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Review Article

Local Drug Delivery In Periodontics: A Review

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ABSTRACT

Periodontal diseases are bacterial infections characterized by inflammation and destruction of the attachment apparatus, often leading to tooth loss. Plaque consists of highly organized bacterial populations. Although plaque appears to be essential for the development, especially initiation of the periodontal disease, it is now widely recognized that the host response to these bacterial pathogens is equally, if not more, important in mediating connective tissue breakdown, including bone loss. Therapeutic approaches for the periodontal diseases must include the modalities that will target the microorganisms as well as modulate the destructive host response. The success of mechanical periodontal treatment is closely related to the patient's performance of daily plaque control. Adjunctive administration of

systemic antimicrobials has been useful in treating recurrent periodontal pockets but the dose necessary to achieve sufficient local concentrations might be associated with side effects. Therefore, local drug delivery systems have been developed as they maintain effective intra-pocket levels of antibacterial agents for extended periods of time, so that they can alter sub-gingival flora and influence the healing of any attachment apparatus.

KEY WORDS: Periodontal disease, Local drug delivery, Intra-pocket medication, Tetracycline, Chlorhexidine, Doxycycline

INTRODUCTION

Periodontal diseases are bacterial infections characterized by inflammation and destruction of the attachment apparatus, often leading to tooth loss.[1] Therapeutic approaches for the periodontal diseases must include the modalities that will target the microorganisms as well as modulate the destructive host response. As the success of mechanical periodontal treatment is closely related to the patient's performance of daily plaque control, recurrent periodontal tissue destruction is almost inevitable in patients who fail to achieve an acceptable plaque control during the active treatment or maintenance phase of periodontal therapy. This has led to the use of chemotherapeutic agent in periodontal therapy. Advances in the technology of local drug delivery and understanding of etiopathogenesis of periodontal diseases have resulted in a number of site-specific, controlled-release methods. Local delivery systems offer the advantages of high concentrations at the target sites with reduced systemic dosing, fewer applications, lesser side effects, and high potential acceptability.[2]

The review article is an attempt to examine different concepts of local drug delivery as applicable in periodontal diseases and to summarize the results of *in-vitro* and *in-vivo* studies demonstrating the major role of these drugs when delivered locally (subgingivally) into the periodontal pockets.

Ideal requisites of locally delivered drug[3]

Before any antimicrobial agent can be recommended for periodontal therapy a number of basic and important conditions have to be fulfilled such as:

1. Drug must show in-vitro activity against the organisms considered most important in the etiology
2. It should be demonstrated that a dose sufficient to kill the target organism can be reached within the subgingival environment

3. At that dose drug should not have adverse effects and finally, it should be specific for periodontal pathogens.

Principles, Goals and Rationale of Local Drug delivery in Periodontics

Local Drug Delivery is based on the principle that periodontal pocket provides a natural reservoir bathed by GCF, which 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.[4]

The primary goal in using an intra-pocket device for the delivery of an antibacterial agent is the achievement and maintenance of therapeutic levels of the drug for the required period of time. Studies suggest that the critical period of exposure of the pocket to an antibacterial agent is in the range of 7 – 10 days.

Rationale of local drug delivery is to place an antibiotic or antiseptic in direct contact with the root surface so that pathogenic organisms that are not accessible to mechanical removal by hand or power-driven instruments can be reduced or eliminated.[4,5]

Pharmacokinetic parameters for local application

In order to achieve the pharmacological objectives of a locally delivered agent, **Greenstein and Tonnetti (2000)**[6] have proposed following three pharmacokinetic parameters for the local drug delivery viz; site of action, adequate concentration and sufficient duration of time. Local drug delivery targets bacteria in the periodontal pocket, soft tissue wall of the pocket, exposed cementum or radicular dentin, but, the presence of subgingival calculus, anatomic anomalies, deep pockets and furcation lesions may pose physical difficulty in placing the drug at intended site. This can be overcome by the use of irrigating solutions delivered intracrevicularly via a cannula or other device. The minimum inhibitory concentrations of antimicrobial agents are at least 50 times higher than for bacteria growing under planktonic conditions, therefore, adequate drug concentration must be maintained at the local site. Also, an adequate drug-microbial contact time must be attained for an antimicrobial agent to act against targeted microorganisms.

Other desirable factors considered important for optimal drug delivery are **periodontal clearance and substantivity**. As the expected half life of a pharmacological agent in the gingival crevice is

about 1 min, this high rate of clearance represents the major obstacle in maintaining effective concentrations of an antimicrobial agent within the pocket. Therefore, a subgingival drug reservoir is required that can release medication to counteract its continuous loss due to crevicular fluid flow. **Substantivity**[6] refers to the property of a substance to bind to soft and/or hard tissues of the pocket, thereby establishing a drug reservoir that is slowly released over a period of time. Therefore, incorporation of drug into various vehicles or devices, prior to placement into periodontal pocket enhances substantivity.

Indications of Local Drug Delivery[3]

The use of local drug delivery may be advantageous in following few situations:

1. Deep pockets with very difficult access for scaling and root planing and in refractory or rapidly progressive periodontitis.
2. Localized deep pockets that fail to respond to repeated scaling and root planing.
3. Medically compromised patients where surgical therapy is contraindicated
4. As an adjunct to mechanical debridement and periodontal regenerative procedures.
5. Sites with acute lateral periodontal abscess (instead of systemic antibiotics).

Contraindications of Local Drug Delivery[3]

1. Patients who are allergic to any component of the local drug delivery system.
2. In pregnant or lactating patients, where the drug being used is known to have harmful effects on the foetus/infant.
3. Aggressive form of periodontitis that may require systemic antibiotics to eradicate the disease.
4. Multiple unresponsive disease sites (pockets).

Advantages of Local Drug Delivery[7,8]

1. Provides drug in an effective concentration that can be maintained there long enough for the desired effect to be accomplished without causing any side effect.
2. It can attain upto 100 fold higher concentration of an antimicrobial agent in the subgingival site compared with a systemic therapy.
3. This route may employ antimicrobial agents not suitable for systemic administration such as various broad spectrum antiseptic solutions, like chlorhexidine.
4. Superinfection and drug resistance are rare.
5. The potentials of daily drug placement into

periodontal pockets as a part of home self care procedure can be performed by a compliant patient.

6. Local antibiotic delivery provides an alternative for treatment of women with a propensity for vaginal superinfections, and for individuals predisposed to gastrointestinal complications (ulcerative colitis) or other adverse reactions, from systemic administration.
7. It reduces the potential problems with patient compliance, as some times seen during systemic therapy.

Disadvantages of Local Drug Delivery[7,8]

1. Inaccessible and deeper pocket areas, furcations cannot be completely dealt with antimicrobial agents.
2. The task of professionally applying local antimicrobial agents in periodontitis patients with numerous advanced lesions is time-consuming and labour-intensive.
3. Antimicrobial agents locally applied into periodontal pockets do not markedly affect periodontal pathogens residing within adjacent gingival connective tissues and on extra pocket oral surfaces (tongue, tonsils, and buccal mucosa), which increases the risk of later reinfection.
4. Personal application of antimicrobial agents by patients as a part of their home self-care procedure is frequently compromised by the patient's lack of adequate manual dexterity, limited understanding of periodontal anatomy and poor compliance and performance with recommended procedures.

Classification of local drug delivery systems

(I) Langer and Peppas (1989)[9] **Classified Controlled Drug Release Polymeric Systems Based on Their Mechanism of Action.**

1. **Diffusion Controlled Systems**
   (a) Matrices
   (b) Reservoirs
2. **Chemically Controlled Systems**
   (a) Erodible systems
   (b) Pendant chain systems
3. **Solvent Activated Systems**
   (a) Osmotic systems
   (b) Swelling controlled systems
4. **Release Induced By External Forces**

(II) Kornman (1993)[10] **has Classified the Controlled Release Local Delivery System As:**

1. **Reservoirs without a Rate Controlling System** like hollow fibers, gels and dialysis tubing.
2. **Reservoirs with a Rate Controlling System** like Erodible Polymeric matrices, Microporous polymer membrane, Monolithic matrices and coated drug particles.

(III) Based On Type of Therapy (Rams And Slots, 1996)[11]

1) **Personally Applied (patient home self-care)**

A. Non-sustained subgingival drug delivery (home oral irrigation)

B. Sustained subgingival drug delivery (none developed to date)

2) **Professionally Applied (in dental office)**

A. Non-sustained subgingival drug delivery (professional pocket irrigation)

B. Sustained subgingival drug delivery (controlled release device)

(IV) Based on Dosage Form (Soskolne WA, 1997)

Devices have been developed in three broad dosage forms:

a. **Fibers e.g.** Tetracycline

b. **Films/slabs e.g.** Chlorhexidine chip

1. Non-degradable films
2. Degradable devices

c. **Injectable systems e.g.** Minocycline

(V) Based On Duration of Action (Greenstein & Tonetti, 2000)[6]

According to the duration of drug release, the local delivery devices used in periodontology can be divided into two classes:

A) **Sustained Release Devices**

- Drug delivery for less than 24 hrs
- Require multiple applications
- Follow first order kinetics

B) **Controlled Release Devices**

- Duration of drug release exceeds 24 hrs e.g. 5% clindamycin in Eudragit
- Films administersed once
- Follow zero order kinetics

Locally delivered Antibiotics/Antimicrobials in Periodontal Therapy

TETRACYCLINES

The tetracyclines are group of antibiotics with a similar antibacterial spectrum but differing pharmacokinetic properties created by various chemical substitutes on hydronaphthacene four-

ringed nucleus.[12] Tetracyclines act by inhibiting bacterial protein synthesis. Tetracyclines have been widely used in the treatment of periodontal diseases. They have been investigated as adjuncts in the treatment of refractory periodontitis, including localized aggressive periodontitis (LAP). Tetracyclines have the ability to concentrate in the periodontal tissues and inhibit the growth of *A. actinomycetemcomitans* and have been shown to arrest bone loss when used in conjunction with scaling and root planing. Other properties of tetracyclines such as collagenase inhibition, anti - bone resorption effect, anti-inflammatory actions and fibroblast attachment are of value in management of periodontal diseases.[13,14]

Tetracycline impregnated fibres are used for subgingival delivery of tetracycline. Each tetracycline-impregnated fibre is 0.5 mm in diameter and is a copolymer of ethylene vinyl acetate and tetracycline hydrochloride. It is extruded as a 23 cm flexible monofilament that contains 12.7 mg of evenly dispersed tetracycline. During a 10-days placement interval, tetracycline-impregnated fibres deliver 25% of available tetracycline and produce a sustained, high level of tetracycline (averaging 1590 µg/ml) in gingival crevicular fluid.[14]

Several controversial issues such as development of antibiotic resistance are associated with placement of tetracycline impregnated fibres.

DOXYCYCLINE

Doxycycline (DOX) is a broad-spectrum antibiotic synthetically derived from oxytetracycline. It is bacteriostatic, inhibiting bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites.[15] Low dose DOX has been shown in a controlled clinical trial to be effective in significantly reducing collagenase activity in the GCF and gingival inflammation (**McCulloch 1990, Aitken 1992, Matisko 1993).** The major benefit with this drug over TCN is better patient compliance since it is usually given only once a day.[16] **Atridox** (for subgingival delivery of doxycycline) 10% is indicated for use in treatment of chronic adult periodontitis to gain clinical attachment, and reduce probing depth and bleeding on probing. The most common were headache, common cold, gum discomfort, pain, soreness, toothache, and tooth sensitivity.[15]

MINOCYCLINE

Minocycline is a semisynthetic derivative of tetracycline and a very potent broad spectrum

antibiotic. Minocycline works by interfering with protein synthesis in the bacterial cell wall.[17] Minocycline administered in a dosage of 200 mg per day for 1 week results in a reduction in total bacterial counts, complete elimination of spirochetes for periods of up to 2 months, and improvement in all clinical parameters.[18]

For minocycline, 3 modes of local application (film, microspheres or ointment) have been applied clinically:

Film: Films of ethylcellulose containing 30% of minocycline cast from ethanol, chloroform, or chloroform with polyethylene glycol were tested as sustained release delivery devices (Elkayam et al l988). The results of the short-term clinical study indicated that the use of the device in periodontal pockets may cause complete eradication of the pathogenic flora from the pocket for 14 days.

Microsphere: Minocycline micro-encapsulated in a resorbable poly (glycolide-lactide) slow release polymer has been studied by **Braswell et al. (1992) and Jones et al. (1994).** 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, 25 mg magnesium chloride, 10 mg eudragit RS, 60 mg triacetine, and glycerin to 0.5 g, supplied in a disposable polypropylene applicator. Each applicator contains the equivalent of 10 mg minocycline in 0.5g ointment. In addition to its antibacterial activity, the inhibitory effects of minocycline against collagenase activity have been reported by **Maehara et al. (1988).** However, against the collagenase activity of human gingival fibroblasts, minocycline caused 2% and 18% inhibition at 10 and 500 µg./ml., respectively, compared with the lower inhibition of tetracycline.

Metronidazole

Metronidazole is selectively toxic to anaerobic microorganisms. After entering the cell by diffusion, its nitro group is reduced by certain redox proteins operative only in anaerobic microbes to a highly reactive nitro radical which exerts cytotoxicity, by damaging DNA and other critical biomolecules.[18] Metronidazole has been used clinically to treat gingivitis, acute necrotizing ulcerative gingivitis, chronic periodontitis, and aggressive periodontitis. It has been used as monotherapy and also in combination with both root planing and surgery or with other antibiotics. Metronidazole has been used successfully for treating necrotizing ulcerative gingivitis. A topical

medication **Elyzol®** containing oil based metronidazole 25% dental gel (glycerol mono-oleate and sesame oil) is available for local application. Elyzol 25% dental gel contains metronidazole in the form of metronidazole benzoate as the active substance. It is designed for application into gingival pockets. After application, the preparation acquires greater flowability and fills the pocket. On contact with the gingival fluid, it forms a highly viscous gel. This is slowly broken down and metronidazole is released gradually from the gel. It is used for the treatment of chronic recurrent periodontitis as an adjunct to conventional therapy. Elyzol 25% dental gel is administered into the periodontal pocket twice, with an interval of one week. Dose is individual, depending upon the number of teeth to be treated. 0.3g of gel is sufficient for the treatment of the pockets of 6-8 teeth. 1g of gel is sufficient for the treatment of pockets of approximately 20 teeth.

Chlorhexidine chip (Periochip)

Periochip (Dexcel Pharmaceuticals, Israel) is an orange brown, biodegradable, rectangular chip rounded at one end that has an active ingredient of chlorhexidine gluconate (2.5 mg) that is released into the pocket over a period of 7-10 days. It has been found to suppress the pocket flora for up to 11 weeks post application **(Stabholz et al. 1986).**[19] The polymer is made from 3.4 mg of cross-linked hydrolysed gelatin, 0.5 mg of gelatin and 0.96 mg of purified water, and contains 2.5 mg chlorhexidine.[15] It is very simple to place into a periodontal pocket, and the swelling of the chip on contact with moisture retains it in place. The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion. The PerioChip should be grasped by the square end using non serrated forceps, so that the rounded end points into, and is inserted into, the periodontal pocket to its maximum depth. It should be placed at the base of the pocket. If necessary, the Periochip can be further maneuvered into position using the tips of the forceps or a flat instrument**).**

Other local drug delivery systems

Herbal control on Periodontitis

- The natural products derived from medicinal plants have proven to be an abundant source of biologically active compounds, many of which have been the basis for the development of new lead chemicals for pharmaceuticals. There are many benefits of herbal drugs such as Herbal drugs have long era of use and better patient tolerance as well as public

acceptance.

- Herbal drugs act as a renewable source, which is our only hope for sustainable supplies of cheaper medicines for the growing world population.
- Availability of medicinal plants is not a problem especially in developing countries like India having rich agro-climatic, cultural and ethnic biodiversity.
- The cultivation and processing of medicinal herbs and herbal products is environment-friendly.
- Throughout the world, herbal medicine has provided many of the most useful and vast variety of drugs to the modern medical science.

There are many herbs which can be used in periodontal diseases such as Eucalyptus extract, Bloodroot, Neem Leaf, Chamomile, Green Tea, Aloevera.[19]

Role of Non-Steroidal Anti-inflammatory Drugs in Periodontics

Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely used to reduce the inflammation and pain in patients suffering from arthritis. There is a possible use for these drugs in the treatment of inflammation associated with periodontitis. . However, the propensity of NSAIDs to cause serious side effects, including gastrointestinal bleeding, has reduced their usefulness. The local application of NSAIDs can avoid these side effects by delivering low doses of drug directly to the affected site.[16]

Technologies for improved delivery [20]

Some of the delivery challenges described above have led to research into technologies such as mucoadhesives, permeability enhancers and enzyme inhibitors as well as modifications to drugs and absorption enhancers that could enhance both topical and systemic transmucosal delivery of drugs.

SUMMARY AND CONCLUSION

Current data suggest that local drug delivery of antimicrobials into a periodontal pocket can improve periodontal health. A substantial amount of information has become available and at present the following trends may be identified with regards to various local delivery systems:

1. As a monotherapy, local drug delivery systems incorporating a variety of drugs can improve periodontal health.
2. There is no single universal drug that would be effective in all situations. Therefore, at

non-responsive sites, bacterial and antibiotic sensitivity testing may be necessary to determine putative pathogens and their susceptibility to specific antimicrobial agents.

3. Local drug delivery often appears to be as effective as scaling and root planing with regards to reducing signs of periodontal inflammatory disease: redness, bleeding upon probing, probing depth, and loss of clinical attachment.
4. Local drug delivery systems usually do not provide a benefit beyond what is achievable with conventional scaling and root planing in the treatment of adult Periodontitis. Therefore, their routine utilization is unnecessary.
5. Local delivery may be an adjunct to conventional therapy. The sites most likely to be responsive to this adjunctive treatment method may have refractory or recurrent periodontitis or specific locations where it is difficult to instrument root surfaces. However, the data are limited to support this concept.
6. At present, there are insufficient data to indicate that one local drug delivery device is clearly superior to all the other systems. However, desired characteristics include ease of placement, controlled release of drugs and resorbability.
7. In conjunction with conventional treatment, systemically administered drugs appear to be as effective as local drug delivery.
8. To date, results from studies assessing local drug delivery systems have not justified extending the time interval between supportive periodontal maintenance visits.
9. There are preliminary, but very limited data, regarding the ability of local delivery to help suppress future disease progression.
10. There are insufficient data to indicate that local drug delivery induces bacterial resistance to antimicrobial agents. Long-term studies are needed to address this important issue.
11. There are limited term data (5 years) evaluating the efficacy of local drug delivery.
12. Additional studies are needed to evaluate if local delivery is effective against tissue invasive organisms.
13. There is a lack of data to support the impression that local drug delivery in

conjunction with root planning reduces the need for periodontal surgery more than scaling and root planing alone.

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