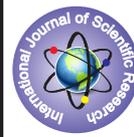


APPLICATIONS OF LOCAL DRUG DELIVERY IN PERIODONTICS: A REVIEW



Pharmacology

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ABSTRACT

The majority of periodontal diseases are caused due to inflammation initiated by accumulation of microbes in the plaque. When this continues, this plaque reaches subgingivally and it becomes difficult for the patient to remove it by conventional brushing. The treatment option available in such scenario is mechanical debridement of the deposits. But in cases of complex root anatomy or apically placed lesion, a clean environment free of microbes and deposits cannot be ensured. Thus we need to search for other methods of mechanical debridement in such situations. One of the effective treatments is the local drug delivery or site specific delivery of drug. In this treatment method, the antibiotic in sufficient concentration reaches the depth of the pocket. In this article; the authors have reviewed the applications of local drug delivery in the management of periodontal diseases.

Introduction

The inflammation in the periodontal tissue is initiated by microbial plaque and bacterial infection. In the periodontal pocket the bacteria form a highly structured and complex biofilm. Traditional treatment options for such conditions include mechanical debridement aimed at removing the subgingival flora and providing a clean, smooth and compatible root surfaces. But, in several instances, the complex anatomy of the root and the location of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load.¹

For the effective treatment, the antibiotic must reach the depth of the pocket and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.

Local drug Delivery also known as Site-Specific delivery is an advanced approach introduced by Goodson et al in 1979. Periodontal pocket provides a natural reservoir bathed by GCF, which is easily accessible for the insertion of delivery devices. The gingival fluid provides a leaching medium for the release of a drug from the solid dosage form and for its distribution throughout the pocket. Thus this makes the periodontal pocket a natural site for treatment with local release delivery system.

Ideal requisites of locally applied drug

According to Greenstein and Tonetti, local application of pharmacological agents must fulfil the following criteria³:

- It must reach the intended site of action
- It must remain at an adequate concentration
- It should last for a sufficient duration of time

Local Drug Delivery abides with all the above steps. The advantage of this mechanism is that it reaches the base of the periodontal pocket which is usually inaccessible to oral mouth rinses, and causes sustained release of a short dose of drug over a long period of time without having to load the dose repeatedly unlike systemic antibiotics and sub gingival irrigation. This helps to reduce or eliminate the pathogenic bacterial count, decreases probing depth, stabilizes attachment and controls or minimizes bleeding which eventually leads to controlling of the disease.^{3,4}

Indications of local drug delivery: cases where surgical treatment is not an option, as adjunct to scaling and root planing, recurrent periodontitis. In patients hypersensitiv to conventional intra canal irrigants like sodium hypochlorite.⁵

Contra-Indications of local drug delivery: Patients with hypersensitivity to the drug. Patients susceptible to infective endocarditis in order to reduce risk of bacteremia. Use of ultrasonic device based drug delivery system is contraindicated in asthmatics, patients with cardiac pacemakers, AIDS and tuberculosis.⁶

Advantages and disadvantages of local drug delivery:

The merits are it attains a 100- fold higher concentration of antimicrobial agent in subgingival sites. Reduces patient dose by over 400 fold thereby reducing chances of drug resistance and side effects caused by systemic antibiotics. Small doses can be administered. Drug maintains contact and effective concentration with the pathogens in the infected area for a prolonged period of time.⁷

The disadvantages of local drug delivery are non- compliance with placement of the drug subgingivally. Lack of manual dexterity.⁵ Does not have any effect on adjacent or nearby structures such as tonsils, buccal mucosa etc. so may cause chances of re-infection.

Classification of local drug delivery system

Greenstein & Tonetti in 2000, classified Local Drug Delivery system based on the duration of action into:³ Sustained release Devices and Controlled Delivery Devices. Intra Pocket devices can be of two types depending on their degradability: Non-degradable and Degradable Devices. Based On the Application, Rams and Slots in 1996 classified local drug delivery system as⁸: personally applied (in patient home self-care) and Professionally applied (in dental office).

Mechanism of action

According to Liechty et al⁹ the drug can follow one of the following mechanisms for controlled release: Desorption of surface bound/ adsorbed drugs ; Diffusion through the carrier matrix ; Diffusion (in the case of nano capsules) through the carrier wall; Carrier matrix.

FIBRES

Fibres, or thread like devices, are reservoir-type systems, placed circumferentially into the pockets with an applicator and secured with cyanoacrylate adhesive for the sustained release of trapped drug into the periodontal pocket. Hollow fibres containing 20% (v/v) chlorhexidine, when placed into periodontal pockets, exhibited a prompt and marked reduction in signs and symptoms of periodontal disease. The disadvantage of the hollow fibres served was that they permitted rapid evacuation of the drug. To retard drug release, drug-impregnated monolithic fibres were developed by adding drug to molten polymers, spinning at high temperature and subsequent cooling. Several polymers such as polycaprolactone (PCL), polyure-

thane, polypropylene, cellulose acetate propionate and ethyl vinyl acetate (EVA) have been investigated as matrices for the delivery of drug to the periodontal pocket.¹⁰

FILMS The most widely used intrapocket delivery device has been the film or slab form. It has been prepared either by solvent casting or direct milling. This form enhances the physical properties. Sustained release devices composed of cross-linked fish gelatin (bycoprotein) containing chlorhexidinediacetate or chlorhexidine hydrochloride in both degradable and non-degradable forms of films have been developed.

NON-DEGRADABLE FILMS: The first description of film form for intrapocket delivery appeared in 1982 and the film was made of methyl methacrylate for the intrapocket delivery of tetracycline, metronidazole, and chlorhexidine.¹¹

DEGRADABLE DEVICES: Films that release drugs by diffusion alone are prepared using water-insoluble non-degradable polymers, whereas those that release by diffusion and matrix erosion or dissolution are made of biodegradable polymers.

A degradable controlled-release device based on formaldehyde cross-linked bycoprotein matrix containing chlorhexidine has been formed. Based on this study, the Perio Chip[®] (Perio products Ltd., Jerusalem, Israel) has been developed for the controlled subgingival delivery of chlorhexidine.¹¹ This film has the advantage over other biodegradable films in which it remains inside the pocket with no additional aids for retention because of the adhesive nature of the Periochip components.

Synthetic biodegradable polymers have also been evaluated for sustained release of drug in the periodontal pocket. Chlorhexidine-loaded Diphen-Denta films were developed and used to be highly effective in patients with gingivitis and generalized periodontitis of light and medium severity.

INJECTABLE SYSTEM: Injecting a drug delivery system into the pocket has numerous advantages. It is a simple procedure with little or no discomfort to the patient. They are also cost effective. All injectable systems can be considered as degradable.¹²

GELS

Gel is applied subgingivally with the help of blunt cannula or syringe. The gel is only marginally effective in decreasing the anaerobic bacterial count. This may be due to the low number of bacteria susceptible to MTZ or due to presence of bacterial biofilm.

Studies have suggested that locally applied controlled release doxycycline (DOX) gel may partly counteract the negative effect of smoking on periodontal healing. The safety profile, long-term retention, antimicrobial activity suggests that tetracycline containing copolymer gels represent a safe and effective biodegradable therapy for periodontitis. Comparative analysis of tetracycline containing dental gels: poloxamer and monoglyceride based formulations have shown that poloxamer and monoglyceride gels, when applied subgingivally, produce a significant improved outcome in moderate to deep periodontal pockets.⁵

Various oleogels and hydrogels for the delivery of tetracycline (2.5%), metronidazole (25%) metronidazole benzoate (40%), as well as a combination of both tetracycline (2.5%) and metronidazole benzoate (40%), has been tested and satisfactory results have been achieved. Chitosan, a novel biodegradable natural polymer, in a gel form (1%, w/w) with or without 15% metronidazole, had demonstrated effectiveness in the treatment of chronic periodontitis.¹³

OINTMENT Antimicrobial ointments which are commercially available are of two types. Those that do not appear to have any sustained release properties. And the second one is a formulation consisting of a water-free mixture of melted glycerol monooleate

and metro diazole benzoate for which a triglyceride, sesame oil, has been added to lower the melting point in order to improve the flow properties of the gel in the syringe. When the mixture comes into contact with water, it sets in a liquid crystalline state. The formulation contains 25% metronidazole as 40% w/w metronidazole benzoate.¹⁴

ROOT CONDITIONING GELS Tetracycline or a mixture of tetracycline and citric acid gels have been used in moderate pockets, using a 5-minute burnishing technique to burnish the gel into the roots subgingivally. Beneficial effects of the acidic gel is that it can cause elimination or diminution of surface smear layer resulting from incomplete removal or translocation of dentin, plaque, calculus and cementum following root planing. An adverse effect caused by the low pH of citric acid is that it delays wound healing.¹⁵

ANTI-INFLAMMATORY GELS Williams and co-workers have investigated the effect of topical application of a nonsteroidal anti-inflammatory drug flurbiprofen on periodontal disease progression in beagle dogs. Dogs treated with 0.3 mg flurbiprofen applied to the gingival margin daily shows considerably less tooth loss than untreated dogs over the 7-month study.¹⁴

STRIPS AND COMPACTS Acrylic strips have been fabricated using a mixture of polymers, monomers and different concentrations of antimicrobial agents. Strips containing tetracycline, metronidazole (MTZ) or chlorhexidine demonstrated a decrease in number of motile rods, notably spirochetes. Tissue adhesive implants were made using n-butyl-2-cyanoacrylate as a drug trapping material and slowly release the drug when used in the structure of a biodegradable local drug delivery device.¹⁶

MICRO PARTICLE SYSTEM Micro particles based system with polyaliphahydroxyl acids such as polylactide (PLA) or polylactide-co-glycolide (PLGA) containing tetracycline has been designed for periodontal disease therapy. PLGA microspheres containing minocycline have been formulated and have been used for the elimination of Porphyromonasgingivalis from the periodontal pocket.¹⁶

Tetracycline-containing microcapsules in Pluronic F127 were reported to form gel at body temperature and hold the microcapsules in the periodontal pocket for the required duration of treatment. PLGA microcapsules and microspheres have been proposed for the delivery of tetracycline and histatins.

Systemic review of the recently added new drugs in local drug delivery system

Author	Aim of study	Major outcome
A R Pradeep et al ¹²	efficacy of subgingivally delivered metformin in treatment of chronic periodontitis	mean reduction of pocket depth
A R Pradeep et al ¹³	efficacy of subgingivally delivered 1.2 % Atorvastatin in patients with chronic periodontitis	mean reduction of pocket depth
Ray C Williams et al ¹⁴	Minocycline spheres in chronic periodontitis	mean reduction of probing depth
A R Pradeep et al ¹⁷	Efficacy of 1 % Alendronate gel in intrabony defects (class II furcation defects)	greater mean percentage of bone fill
Renvert et al ¹⁸	Efficacy of ocal minocycline microspheres in periimplantitis	Significant reduction in mean probing pocket depths.

Summary and conclusion

The requirements for treating periodontal disease include a means for targeting an anti-infective agent to infection sites and sustaining

its localized concentration at effective levels for a sufficient time while concurrently evoking minimal or no side effects. This chapter has discussed the various local drug delivery devices used in treating periodontitis. The following conclusions can be made:

- It is used effectively in controlling tissue associated bacteria
- It eradicates the periodontal pathogens for several weeks
- It is effective for treating single rooted teeth than multi rooted teeth
- It treats shallow periodontal pockets and recurrent periodontal disease.

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