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Role of Local Drug Delivery Agents in the Treatment of Periodontal Diseases

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ABSTRACT

Removal of the plaque biofilm mechanically forms the mainstay in the management of periodontal diseases. Mechanical debridement has its inherent limitations and frequent use of antibiotics is essential for complete resolution of the lesion. Antibiotics, when used directly into the site have more advantages than when administered systemically. This review highlight the rationale and beneficial effects of locally delivered agents.

Key words: Periodontitis; Root planing; antibiotics.

INTRODUCTION

Periodontal diseases are poly microbial infections resulting in an inflammatory reaction mounted by the host tissue with in adverterant tissue destruction. Though removal of the biofilm by mechanical instrumentation is the mainstay management for the treatment of periodontal disease, prudent use of chemotherapeutic agents especially in the form of locally administered drugs becomes mandatory to produce ideal results.

This article focuses on the use of drugs/ agents which are delivered locally into the pocket to treat periodontal disease.

Limitations of mechanical debridement

Frequently, treatment of periodontal disease involves the use of locally administered agents due to the following therapy of mechanical debridement[1]

- Unfavorable anatomy
- Intra oral microbial translocation
- Tissue invasive organisms
- Bacterial invasion into dentinal tubules

Ideal requisites of locally administered drugs[2]

- Must deliver the drug to the base of pocket.
- Must have microbiologically effective concentrations in the pocket.
- Be there for sufficient period of time.
- little or no effect on host tissues
- Retentive after placement.
- ease of placement and cost effective
- biodegradable

Classification

Locally delivered drugs can be classified as follows:

Based on application:[3]

i. Personally applied

a. Nonsustainedsubgingival delivery – home oral irrigation

b. Sustained subgingival drug delivery – none developed to date

ii. Professionally applied in dental office

a. Nonsustainedsubgingival delivery – pocket irrigation

b. Sustained subgingival drug delivery – controlled release device

Based on the duration of medicament release:[4]

a. Sustained release devices – designed to provide drug delivery for less than 24 hours.
b. Controlled release devices – designed to provide drug release that at least exceeds 1 day, or for at least 3 days following application.

Based on degradation

a. biodegradable
b. nonbiodegradable

Based on physical form:[5]

a. Fibers – eg tetracycline
b. Films/slabs – eg chlorhexidine chip
c. Injectable form – eg minocycline

Controlled Release Local delivery systems

- Reservoirs without rate controlling systems
- Reservoirs with rate controlling systems

Advantages

- can attain 100 fold higher concentrations
- can employ agents that are not suitable for systemic administration,
- with patient compliance.
- alternative for patients predisposed to adverse reactions from systemic antibiotic administration.
- Reduced risk for drug resistant microbe development at nonoral body sites.
- increased access to the site.
- lower total drug dosage.

Disadvantages

- Difficulty in placing therapeutic concentrations into deeper part of periodontal pockets and furcation lesions.
- Time consuming and labor intensive
- Do not have effect on bacteria residing on extra pocket oral niches
- Cannot be used for aggressive periodontal diseases.

Indications

- As an adjunct to root surface instrumentation in pockets of 5 mm or greater .
- Localized recurrent pockets in patients under supportive periodontal therapy.
- Non responding sites to conventional therapy in well motivated patients.
- Contraindications:
- allergic to particular drug used.
- as a monotherapy.
  to pregnant and lactating mothers (for tetracycline group of drugs).
- to be used with caution in patients with history of immune deficiency (to prevent the overgrowth of candida or other resistant organisms).

Adverse effects[6]

- Allergic reactions
- might produce resistant strains or overgrowth of intrinsically resistant organisms.
- occurrence of candidiasis especially.
- pain on insertion.
- burning sensation on insertion (with Chlorhexidine)
- development of abscesses
- interference with taste

Various drugs used as controlled release systems

Tetracycline

Tetracyclinesare broad spectrum antibiotics with activity against both gram positive and gram negative organisms consisting of four fused cyclic rings and the various derivatives consist of only minor alterations of the chemical constituents attached to this basic ring structure. Tetracycline, Doxycycline and Minocycline are commonly used with similar spectrum of activity. Hence resistance to one indicates resistance to all the three. They are considered as bacteriostatic agents but may have bactericidal effects in high concentrations. These drugs principally acts by inhibiting protein synthesis.

In addition to its antibacterial action, it also possess the following functions:[7]

1. Inhibits most of mammalian collagenases
2. Demineralizes dentin cementum and dentin, when applied topically thereby enhancing attachment of fibroblasts to the tooth surface

Advantage of tetracycline as controlled release systems includes its high substantivity; after local delivery have been detected at 1-20µm within epithelial tissues, detectable in crevicular fluid several weeks following application and attaining high concentration in crevicular fluid.

Tetracycline fibers (Actisite)

Tetracycline is available in the formn of fibers which, if placed locally can control or treat periodontal disease. They are non-resorbable cylindrical drug delivery devices made of a biologically inert, plastic co-polymer loaded with 25% tetracycline HCL powder. They are 23 cm in length and 0.5 mm in diameter. The fiber is flexible, and can be folded on itself to nearly fill the pocket and able to produce and maintain a concentration of 1, 300µg/ml for a period of 7 days with mean concentrations of 43µg/ml in the superficial portions of the pocket wall. At a concentration more than 150 times achieved by systemic tetracycline, these fibers provide bactericidal concentration of tetracycline.

Types of fibers

- Hollow fibers: cellulose acetate fibers are filled with tetracycline and they provide only sustained release system.
- Monolithic fibers: prepared by melt extrusion technique, wherein, a mixture of 25% tetracycline HCl and 75% ethylene vinyl acetate was heated to 214 C and extruded as 0.5 mm fiber and they provide a controlled release system.
- Resorbable fibers:**Minabe et al** [8] described a device in which tetracycline is incorporated into cross-linked collagen matrix, atelocollagen, capable of delivering tetracycline in the crevicular fluid at therapeutic levels for upto 10 days after insertion and drug levels ranged from 17 to 180µg/ml.

Technique

- An individual or several teeth can be treated at a time. Short lengths of fiber, 2-3 inches are taken in a cotton forceps and placed at the opening of the pocket o be treated. The fiber might be folded on itself and the folding procedure might be repeated until all the pockets are nearly filled. Interproximal pockets should be packed from both the buccal and the lingual sides. After placement, the area is isolated with cotton rolls or gauze, tooth dried with the air syringe, and a drop of tissue adhesive applied at each interdental area as well as facially and lingually. Alternatively, periodontal pack can be placed.Fibers should be in place for 7-14 days. Fiber removal (in case of non-resorbable fibers), is fairly simple. They can be teased out of the pockets with a curette.

Instructions to be given to the patient

- not to brush or floss the treated areas until fibers are removed.
- To rinse with chlorhexidine mouth rinse while the fibers are in place and for 1 week after their removal.
- Advised to return back to normal original oral hygiene procedure after 1 week or after fiber removal (in case of non-resorbable fibers).
- To come for recall visit at 4-6 weeks.

Comparison between local and systemic drug delivery systems

Local Drug Delivery	Systemic delivery
1. High concentration in the pocket	1. Less concentration in the pocket
2. Minimal side effects	2. More adverse effects
3. Less reliance on patient compliance	3. Patient compliance is relied on
4. Avoids exposure of drug to non oral sites	4. Whole body is exposed to the drug
5. Comparatively less penetration achieved	5. Delivery to base of the pocket achieved
6. Potential reservoirs not treated	6. Treat potential reservoirs of bacterial re infection
7. Tissues invasive organisms not always affected	7. Affect tissue invasive organisms
8. Takes more time	8. Takes less time
9. Have a learning curve	9. Do not have

Doxycycline polymer (Atridox)

A biodegradable formulation containing 10% by weight doxycycline, 33% by weight poly (DL-Lactide) and 57% by weight N-methyl 2-pyrrolidone was developed. It is a liquid biodegradable system that hardens when placed in periodontal pocket.

Technique of placement

Liquid delivery system containing 10% doxycycline hyclate is contained within a syringe that has a blunt ended 23 gauge cannula attached. The cannula has a diameter of a periodontal probe, which is bent is used in a similar diagnostic and tactile manner. The tip of the cannula is introduced to the depth of the pocket and the drug is expressed out. As it begins to harden on contact with the moisture and during the 1-2 minutes of hardening, it is packed into the pocket using the underside of the moistened curette or other blunt-ended instrument. Immediately after administration, the polymer slightly protrudes from the pocket orifice. Periodontal dressing or adhesive is used as an aid in retention of the system.

Minocycline (Dentomycine and Periocline)

Three modes of local application are available: film, microspheres or ointment. It is a bacteriostatic antibiotic. The concentration of minocycline in the pocket was 1300 µg/ml, I hour after single topical administration of 0.05 ml ointment and decreased to 90 µg/ml after 7 hours.

Film: Ethylcellulose containing 30% of minocycline cast from ethanol, chloroform or chloroform with polyethylene glycol were tested as sustained release devices.

Microspheres:Minocycline micro-encapsulated in a resorbable poly (glycolide-lactide) slow release polymer (Braswell et al), this can be administered by means of disposable plastic syringe. The volume of microspheres in each syringe is 4 mg which is equivalent to 1 mg of minocycline base.

Ointment:It is a light yellow colored ointment base of 20 mg hydroxyethyl cellulose, 10 mg eudragit RS, 60 mg triacetine and glycerine 0.5 g, supplied in a disposable polypropylene applicator and each applicator contains the equivalent of 10 mg minocycline in 0.5 g ointment.

Repeated applications of 2% minocycline, 1 applications per week for 4 weeks, 2 applications at intervals of 1 or 2 weeks, 3 applications at 2 weekly intervals were effective.

Metronidazole

It is a 5-nitroimidazole compound specifically targets anaerobic microbes but has essentially no activity against aerobic or microaerophilic bacteria but its hydroxyl metabolite enhances its effect even against other group of bacteria.Upon entry into an organism, metronidazole is reduced at 5-nitro position by electron transport proteins The reduction of parent molecule produces free radicals. These react with bacterial DNA causing cell death. Hence it is primarily a bactericidal agent.Serum concentration of Metronidazole has shown to attain MIC levels for most periodontal pathogens and it is found to eliminate spirochetes from ANUG lesions.

Metronidazole dental gel (Elyzol)

This is a bioabsosbable delivery device containing 25% Metronidazole benzoate in a matrix consisting of a mixture of glyceryl mono-oleate and sesame oil. The gel is subgingivally placed with a syringe and a blunt cannula. Decay of the drug concentration in crevicular fluid follows an exponential pattern which is compatible with sustained drug delivery. A substantial amount of this drug can be swallowed, or absorbed through the mucosa, as indicated by peak plasma concentration observed 2-8 hours following administration.A substantial amount of this drug can be swallowed, or absorbed through the mucosa, as indicated by peak plasma concentration observed 2-8 hours following administration.

Chlorhexidine

It is a topical antiseptic belonging to the family of bisguanides. It is mainly active against gram positive group of organisms. It is bacteriostatic at lower and bactericidal at higher concentrations. It has been detected in excess of 125 µg/ml in crevicular fluid for 1 week following a single application.

Chlorhexidine chip (Periochip)

It is a bioabsorbable device comprising 34% Chlorhexidine in a cross linked gelatin matrix. Each chip is 5 mm long, 5 mm wide, and 1 mm thick pliable strip loaded with 2.5 mg of Chlorhexidine.

Technique of placement

After scaling and root planing, the chip is grasped in a cotton forceps and gently inserted into the pocket. It is advisable to dry the area before placing the chip. As burning sensation is reported after the chip placement, placement of multiple chips around a single tooth may result in discomfort. The chip degrades in a period of 7-10 days and requires no retentive system.

Ofloxacin

Ofloxacin belongs to quinolone family which constitute a group of 1,8naphthyridine derivatives and are synthetically produced drugs. They are considered to be bactericidal as they inhibit the enzyme DNA replication by acting on the enzyme DNA gyrase. The bactericidal effect can only occur in the presence of competent RNA and protein synthesis. The imbalance of inhibited DNA replication and continued protein synthesis results in inhibition of cell division.

Ofloxacin inserts (PT-01)

PT-01 is a soluble insert, with both fast and sustained release parts containing 10% w/w ofloxacin, and showed a constant drug level of above 2 mg/ml, (minimum MIC for most pathogenic organisms) which could be sustained for up to 7 days. The controlled release system exhibited a biphasic pattern with a rapid early release phase peaking at approximately 12µg/ml and stabilizing at approximately 2µg/ml from day 3 to 7 following insertion.

Azithromycin

This belongs to azalide group of antibiotics, derived from macrolides. It has a broad spectrum activity against a number of bacteria including gram negative anaerobes and provides excellent and prolonged drug concentration in tissues and serum. It has got a good in vitro activity against all serotypes of A.a, and P.g. it is predominantly a bacteriostatic drug and interfere with bacterial protein synthesis by binding to 50s ribosomal unit. It can penetrate both healthy and diseased periodontal sites and to maintain chemotherapeutic levels in excess of the MICs of majority of periodontopathogens.

Azithromycin at 0.5% concentration in an indigenously prepared bioabsorbable controlled-release gel as an adjunct to non-surgical mechanical therapy in the treatment of chronic periodontitis was evaluated by comparing with scaling and planing alone. Although both treatment strategies seemed to benefit the patients, the adjunctive use of 0.5% azithromycin as a controlled drug-delivery system enhanced the clinical and microbiologic results and the mean concentration of azithromycin at all observed periods (baseline to 28 days) is more than >2 µg/ml which has a potent antibacterial activity.

CONCLUSION

- The current data suggest that local delivery of antimicrobials into the periodontal pocket can improve periodontal health. However, they do not provide a superior result to scaling and root planing.[9]
- In conjunction with scaling and root planing, the adjunctive use of local drug delivery devices may enhance the results in sites which do not respond to conventional therapy.

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