days.

Drugs used for local drug delivery

Different drugs used for local delivery are tetracyclines including doxycycline and minocycline, metronidazole and chlorhexidine. Tetracyclines are bacteriostatic for many pathogens at concentrations found in the gingival crevicular fluid after systemic administration (3-6 microgram/ml). However, local delivery of these agents provides high concentrations that are bacteriocidal. Local application of tetracyclines has been associated with minimal side effects. Metronidazole's spectrum of activity is relatively specific for obligate anaerobes. Chlorhexidine is an antiseptic, which adheres to organic matter and demonstrates low toxicity when
applied topically and not adsorbed well into the tissues.

**Periochip**

Periochip, the controlled subgingival delivery of chlorhexidine, was developed by Perio Products Ltd, Jerusalem, Israel and it is the only available commercial product. This is a 5 mm x 4 mm x 0.3 mm film containing 2.5 mg of chlorhexidine gluconate which is incorporated in a biodegradable matrix of hydrolyzed gelatin cross linked with glutaraldehyde. The matrix also contains glycerin and purified water. It weights about 7.4mg and should be stored under refrigerated condition at 20-80°C. It was first introduced into U.S. dental market in 1998. Room temperature periochip, which provides the added benefit of being easy to store, and simple to use was introduced in 2002. It comes in boxes of 10 chips. Shelf life is 2 yrs. Each chip is individually packed in a separate compartment of an aluminum blister pack.

Soskolne et al conducted an in vivo estimation of the chlorhexidine release profile of the Periochip in the GCF, plasma and urine in 1998. Release profile of Periochip cross linked hydrolyzed gelatin matrix into the gingival crevice was evaluated in a 10 day pharmacokinetic study and the results indicate that periochip can maintain clinically effective levels of chlorhexidine in the gingival crevicular fluid of periodontal pockets for over 1 week with no detectable systemic absorption.

**Chlorhexidine**

is one of the most effective topical agents, long been used as an effective antimicrobial agent. It was introduced in U.S in 1986. Its efficacy as a topical rinse to inhibit dental plaque and gingivitis has been well established in study periods for 2 years without evidence of development of any bacterial resistance. (Rindom Schiott, Briner, Loe). It 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.

Chlorhexidine has been shown to be an effective agent in plaque inhibition (Loe et al 1976) because it is well retained in the oral cavity, reacting reversibly with receptors in the mouth due to its affinity for hydroxyapatite and acidic salivary protein (Rolla, Loe and Schiott 1970). Two daily rinses with 10 ml of a 0.2% aqueous solution of chlorhexidine digluconate almost completely inhibited the development of plaque, calculus and gingivitis in the human model for experimental gingivitis.

Comparison of local delivery systems

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Number of patients</th>
<th>Probing Depth Reduction</th>
<th>Clinical attachment level</th>
<th>Probing Depth Reduction</th>
<th>Clinical attachment level</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine chip</td>
<td>Jeffcoat etal</td>
<td>447</td>
<td>0.65 mm</td>
<td>0.58 mm</td>
<td>0.95 mm</td>
<td>0.75 mm</td>
<td>9 months</td>
</tr>
<tr>
<td>Chlorhexidine chip</td>
<td>Soskolne etal</td>
<td>118</td>
<td>0.70 mm</td>
<td>0.31 mm</td>
<td>0.16 mm</td>
<td>0.47 mm</td>
<td>6 months</td>
</tr>
<tr>
<td>Tetracycline fiber</td>
<td>Newman etal</td>
<td>105</td>
<td>1.08 mm</td>
<td>__</td>
<td>1.81 mm</td>
<td>__</td>
<td>6 months</td>
</tr>
<tr>
<td>Doxycycline polymer</td>
<td>Polson etal</td>
<td>179</td>
<td>1.30 mm</td>
<td>0.80 mm</td>
<td>1.80 mm</td>
<td>1.00 mm</td>
<td>9 months</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Vansteenberg etal</td>
<td>103</td>
<td>1.4 mm</td>
<td>0.8 mm</td>
<td>1.7 mm</td>
<td>0.8 mm</td>
<td>3 months</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Graca etal</td>
<td>26</td>
<td>2.30 mm</td>
<td>1.56 mm</td>
<td>2.64 mm</td>
<td>1.95 mm</td>
<td>3 months</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Ainamo etal</td>
<td>206</td>
<td>1.30 mm</td>
<td>__</td>
<td>1.30 mm</td>
<td>__</td>
<td>6 months</td>
</tr>
</tbody>
</table>
Chlorhexidine has very low systemic toxic activity in humans and has not produced any appreciable resistance to oral microorganism and has not been associated with any teratogenic alterations. Chlorhexidine is safe, clinically effective in reducing plaque and gingivitis, has substantivity, effects the pathogenic flora and is acceptable in terms of taste, cost and ease of use.

Effects on oral bacteria:

Short-term use of chlorhexidine causes a striking reduction in the number of oral microorganisms. In the absence of other oral hygiene measures, chlorhexidine has been shown to reduce the number of bacteria in saliva by 85% after 24 hrs. A maximum reduction of 95% occurred around 5 days, after which the numbers gradually increased to maintain an overall reduction of 70-80% at 40 days (Schiött et al 1970). The susceptibility of different strains of bacteria to chlorhexidine has been reported by Emilson (1977) in a study of a series of clinical specimens including dental plaque. A broad range of susceptibility was demonstrated amongst both gram +ve and gram -ve strains. Studies show that a 3-day exposure of the pocket flora to the sustained release of chlorhexidine significantly reduced the relative number of spirochetes and motile rods in periodontal pockets to negligible amounts.

Stanley studied the invitro effects of chlorhexidine on subgingival plaque bacteria in 1989. Susceptibility to chlorhexidine of a range of bacteria may be isolated from subgingival plaque. The minimum inhibitory concentration (MIC) of chlorhexidine for 52 strains of bacteria ranged from 8-500 microgram/ml. Administration of chlorhexidine reduced subgingival bacteria and improved clinical health.

In a developing country with a high prevalence of periodontitis, any strategy that arrests or prevents the progression of periodontitis will be definitely useful. If chlorhexidine adjunct to scaling and rootplaning can reduce the need for surgery, it can be used for maintenance phase, for patients not willing for surgery, for temporary stoppage in deep lesions and patients with systemic disease.

Structure of chlorhexidine

Two symmetric 4 chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain.

Mechanism of action:

The bactericidal effect of the drug is due to the cationic molecule binding to extra microbial complex and negatively charged microbial cell walls, thereby altering the cells osmotic equilibrium. It inhibits plaque formation by following mechanism (Rolla and Melsen)

1. By binding to anionic acid groups on salivary glycoproteins thus reducing pellicle formation and plaque colonization.
2. By binding to salivary bacteria and interfering with their adsorption to teeth.

Spectrum of activity:

Effective against gram +ve, gram -ve and yeast organism. It is also effective against candida albicans. The slow release of the drug from its retention site provides a prolonged bactericidal effect (12-24hrs)

Metabolism:

The drug is poorly absorbed from gastrointestinal tract and 90% of retained drug is excreted in the faeces and remainder via urinary tract.

Adverse effect:

(1) Staining of teeth (2) Dulling of taste sensation (3) Carcinogenicity

Staining:

Yellow brown stain on tooth is seen by the formation of Iron suphide (Iron which is originated from diet and sulphur from exposed thiol groups from denatured proteins).

Carcinogenecity:

Parachloroaniline (PCA) an industrial chemical is found in chlorhexidine products as a trace contaminant. It forms a breakdown product subsequent to prolonged shelf life or exposure to high temperature. Keeping chlorhexidine solution in a dark refrigerated bottle can retard this. Risk assessment associated with chlorhexidine application must be based upon
actual applied dosages. When the levels of PCA exceed 20 mg/liter of urine, workers in clinical plants should be referred for medical treatment.

**Importance of chlorhexidine chip in periodontal therapy**

If the progression of periodontitis can be arrested by chlorhexidine chip preventing complication, it can be accepted as a routine strategy. Routinely probing depth of > 4 mm may be an indication for periodontal surgery, which increases morbidity and expense to the patient. Surgery is the only treatment in furcation defects, intrabony defects, deep and tortuous pockets where non-surgical treatment fails. Disadvantage of flap-surgery includes gingival recession leading to tooth elongation and causing sensitivity and esthetic problems. If adjunctive use of sustained release chlorhexidine reduces pocket depth, a second placement of the chip should be considered where pocket depth remains >5 mm.

Pooled data from controlled clinical trials from 10 centers have shown that the adjunctive use of chlorhexidine chip results in significant reduction of probing depth, significant improvement in attachment level, compared with scaling and root planing alone and Jeffcoat et al in 1998 suggests that the chlorhexidine chip is a safe and effective adjunctive chemotherapeutic agent for the treatment of periodontitis.

Killoy in his article in 1998 stressed the importance of chlorhexidine chip in conjunction with scaling and root planing when compared to scaling and root planing (SRP) alone. This delivery system in combination with scaling and root planing has shown significant improvement in pocket depth reduction, attachment gain and BOP.

**Collagen membranes for local drug delivery**

Different types of collagen based membranes have been tested for local drug delivery. A degradable controlled release device based on formaldehyde cross-linked Bycoprotein matrix-containing chlorhexidine has been described by Steinberg et al 1990. Bycoprotein is a hydrolyzed gelatin of bovine origin. A new sustained release chlorhexidine in fish collagen membrane Periocol was developed by Eucare Pharmaceuticals, Chennai, which is similar to Periochip.Periocol has two contents-chlorhexidine and collagen. The source of collagen is from the air bladder of fresh water fishes. These groups of fishes are used as food in many parts of our country. The air bladder in them is an accessory respiratory organ used for a real respiration. This chip is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip is 4x5 mm and thickness is 0.25 - 0.32 mm and 10 mg wt. The chip is sterilized by gamma irradiation at 2.5 mega rads and is individually packed.

Collagen is a natural protein, which is chemotactic for fibroblasts, enhances fibroblast attachment via its scaffoldlike fibrillar structure and stimulates platelet degranulation, thereby accelerating fibers and clot attachment. They are resorbed after 30 days, however their coronal edge degrades within 10 days. Here we are using collagen as a vehicle for the subgingival delivery of chlorhexidine. The membrane is shaped in the form of a chip of dimensions 4x5mm for insertion into the periodontal pocket.

Application of this chip in chronic periodontitis as an adjunct to scaling and root planing procedures has shown reduction in probing pocket depth, gingival bleeding and clinical attachment level compared to scaling and
rootplaning alone. Chlorhexidine chip when used as an adjunct to scaling and root planing significantly reduces loss of alveolar bone and improve the clinical signs of periodontitis.

Studies by Soskolne W.A in 1999 indicate that an initial peak concentration of chlorhexidine in gingival crevicular fluid at 2 hr. post chip insertion (2007/µg/ml) with slightly lower concentrations of between 1300-1900 µg/ml being maintained over the next 96 hours. Total chip degradation has occurred between 7 and 10 days after insertion.

Procedure
Tooth with probing pocket depth of >5 mm are selected for the placement of chip. After thorough scaling and root planing, dry the area and chip is inserted into periodontal pocket with tweezers. After placement of the chip the area is protected with periodontal pack. Patients are asked to refrain from brushing and flossing the area for 7 days. After 7 days, they are recalled for pack removal and evaluated for any inflammatory response.

Placement of the chip is shown below

Conclusion
- The chip is a new armamentarium that can be easily incorporated into the artillery of a dental practitioner for the management of chronic nature of periodontitis. This offers the clinician a new method of achieving and maintaining periodontal stability and thus prevention of further periodontal morbidity and subsequent problems like loss of tooth, periodontal abscess, tooth mobility and pain.
- As a monotherapy, local drug delivery systems incorporating a variety of drugs can improve periodontal health.
- Chlorhexidine chip is a new apparently cost effective treatment option for non-surgical periodontal therapy. Adjunctive use of chlorhexidine chip could reduce periodontal surgical needs significantly at little or no additional cost.
Local drug delivery appears to be as effective as scaling and root planing with regards to reducing signs of periodontal inflammatory disease - redness, bleeding on probing, probing depth and loss of clinical attachment.

Local delivery may be an adjunct to conventional therapy.

References