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Local Drug Delivery systems in Periodontics: Aiming the Target

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ABSTRACT

Periodontal diseases are complex bacterial infections which needs a combined antimicrobial approach to get rid of it. Lately various newer treatment modalities have come for the management of periodontal diseases, Antimicrobial therapy is one of them, but due to several adverse effects with systemic antibiotics– locally delivered agents were introduced. Local administration of drugs directly into the pocket provides greater concentration of drugs directly and reduces the side effects; Local application of antimicrobial agents reaches to a level of about 32-64 micrograms/ml. which is not achievable through systemic route. In the presence of locally confined target organisms, local therapy may be particularly successful, whereas systemic administration may reach widely distributed microorganisms. This paper is aimed at reviewing the role & effectiveness of local drug delivery systems in periodontal diseases.

Keywords: Periodontal diseases, Antimicrobials, Pathogens, Chemotherapeutics

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INTRODUCTION

Periodontal diseases are infections and inflammation of the periodontium, as there is a bacterial etiology, an immune response, and tissue destruction [1]. The pathogens associated with periodontal diseases are vulnerable to a range of antiseptic and antibiotics [2]. Rinsing, irrigation, systemic administration and local application using sustained and controlled delivery devices have been used in delivering antimicrobial agents into periodontal pockets [3].

At a bacteriostatic or bactericidal concentration, the ability of an anti-microbial agent to be delivered to target periodontal infections at the base of pocket determines the success of any drug delivery system. The administration of antibiotics and the introduction of antimicrobial agents in periodontal pockets may be effective adjuncts to conventional periodontal therapy. Vehicles for delivery of chemotherapeutic agents locally include dentifrices, mouthrinses, chewing gum, and slow release devices. These are found to be an inefficient delivery system in periodontitis, because they fail to direct drug delivery into the periodontal pocket [4].

All local delivery systems aim at delivering high concentrations of an antibiotic or antimicrobial directly to the site of the periodontal infection. The five main antimicrobial agents employed are Tetracycline hydrochloride, doxycycline, minocycline (broad spectrum antibiotics) and the other two are chlorhexidine and metronidazole [3]. The local drug delivery systems that have undergone preliminary assessments are Tetracycline hydrochloride (Actisite), chlorhexidine (Periochip), doxycycline (Atridox), metrinidazole (Elyzol dental gel),minocycline (periocline) [5].

LOCAL DRUG DELIVERY

Local drug delivery system is effective in delivering a higher concentration of the antimicrobial agent, locally at the affected site for a prolonged period with minimum systemic toxicity or absorption. Its application can improve periodontal health and its efficacy in reduction of signs of periodontal inflammatory disease, redness, bleeding upon probing and loss of clinical attachment can often be compared with phase I periodontal therapy that includes, scaling and root planing. The local drug delivery system has used antimicrobial agents to control the microbial cause of periodontal diseases, which has emerged to eradicate distinct pathogens or abolish destructive host response. They inherit the antibiotic action towards the target microorganisms, and disparate criterions such as vigor of permeability, innate efficacy and substantively of the drug, dictate the success of the therapy. The objectives of local drug delivery as an antimicrobial agent are to target specific periodontal pathogens thus altering sub gingival microbiota and creating a healthy periodontal environment.

Numerous attempts have been made to use antimicrobial agents to control the microbial cause of periodontal disease. W.D.Miller was the first to explore the propinquity between periodontal disease and bacteria. In 1880, he prescribed the use of an antimicrobial mouthrinse (Listerine) to aid against pyorrhea alveolaris. Antimicrobial agents are the chemotherapeutic agents that help in decreasing the quantity of bacteria by categorically targeting certain organisms or by comprehensively decreasing all bacteria. Antibiotics are a form of antimicrobial agents produced or obtained from other microorganisms that have the capacity to wipe out different microorganisms or constrain their growth.

Chemotherapeutic agents can modify the host to promote its ability to resist bone loss or aids in its ability to regenerate bone. Many chemotherapeutic agents can be delivered locally; thereby achieving greater concentrations locally and eliminating the systemic side effects to a maximum level.

INDICATIONS

1. Periodontal patients with successful phase 1periodontal therapy.
2. Medically compromised patients with Periodontitis where surgical therapy is contraindicated.
3. As an adjunct to mechanical debridement or as sole therapy.
4. Patients having recurrent or refractory periodontitis.
5. During periodontal regenerative procedures.

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CONTRAINDICATIONS

1. Periodontal patients with hypersensitivity reaction to any of the antimicrobials agents.
2. Local delivery of metronidazole preparations, contraindicated in alcoholics.
3. Irrigation devices are contraindicated in patients susceptible to infective endocarditis to avoid the risk of bacteremia.
4. Antimicrobial agents through ultrasonic scalers are contraindicated in patients with cardiac pacemakers, asthmatics and infective conditions (AIDS, TB etc.).

ADVANTAGES OF LOCAL DRUG DELIVERY SYSTEM [6]

Most of the complications associated with systemic therapy are averted by Local drug delivery system by limiting the drug to its target site with minimal or no systemic concentration. A 100 fold higher concentration of antimicrobial agents is attained by local route of drug delivery in sub gingival sites when compared with systemic drug regimen of equal dose.

Potential problems with patient compliance are eliminated by professional application of local antimicrobial agents in periodontal pockets. Local antibiotic delivery is an alternative treatment for women with predilection for vaginal super infection, and for individuals predisposed to gastrointestinal tract complications (ulcerative colitis) or other adverse reactions, for systemic administration of antibiotic. The risk of developing drug resistant microbial populations at normal body sites is also diminished. It inhibits or kills the putative pathogens by reaching the site of infection, the specific site.

Local drug therapy has three potential advantages

1. Decrease drug dose
2. Increase drug concentration
3. Reduce systemic side effects such as G.I.T distress

DISADVANTAGES [7]

The disadvantages of local antimicrobial treatment of periodontitis include difficulty in placing therapeutic concentration of the antimicrobial agent into deeper parts of periodontal pockets and furcation lesions. Antimicrobial agents locally applied into periodontal pocket do not markedly affect the periodontal pathogens residing within adjacent gingival connective tissue and / or extra pocket oral surface (tongue, tonsils, buccal mucosa), which increases the risk of later reinfection and disease recurrence in treated areas .Treating multiple sites may be time consuming and laborious with high relative cost.

ADVANTAGE OF LOCAL DRUG DELIVERY IN PREFERENCE TO SYSTEMIC ANTIBIOTICS [7]

The potential benefits to be achieved from local delivery devices have been discussed by Goodson 1989 those include.

- Better patient compliance.
- Enhanced or improved pharmacokinetic responses.
- Improved drug access to the site of disease.
- Lower total drug usage.
- Alternative to systemic antibiotics.
- Elimination of non-oral effects due to extremely low serum drug levels.
- Decreased risk of developing drug resistant microbial community in non-oral sites.

Whereas the drawback of systemic antibiotic therapy is that the drug is dissolved by dispersal, systemically and only the small portion of the total dose actually reaches the sub gingival micro flora in the periodontal pocket. Adverse drug reactions are more likely to occur if the drug is distributed via systemically. Prolonged intake of antibiotics in large doses may lead to development of resistant pathogenic strains. Also

the drug levels are not maintained at a constant level over a period of time and at desired site of action due to fluctuations in absorption and distribution profiles [8].

According to Gibson, an ideal antibiotic for the use in prevention of periodontal disease should have a specificity for periodontal pathogens; non-toxic, allogeneic and inexpensive. Combination of drug may be necessary to eliminate putative pathogens in some periodontal disease conditions.

CLASSIFICATION OF LOCAL ANTIMICROBIAL AGENTS (According to use):

A. Personally applied (In patient home self-care).

I. Non-sustained sub gingival drug delivery (Home oral irrigation).
II. Sustained sub-gingival drug delivery. (None developed to date).

B. Professionally applied (In dental clinic).

I. Non sustained sub-gingival drug delivery. (Professional pocket irrigation)
II. Sustained sub-gingival drug delivery. (Controlled release device).
III. Reservoirs without a rate controlling system.eg. Hollow fibers.
IV. Reservoirs with a rate controlling system.
E.g. Solvent action on coated drug particles, Microscope polymer membrane, Monolithic matrices, Erodable polymeric matrice

CLASSIFICATION OF LOCAL ANTIMICROBIAL AGENTS (According to placement of local delivery agents)

A. Supra gingival Sustained release devises

I. Topically applied antibiotic adhesive.
II. Sustained released varnishes of chlorhexidine and arginine.
III. Chlorhexidine polymer coating.
IV. Cetylpyridinium chloride (CPC) methacrylic acid co polymer.

B. Sub- gingival sustained release devices

1. Locally applied antimicrobial gels.
e.g.Chlorhexidine gels, Metronidazole gels, Clindamycin hydrochloride gel, Root conditioning gels.
2. Locally applied anti- inflammatory gel e.g. Flurdiprofen
3. Sustained release of antimicrobials with dialysis tubing or acrylic strips.
E.g. Chlorhexidine, Metronidazole, Tetracycline hydrochloride
4. Locally delivered antimicrobial ointments minocycline hydrochloride ointments.
5. Controlled release devices: Films, Inserts, membranes& Bio resorbable polymers.
E.g. Ofloxacin, Doxycyline, Chlorhexidine, Methylene blue
6. Non-resorbable release devices
Tetracycline loaded ethylene vinyl acetate fibers.

VEHICLES FOR LOCALDRUG DELIVERY:

Vehicles used for supragingival drug delivery are mouth rinses, irrigation agents, chewing gums; and those used for sub gingival drug delivery are controlled – release system, hollow fiber, monolithic fiber, acrylic strips and gels.

SUPRAGINGIVAL

MOUTHRINSES: It is useful in reducing inflammation associated with gingivitis but they do not permeate well into periodontal pockets. The daily use of Chlorhexidine gluconate mouth rinses is profoundly advocated post surgically (1-4 weeks) and in patients with certain diseases with oral manifestation, such as

acquired immuno deficiency syndrome (AIDS) and blood dyscriasiasis. It is also recommended for those unable to perform adequate plaque control due to physical or mental inabilities.

IRRIGATION AGENTS: Oral irrigation decreases gingivitis scores even when water alone is used as the irrigant. The clinical improvement results from a decrease in subgingvial micro flora.

CHLORHEXIDINE CLUCONATE: This is the only prescription antimicrobial mouth rinse approved by FDA and ADA for reduction of gingival inflammation. It is marked as U.S. as 01.2% solution (Peridex and Periogard) Delivering Chlorhexidine gluconate into the periodontal pockets by means of an oral irrigator.

STANNOUS FLUORIDE PREPARATION: It has an antibacterial property. Direct pocket lavage with 1.64% stannous fluoride reduces bleeding index scores and prevents spirochetes and motile bacteria.

PHENOLIC COMPOUND: It is an antiseptic and disinfectant. This group includes a mouth rinse, Listerine which reduces gingivitis when used twice daily. It has got decreased side effects e.g. Staining and decreased cost.

DENTIFRICES: Dentifrices are aids for cleaning and polishing tooth surfaces. Antibacterial agents can be incorporated into dentifrices to provide these agents include – chlorhexidine stannous fluoride, Zinc citrate triclosan.

Dentifrices are inefficient delivery system for periodontal diseases because they fail to direct drug into the periodontal pocket.

CHEWING GUMS: Chewing gums that release antimicrobial agents have also proved ineffective at treating periodontal diseases.

SUBGINGIVAL CONTROLLED RELEASE LOCAL DELIVERY SYSTEM

They are manufactured in such a way so that a higher concentration of the chemotherapeutic agents is achieved over a prolonged period of time at a particular site specifically into periodontal pockets; eg: retraction cord. Controlled release local drug delivery systems can be classified as reservoirs with a rate controlling system and reservoirs without a rate controlling system. These systems release chemotherapeutic agents very swiftly and qualify only as sustained – release devices.

Erodible polymetric matrices, polymer membranes, monolithic matrices, and coated particles are included as reservoirs with rate controlling system. Reservoirs without rate- controlling system include hollow fiber, gels and dialysis tubing.

RESERVOIR DEVICES

Diffusion reservoir devices and pumped reservoir systems form this group of controlled release systems.

A) DIFFUSION RESERVOIR DEVICE

In diffusion reservoir device a solid core of drug is surrounded by an inert diffusion barrier it may be in the form of dialysis tubing release occurs the concentration gradient of the membrane, normally made of a homogeneous polymetric film such as silicon rubber nylon or polyethylene. These devices are easy to manufacture and give the constant release profiles required by many therapeutic regimes

B) PUMPED DEVICE

Consists of a reservoir of the drug and a pump in a compartmentalized device; polymer- based devices commonly utilize osmotic pumps the uptake of water into the outer compartment of device compresses an inner membrane thus driving the drug through an exit portal .

ETHLENE VINYL ACETATE (EVA)

The EVA system is based on polymer technology; with tetracycline being dispersed with a solid (monolithic) polymer of EVA.EVA fibers have found to be to be bendable and to sustain delivery of tetracycline for up to 9 days. 4146 A formulation of 25% tetracycline in EVA (Actisite) has been developed as 0.5 mm non-biodegradable film. This fiber is placed into a periodontal pocket and is maintained there for 10 days by application of a cyano acrylate adhesive. The use of these fibers alone resulted in probing depths reduction of approximately 1 mm, compared with an approximate reduction of 0.5 mm in pockets scaled and root planed.

ACRYLIC AND ETHYL CELLULOSE STRIPS

Some investigators have incorporated chemical agents into acrylic strips2 suitable dimension for local periodontal drug delivery in most cases drug was released in 1 day by this method giving it short lived antimicrobial value. Golomb and associates reported the use of cellulose strips containing either chlorhexidine or metronidazole; effective drug levels were found for up to 6 days. The material chosen was a cold cure polyethymethacrylate, orthoresin, chloxidine acetate powder was added at 10%, 20%, 30%, 40%, 50%, by weight to the powder (Polymer) phase of the material.

Acrylic strips released chlorhexidine up to 14 days period and antimicrobial activity was maintained. All drugs were released at high levels day one followed by marked fall in release thereafter. These strips appear to have potential drug delivery to periodontal pockets.

GELS

Gels containing 2% minocycline are marketed as dentamycin in Europe periocline in Japan and 25% metronidazole as Elyzol in Europe. These gels allow antibiotics to be syringed into the periodontal pocket.

BIODEGRADABLE CONTROLLED – RELEASE DEVICE

These devices offer the advantage of not needing to be removed however; another visit is needed to check healing. Steinberg. D. Friedman et al 1990 [9].

DISCUSSION

The main aim of periodontal therapy has been directed at altering the periodontal milieu to one which is less conducive for bacterial plaque retention in the environs of the gingival tissues, in particular marginal attachment apparatus. The therapeutic regimes to achieve this aim would include some or all the following procedures.

- Instruction in oral hygiene techniques.
-To achieve an adequate level of oral cleanliness.
-Scaling and root planing.
-Surgical elimination of pockets or other anatomical defects which aid bacterial retention and interfere with plaque removal with the increasing awareness of the bacterial etiology of periodontal disease (Socransky SS 1970 [12] :Jorgen Slot 1979 [13]) A direct approach using antibacterial agents has become an essential part of the therapeutic armamentarium .

To date use of controlled local drug delivery to treat periodontal disease has concentrated on the use of antibacterial agents.

The benefits of using control delivery devices include:

-Better patient compliance.
-Enhanced or improve pharmaco kinetic response.
-Improved drug access to the site of disease.
-Lower total drug doses.
-Alternative to systemic antibiotics.

-Drug level.
-Decreased risk for developing drug-resistance microbial population at sites other than the oral cavity.
On review of the existing controlled local drug delivery system, it is necessary to keep in mind that drug should meet five criteria to be effective in treating disease.

A) Inhibit or kill the putative pathogen.
B) Reach the desired site.
C) Have adequate local concentration.
D) Be there on required site for long time.
E) Do no harm the patient.

A variety of local drug delivery systems have utilized different drugs that have addressed the utility of these devices as mono-therapy that can improve periodontal health.

In order to determine the putative pathogens and their susceptibility to specific antimicrobial agents sensitivity testing may be necessary.

The effectiveness of Local drug delivery can often be compared with scaling and root planing with regards to reduction in the sings of periodontal inflammatory disease; redness, bleeding on probing, probing pocket depth and loss of clinical attachment. But the major disadvantage of it is it usually does not provide a benefit beyond what is achievable with conventional scaling and root planing in the treatment of adult periodontitis. It can also be used in combination with conventional therapy. In the present scenario there is no sufficient data that clearly specifies that indicates the superiority of one local drug delivery device than other systems. The drug delivery systems are designed such that it includes ease of placement, sustained release of the drug and resorbability. Systemically administered drugs that are used in conjunction with conventional treatment, appear to be as effective as local drug delivery.

Very limited term data (5 years) is available for evaluating the efficacy of local drug delivery; so long term studies are in much need to substantiate the fact that it induces bacterial resistance to antimicrobial agents. Its effectiveness against tissue invasive organism can be evaluated by conducting additional studies. Whether local drug delivery in conjunction with root planing reduces the need of periodontal surgery more than scaling and root planning is still under extensive research.

Although the conventional periodontal therapies cannot be substituted by the use of local drug delivery but they do have a place in the treatment of periodontitis and offer additional methods to aid in the control of periodontal diseases.

CONCLUSION

When considering the use of a local drug delivery system the clinician has to evaluate the efficacy of the product, ease to use, availability and cost. From various studies conducted it can be suggested that local drug delivery of antimicrobial agents has its own place as an adjunct to mechanical & surgical intervention in periodontal therapy for treatment control. It is also used as a part of maintenance phase of periodontal therapy along with plaque control by patients

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