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LOCAL DRUG DELIVERY IN PERIODONTICS: A REVIEW

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ABSTRACT

Periodontitis is a multifactorial disease that mainly affects the supporting tissues of the teeth. Treatment options like mechanical debridement and administration of antimicrobial drugs have been applied in the management of periodontal diseases. The local drug delivery (LDD) system is one of the potentially effectivemethod in the management of periodontal diseases. It is not suitable for use as a monotherapy since it performs better clinically when used in conjunction with scaling and root planing.

KEYWORDS: Local drug delivery; periodontitis;antimicrobials

INTRODUCTION

Periodontal disease is caused bymany pathological conditions that affects the tooth supporting structures. It is well known that pathogenic microflora in the periodontal pocket and localised bacterial infection are the causes of periodontal disease.

Conventional treatments like mechanical debridement, which removes subgingival flora and creates a clean, smooth, and biocompatible root surface, may not always be effective in treating bacterial infections because of the intricate anatomy of the root and the location of the lesion.

Antibacterial drugs are utilised in conjunction with mechanical debridement for the management of periodontal infections. The outcome has limitations as a result of inaccessibility. Since the periodontal pocket creates an ideal atmosphere for the growth of anaerobic pathogenic bacteria, antibiotics must enter the periodontal pocket deeply in order to be effective. [1]

Antimicrobials such as metronidazole, chlorhexidine, minocycline, doxycycline, and tetracycline can be locally administered into the mucosa in addition to non-surgical therapy.

When these drugs are applied to periodontal pockets, they can reduce or eradicate the growth of periodontopathogenic microorganisms and alter the tissues' inflammatory

response.(Greenstein and Tonetti,2000)Hence, the aim of this review article is to compile all the latest local drug delivery agents and their therapeutic benefits.

HISTORY:

In 1979, Dr. Max Goodson et al. made the initial proposal. Chlorhexidine was further studied by D. Steinberg et al. (1990) as a local drug delivery method. A study in 1998 by Stoller et al. examined doxycycline hyclate.[2]

CLASSIFICATION

1. LANGER & PEPPAS (1981)

Based on their mechanism of action.

a. Diffusion controlled systems.
b. Chemically controlled systems.
c. Solvent activated systems.
d. Release induced by external forces.

2. KORNMAN (1993)

a. Reservoirs without a rate controlling system.
b. Reservoirs with a rate controlling system.

3. RAMS ANS SLOTS (1996)

Based on application of therapy.

a. Personally applied.
   i. Non-sustained subgingival drug delivery
   ii. Sustained subgingival drug delivery.
b. Professionally applied.
   i. Non-sustained subgingival drug delivery
   ii. Sustained subgingival drug delivery.

4.SOSKOLNE WA (1997)

Based on dosage form.

a. Fibers e.g. Tetracycline.

Films / slabs e.g. Chlorhexidine chip.

i. Non-degradable films

ii. Degradable films

injectable systems e.g. Minocycline

5. GREENSTEIN &TONETTI(2000)- Based on duration of action

a. Sustained release devices

b. Controlled release devices

6. SOSKOLONE WA FRIEDMAN M. - Depending on degradability:

a. Non-degradable devices

b. Biodegradable devices[3]

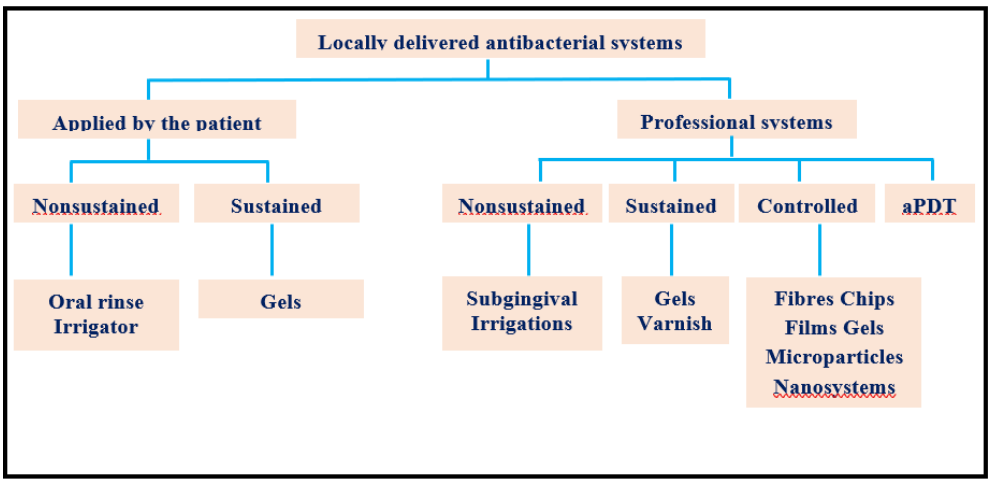

Figure 1: Classification of locally delivered antibacterial systems.[4]

USES

1. It can be used in addition to scaling and root planing and maintenance therapy.
2. Devices may be sustained release (drug delivery for less than 24 hrs) or controlled release (drug delivery for more than 24 hrs).
3. No gastrointestinal tolerance occurs.
4. There are no side effects that are seen on intake of the systemic antimicrobials.[5]

5. In the subgingival site, LDD concentrations increase by 100-fold.
6. Used in place of certain antimicrobial agents that are not suitable for systemic administration e. gsome broad-spectrum antiseptic solutions.
7. Less invasive incomparision to the surgical intervention.

Most important local drug delivery agents along with their commercial names have been listed in Table 1[6]

Table 1: Local drug delivery agents[6]

Drug	Delivery	Product available	Dosage form and concentration
Metronidazole dental gel	Sustained	Elyzol (25%)	Biodegradable gel
Minocycline	Sustained	Dentomycine gel(2%)	Biodegradable gel
		Arestin(2%)	Biodegradable mix in syringe
Tetracycline fiber	Controlled	Acticite (25%)	Nonresorbable fiber
		Periodontal plus AB	Resorbable fiber
Chloehexidine chip	Controlled	Periochip(2.5mg)	Biodegradable device
		Periocol (2.5mg)	Biodegradable gel
		Chlosite(1.5%)	
Doxycycline polymer	Controlled	Atridox (10%)	Biodegradable

LIMITATIONS

1. Patients having a history of known hypersensitivity to the antimicrobial used as a local medication should not use it.
2. In patients with asthma and infectious diseases including AIDS and tuberculosis, administering the antibiotic via ultrasonic devices is not advisable.[7]
3. Administration is cumbersome (deeper periodontal pockets/furcation areas).
4. Time taking procedure.
5. Comparatively expensive.[8]

RATIONALE

The majority of systemic antimicrobials are linked to microbial resistance due to improper use, inability to reach the infection site and obtain sufficient concentration, and inadequate tissue penetration.[9]

The therapeutic goal of LDDS is met by directly applying antimicrobial agents to the periodontal pocket and subgingival sites. This releases the active drug in a controlled,

sustained manner to defend the microbial attack while minimising any negative side effects on non-oral systemic/body sites.[10]

An ideal LDDS should not irritate tissues, simple to administer, and be biodegradable and biocompatible.[11]

IDEAL REQUIREMENT OF LOCALLY DELIVERED DRUG :

1. The medication should enter the pocket at the base.
2. It should work exclusively against periodontal infections, not commensal microorganisms.
3. The dose should be sufficient to kill the pathogenic microorganisms without causing any adverse effects.
4. Substantivity.
5. Long shelf life.
6. It should be both biodegradable and biocompatible.
7. It should be easy to place.
8. Should not be expensive[12,13,14]

ADVANTAGES:

1. The technique is suitable for agents which cannot be given systemically, such as chlorhexidine.
2. Minimal amount of drug can be administered.
3. The chances of added Superinfection and resistance to the drug are very low.
4. frequency of drug administration is less.[15]

DISADVANTAGES:

1. Difficult to place into the inaccessible sites of the furcation lesions.
2. Does not have any effect on adjacent structures such as tonsils , buccal mucosa etc so it can cause reinfection.
3. Requires more time.
4. In presence of generalized pockets , other periodontal therapies should be used.

VARIOUS DRUGS/AGENTS USED IN THE LOCAL DRUG DELIVERY SYSTEM

1. Tetracycline

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2. Doxycycline
3. Minocycline
4. Metronidazole
5. Chlorhexidine

TETRACYCLINE:

Tetracycline is used to treat periodontal infections. It is bacteriostatic in nature; it prevents tissue collagenase activity and inhibits the formation of bacterial proteins.[16.17,18]

FIBERS(ACTISITE):

These are plastic copolymers (ethylene and vinyl acetate) that are non-resorbable, inert to biological activity, and usually regarded as nontoxic. They are filled with 25% w/w tetracycline HCL powder and are packaged as a 0.5 mm diameter by 23 cm long thread. Collagen films served as a base for the fabrication of bioresorbable tetracycline fibres, which are currently marketed under the name PERIODONTAL PLUS AB.
(Fig 2).

Figure 2: Periodontal plus ab[18]

GELS:

The aim of Tetracycline Serratiopeptidase Fig. (3), which contains periodontal gel, was to lower the concentration of polymer and get a suitable viscosity at a lower concentration of pluronic acid.

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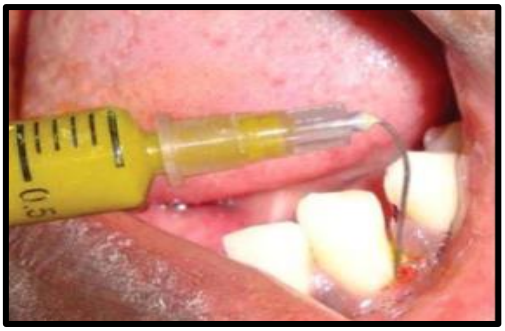

Figure 3: Application of Tetracycline Gel [18]

Doxycycline:

Probing depth reduction and clinical attachment were both accomplished using 10% doxycycline hyclate, a local delivery antibacterial drug. This biodegradable liquid system solidifies when it is inserted into the periodontal pocket.[18.17]

Minocycline:

A semi-synthetic tetracycline, minocycline HCL is one of the most potent antibiotics against microorganisms linked to periodontitis.

The methods of local application are

1. Film
2. Microspheres
3. Ointment.

FILM;

Ethyl cellulose films that consists of 30% of minocycline totally removes the harmful pathogens from the periodontal pocket within two weeks.[17]

Microspheres:

There is a novel type of minocycline microspheres (ARESTIN) Fig. (4) that can be administered locally and have a sustained release for subgingival insertion. The polymer is hydrolyzed by the gingival crevicular fluid, which releases minocycline and does for at least 14 days before fully resorbing.[17]

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Figure 4: Arestin (Microspheres)[17]

OINTMENTS:

2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkyl-methacrylate, triacetate & glycerine.

Metronidazole:

A viscous-consistency metronidazole 25% that is based on oil is given topically to the periodontal pocket as Elyzol (Fig. 5). According to one trial, using combination therapy for probing depth reduction produced better results throughout a nine-month observation period. 16,17

Figure 5: Elyzol(Metronidazole)[16]

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CHLORHEXIDINE:

Chlorhexidine is an antimicrobial and antibacterial agent that is a member of the biguanide family. Mouth rinses containing chlorhexidine have only temporarily that affects the microbiota in the pockets.[16]

PERIOCHIP:

A tiny chip made of water, glycerine, and a biodegradable hydrolyzedgelatin matrix that contains 34% chlorhexidine cross-linked with glutaraldehyde Figure (6). In vitro, the chip distributes chlorhexidine in a dual pattern. About 40% of the chlorhexidine is released in the first 24 hours, and the other 40% is released over the course of 7–10 days in an almost linear fashion.[17]

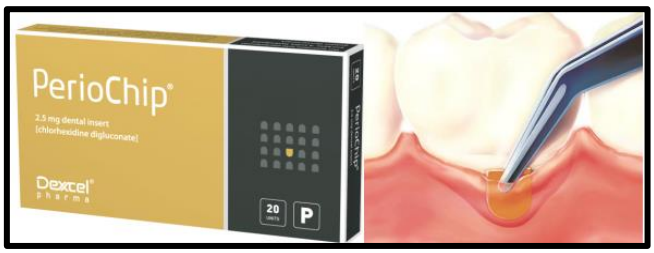

Figure 6: Application of Periochip(Chlorhexidine).[17]

PERIOCOL-CG:

The procedure involves preparing a collagen membrane with 2.5 mg of chlorhexidine. Their coronal edge fades in 10 days, and it has been demonstrated that it resorbs after 30 days.[17]

Figure 7: Application of Periocol-CG.[17]

CHLOSITE:

It consist of 1.5% chlorhexidine of xanthan type (Xanthan gel - saccharide polymer).

Figure 8: Chlo-Site[16]

HERBAL AGENTS USED IN LOCAL DURG DELIVERY

The comparatively safe nature of herbal extracts has led to a surge in the use of the herbal product recently.

Neem: Neem leaf extract has the potential to lower the amount of bacteria in dental plaque, which is responsible for the onset and advancement of periodontitis.[19]

Aloe vera: The most widely used medicinal cactus plant in the Liliaceae family is aloe vera. It functions well to lessen edema, irritation, and bleeding in the gingiva.[20]

Lemon Grass: Essential oil of lemongrass seems to be a useful local drug delivery in addition to mechanical nonsurgical periodontal therapy when used at a concentration of 2%.[21]

Green Tea: Because green tea includes a variety of biologically active compounds, including flavonoids like catechins and their derivatives, it is a useful local medication delivery agent. Mageed MJ et al .[22]investigated the antimicrobial effects of green tea extracts on Porphyromonasgingivalis, and he found that alcoholic green tea extract was able to inhibit Porphyromonasgingivalis.

Tea Tree Oil: Elgendy Et al [23]suggested that TTO is effective as an adjunctive treatment of scaling and root planing on the clinical parameters.By inhibiting the synthesis of inflammatory cytokines and downregulating the activity of enzymes such as cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase, curcumin controls the inflammatory response.[23]

Oak: Oak has been used as a local drug delivery agent in periodontal diseases.[24]

Coriander: Yaghini J conducted a randomized, double blinded controlled trial to evaluate the clinical effects of subgingival application of herbal gel (extracts of oak and coriander) in periodontal pockets. The results showed that statistically significant improvements in periodontal indices.[25]

Babul: Its produces tannins (24-42%) that contains properties like analgesic and anti-inflammatory.[26]

Bakul: Lupeol, which is one of the primary pharmacologically active components in bakul, possesses anti-inflammatory and antimicrobial qualities.[27]

Pomegranate: Gomes LA44 (2016) did a study to evaluate the antimicrobial activity of pomegranate glycolic extract (PGE) against the periodontal pathogen Porphyromonasgingivalis by using Galleria mellonellaas in-vivo model and results were significant.

CONCLUSION

The goals of local medication delivery are to reduce the loss of drugs and degradation, avoid negative side effects, and maximise drug bioavailability at the area of the lesion.When local drug administration is used in conjunction with scaling and root planing, it can help improve outcomes in periodontal pockets where traditional therapy is less effective.The previous researches showed that the adjunct application of local drug administration may yield a specific but limited positive effect. In addition, with use of local drug delivery, theside effects of systemic chemotherapeutic drugs can be avoided, and the likelihood of bacterial strains becoming resistant to drugs can be decreased, by carefully administering antimicrobial drugs.

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