MAR Dental Sciences

Review Article

Local drug delivery: A Brief Review

Tarndeep Kaur Sekhon*, Bikramjit Singh Sekhon[1]

1. BDS, BRS Dental College and Hospital Panchkula, Haryana, India.

***Corresponding Author: Tarndeep Kaur Sekhon, BDS**, BDS, BRS Dental College and Hospital Panchkula, Haryana, India. Email: tarndeepchahal22@gmail.com

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Abstract

Periodontitis is a multifactorial disease where periodontal pathogens trigger chronic inflammation and immune responses. Mechanical debridement has always been the first line of defense. Other non-surgical methods include antimicrobials, Local drug delivery. Each drug delivery system has its pros and cons. Local drug delivery aims to deliver antimicrobial agents to subgingival diseased sites. It is placed in periodontal pockets. This review aims to summarize various types of Local drug delivery system and their advantages and disadvantages.

Keywords: *Periodontitis, Mechanical debridement, Local drug delivery, periodontal pockets.*

Introduction

Periodontal disease starts as an inflammatory reaction confined to gingival tissue but when left untreated involve periodontal ligament, alveolar bone, and cementum resulting in the formation of pocket which provides habitat for the growth of pathogenic anaerobic microorganisms. This affects the oral cavity adversely leading to tooth migration, tooth mobility, tooth loss, and ultimately an increase in masticatory dysfunction **(**1**)**. Treatment of periodontitis routinely includes maintenance of oral hygiene by use of mouth rinses, subgingival irrigation, and application of local drug delivery systems. These

mouth rinses are effective only for supragingival biofilm control as they do not gain access to the subgingival environment. Subgingival irrigation is also not that effective as they are rapidly clear by gingival crevicular fluid (GCF). Non-binding drugs become ineffective within 15 minutes following application.

So, to overcome these disadvantages Dr. Max Goodson of the Forsyth Dental Research Center in the 1970s pioneered the field of the local drug to treat periodontitis. He used tetracycline in hollow fibers **(2)**. A Local Drug delivery system is defined as a device that consists of a drug reservoir and a limiting element that control the rate of medicament release **(3)**. A periodontal pocket is a natural site for treatment with LDD as gingival crevicular fluid provides a hydrated environment that boots the distribution of the drug throughout the pocket **(4)**.

The success of every drug delivery system depends upon its ability to deliver the antimicrobial agents at a bacteriostatic or bactericidal concentration at the base of the pocket. Local drug delivery system should meet the following requirement to be effective **(5)**:

- Inhibitor kill the putative pathogen
- It should be inadequate concentration
- It should be biocompatible and biodegradable
- It should stay long enough
- It should be easy to place and economical

Rationale

The rationale behind the use of Local Drug Delivery is to disinfect pathogen reservoirs by delivering high concentration antibiotic or antimicrobial directly to the site of periodontal infection and facilitates the retention of a medicament for a required period to combat the microbial attack, simultaneously minimizing its undesirable effects on non-oral systemic/ body sites **(4)**. They are available in the form of gels, strips, fibers, films, irrigating systems, vesicular systems, microparticles, and nanoparticles.

Advantages of using LDD over systemic antimicrobial agents (6):

1. Minimal invasive and direct application at the site of infection.
2. Avoidance of gastrointestinal issues and first-pass metabolism.
3. Reduction in dose and frequency of drug administration.
4. Improve patient compliance

5. Serves as an ideal means to incorporate the agents that are not for systemic administration such as chlorohexidine.
6. Development of bacterial resistance

Classification:

According to Kornamm (6) (Based on rate-controlling form)

LDD is broadly divided into two types:

1.Reservoir without rate control (effective only for 24 hours, follow first-order kinetics)

Examples: Gels -Doxycycline (Atridox), hollow fibers Tetracycline (Actisite), and dialysis tubing

2.Reservoir with rate control (effective for more than 24 hours, follow zero-order kinetics)

Examples: polymeric matrics, polymer membrane.

According to Rams and Slots (7) 1996 (Based on Usage)

1.Personally applied (Inpatient home-care)

They can be supragingival home irrigation devices, subgingival home irrigation devices, and marginal home irrigation devices.

a. Non-sustained drug delivery

Examples: Oral irrigators -Water Pik, Soft cone rubber tips- Pickpocket

2.Professionally applied (In dental office)

a. Non-sustained drug delivery

Examples: supragingival and subgingival irrigators Povidone-iodine

b. Sustained drug delivery

Examples: hollow fibers, gels

According to Soskolne WA, 1997 (8) (Based on Dosage Form)

1. Fibers (Tetracycline)
2. Film/slab (Chlorohexidine chip)
3. Injectable Systems (Minocycline)

Indications (9)

1. Isolated periodontal pockets (more than 5mm)
2. As an adjunct to mechanical debridement
3. A patient who is medically compromised and hence, surgery is contraindicated
4. A patient suffering from recurrent or refractory periodontitis
5. During periodontal regenerative procedures
6. Patient not willing for flap surgery
7. Patient with periodontal abscess
8. In cases of an ailing or failing implant
9. Grade-II furcation involved cases

Contraindications (10):

1. The use of LDD has failed to control periodontitis
2. In pregnant or lactating patients
3. Patient with infective endocarditis
4. Patient with hypersensitivity reactions
5. Multiple sited with periodontal depth more than 5mm within the same quadrant.
6. Patient with renal failures
7. Children below 12 years of age
8. Patient with asthma and cardiac pacemakers.

Various drugs used as LDD

1.Tetracyclines:

It is a broad-spectrum antibiotic that has activity against both gram-positive and gram-negative bacteria. Goodson's first delivery device consists of hollow fibers of cellulose acetate filled with tetracyclines in 1979. It consists of four fused rings and their various derivates consist of a minor alteration of chemical constituents. Besides antibacterial action, it also demineralizes dentin cementum and dentin and enhances attachment of fibroblasts to the tooth surface.

Advantages:

1. Detectable in higher concentrations GCF several weeks following applications.
2. Anti-inflammatory actions
3. Anti- bone resorption effects
4. Collagenase inhibitors
5. Has high substantivity

Disadvantages

1. Drug resistance
2. Ability to kill benign bacteria associated with health as well as pathogens.
3. Not prescribed for pregnant women

a) Tetracycline fibers (Actisite)

It consists of an ethylene-vinyl acetate polymer that contains about 25% of saturated tetracycline HCl. It is marketed in the length of 23cms and 0.5 mm diameter containing 2.7 mg of tetracycline HCl of flexible yellow fibers and is non-resorable **(11)**. Single or several teeth are treated together. It is approved by FDA in 1994.

Technique:

Tetracycline fibers have some amount of memory and thus can be bent. The optimal site for the use of fibers are pockets that bleed on probing and do not respond to mechanical therapy. 2-3 inches of fiber with the help of forceps is placed in the pocket. The pocket is filled below the gingival margin because gingival shrinkage is known to occur. In a case with interproximal pockets, fibers are packed from both

facial and lingual sides. After placement, the area is isolated with cotton and a drop of adhesive is applied. Fibers are placed for 7-14 days. The patient is advised not to brush or floss in the treated area until fibers are removed and chlorhexidine mouthwash is prescribed twice a day.

Disadvantages

1. More length of twice is required for placement
2. Need for a second appointment for removal of fibers
3. Sometimes result in oral candidiasis
4. Can cause discomfort to the patient when removed

b) Periodontal Plus AB

These are bioresorbable tetracycline fibers that have been developed with the base of collagen film. It offers the advantage of no further appointment for its removal after 7 days. It has a dual-mode of action by enables the active agent and vehicle to be able to work positively towards the repair of the periodontal lesion.

c) Tetracycline Gel

Tetracycline-Serratiopeptidase is also known as a 20% pluronic gel containing periodontal shows significant improvement in periodontal disease along with scaling and root planning **(12)**.

2.Doxycycline (Atridox)

It is a gel system that contains about 10% of doxycycline, 33% of poly DL-Lactide, and 57% N-methyl 2-pyrrolidine in a syringe. It is available in two syringes that are coupled together before use and mixed by moving the contents of the syringes back and forth for 100 cycles. The delivery syringe is attached to a 23-gauge blunt cannula and the material is injected into the periodontal pocket. The material is gently in overflow consistency packed in the pocket with the cord packing instrument or the back of a curet. The patient is advised to avoid blushing, flossing, or eating in the treated area for a minimum of 7 days.

Advantage: Biodegradable so no need for a second appointment.

3.Minocycline

a) Arestin

It belongs to the tetracycline group and is a bacteriostatic antibiotic. Minocycline microspheres consist of minocycline hydrochloride microencapsulated in a bioabsorbable polymer of polyglycolide. They are dispensed sub gingivally using a disposable plastic cartridge on a stainless-steel handle by inserting the tip to the base of the pocket. The microspheres are 20-60 microns in diameter. Resorption time is 21 days.

Advantages

1. Material is bioadhesive on contact with moisture and does not require additional adhesives.
2. Microspheres maintain therapeutic drug concentrations for 14 days.
3. No need for a second appointment as it is biodegradable.
4. Anti-collagenase property against pathogens
5. Higher lipid solubility ensures rapid passage through the lipid bilayer of bacteria.
6. Enhance the activity of gingival epithelial cells to participate in the early inflammatory phase of wound healing **(13)**.

b) Periocline/ Dentamycin

It is an ointment system that contains 2% minocycline hydrochloride and is applied using a syringe. It consists of a matrix of magnesium chloride, hexahydrate, glycerol, triacetin, and ammino methacrylate. It is a light yellow color ointment.

Disadvantages: more appointments are required as 1 application per week for 4 weeks.

4) Metronidazole

It is a nitroimidazole compound that has a bactericidal action against anaerobic microorganisms. It disrupts the bacterial DNA synthesis by its hydroxy metabolites.

a) Elyzol

It is also a gel system that contains 25% metronidazole in a glyceryl mono-oleate and sesame oil base. It is applied into the pocket by means a syringe and blunt cannula. It is applied in viscous consistency to the pocket which upon coming in contact with body heat liquefies and then hardens again, forming crystals in contact with water.

5) Chlorhexidine

Available in the form of varnishes, gels, mouth rinses and chips to be used as local drug delivery. It is a biguanide that acts by binding to the anionic group on salivary glycoprotein that reduces pellicle formation and plaque colonization.

a) PerioCol CG

It consists of fibrillar collagen type-I of about 25 mg of chlorhexidine, impregnated with about 2mg of tetracycline hydrochloride sterilized with gamma irradiation. They release tetracycline for about 8-12 days. It is biocompatible but is not recommended for the patient with hypersensitivity of tetracycline hydrochloride **(14)**.

Advantages

1. Resorbable so no need for a second appointment.
2. Chemotaxis for fibroblast, enhance fibroblast attachment
3. Excellent hemostatic properties

b) Periochip

It is a biodegradable device of 4X5X0.35mm of orange color chip composed of hydrolyzed gelatine matrix, cross-linked with glutaraldehyde and also contain glycerine and water into which 2.5 mg chlorhexidine gluconate is incorporated. It releases chlorhexidine in vitro in a biphasic manner.

6.Nanoparticles

This system reduces the frequency of drug administration and provides a uniform distribution of the drug. It is composed of 2-hydroxyethylmethacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA) **(15).** The polymer-based nanoparticles were prepared via micellar polymerization that result in the formation of a white powder with particle size in the range of 50-180nm.

Advantages

1. Increases stability
2. Controlled release rate
3. Their small size makes them accessible to the area where other material cannot reach.
4. Have bioadhesive property
5. High dispersibility in the aqueous medium

Disadvantages:

1. Expensive
2. They have low activity compared to free enzymes

7) Vesicular systems

Jones and Kaszuba introduced vesicular liposomal systems and found them effective for the delivery of triclosan to target periodontal biofilms. It consists of succinylated ConcanavalinA bearing liposomes. This system is designed to mimic the bio-membranes in terms of structure and bio-behaviour **(16)**.

Conclusion

As a monotherapy, LDD systems incorporate a variety of drugs to improve periodontal health. There is no universal drug that would be effective in all situations. LDD appears to be as effective as scaling and root planning with regards to reducing signs of inflammation. Tetracycline fibers show excellent results when used in refractory periodontitis cases. Mechanical instrumentation can be technically demanding, time-consuming and in some defects ineffective whereas LDD on other hand is simple to use and conceivably in the future be delivered to the patient. Hence, can be used as an adjunct to scaling and root planning.

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