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Review Article

Perioceutics in the management of Periodontal Disease

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ABSTRACT

Periodontal disease is an immuno-inflammatory condition involving the tissues that surround and support the teeth. Till date back bone of periodontal treatment is still mechanical removal of plaque and calculus deposits from supra and sub gingival environment whereas complete elimination of these deleterious agents are quite unrealistic as the pocket depth increases. Intra pocket administration of drug via local drug delivery system have shown to achieve better clinical results when used as an adjunct to conventional non-surgical periodontal therapy, as periodontal pockets holds gingival crevicular fluid for the controlled release delivery of antimicrobials directly. This has steered the field of perioceutics which involves usage antimicrobial as well as host modulatory agents for the benefit of periodontium. Innovations in Perioceutics have led the researchers to have minimum usage of antibiotics as they develop resistance against microorganisms with side –effects. Presently focus is towards development of new Local Drug Delivery [LDD], host modulating agents, antibodies, biofilm which yield faster and safer results. In the article various locally delivered perioceutic agents are assessed with regard to their purpose, characteristics it possess, effectiveness as a monotherapy, incomparsion to scaling and root planning, and ability to enhance conventional treatment. Furthermore, arguments related with local delivery are addressed

Key words: Antimicrobials, Bacteriostatic, Immune response, Host, Periodontal pocket.

Key message: Local drug delivery offers the clinician a new technique achieving and maintaining periodontal stability and thereby preventing further disease and subsequent problems like gum bleeding, mobility of tooth, pain and loss of tooth, periodontal abscess, tooth mobility and pain.

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INTRODUCTION

Infections affecting the supporting structures of the tooth are denoted as periodontal diseases. In the earliest stage the infection affects the gums/gingiva and as disease progress, the supporting structures of the tooth which includes cementum, periodontal ligament and alveolar bone are affected resulting in loosening and prognosis of tooth. Periodontitis is most common disease entity affecting oral cavity next to dental caries. Basically periodontal diseases are bacteria induced infections where inflammation and destruction of the attachment apparatus occurs, often leading to tooth loss.[1] Ignorance amongst population about oral care is the most prompting factor for increased incidence of periodontal disease.[2] Periodontal diseases are multifactorial in nature which requires plaque for initiation followed by host microbial interactions. *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Bacteroides forsythus* and *Treponema denticola* are considered important causative organisms.[3]Periodontal pockets are favorable area within the gums created by periodontopathic pathogens where access to routine cleaning are difficult leading to destruction of soft tissues supporting teeth and clinical attachment. Microorganisms reside in large numbers within the pocket and start releasing toxic substances harmful to host. In response to above the host as a part of immune response counteracts by releasing enzymes like MMPs (matrix metalloproteinase); inflammatory mediators like cytokines, prostanoids initially meant for defense and in later stages are responsible for destruction of periodontal tissue.[4] Treatment strategy for the periodontal diseases must include the approaches that will target the microorganisms as well as modulate the destructive host response.

Heska Corporation first introduced the term perioceutic which is combination of terms periodontal and therapeutic which includes antimicrobial and host modulatory therapy in the management of periodontal disease along with mechanical debridement.[4] Even though mechanical debridement removes plaque which contains microorganisms, it's impossible to completely eradicate all virulence factors; therefore antibacterial therapy is recommended as supplementary measure. When antimicrobials are administered systemically it exposes the body to large dose causing antibiotic resistance, adverse drug reaction and side effects, causing organ damage making it less patient compliant.[3,5] Moreover less concentration of drug is achieved in Gingival Crevicular Fluid [GCF] when given systemically due to loss of drug during circulation to other parts of the body.[6] Periodontal pockets form the primary source of infections with regard to periodontal infections; local drug delivery in the form of intra-pocket administration of drugs will prove to be more advantageous than systemic administration.[3,7] Due to tissue invasive nature of some periodontal pathogens using mechanical therapy alone is ineffective. Therefore local administration of drugs can deliver higher concentrations directly into diseased sites reducing the microbial load. As a result advances in the local drug delivery [LDD] targeting periodontal pocket is a better approach in Perioceutics as high concentrations of drug at the target sites are attained with reduced systemic dosing, less applications, minor side effects, and high potential acceptability.[8] The review article is an effort to examine various concepts of local drug delivery as relevant in periodontal diseases and to review the results of *in vitro* and *in vivo* studies demonstrating the chief role of these drugs when delivered direct into the periodontal pockets.

Rationale and Goal of Local Drug delivery in Periodontics

Periodontal disease management has been directed at altering the periodontal surroundings to one, which is less favorable to the retention of bacterial plaque in and around gingival tissue.

Active phase of the disease can be changed intensely by decreasing the plaque levels.

Standard regimens to achieve this aim include

(1) Patient motivation and oral hygiene instructions
(2) Supra gingival scaling
(3) Correction of plaque retention local factors pertaining to restorative dentistry
(4) Subgingival scaling and Root planing
(5) Surgical elimination of pockets etc.

Principle behind LDD is that GCF contained within the pocket serves as a leaching medium for the discharge of a drug from the solid dosage form and for its dispersal throughout the pocket, making it a regular spot for treatment with local release delivery system.[9,10] The rational for the use of the local drug is to remove any residual infective /inflammatory element still harboring in the periodontal apparatus that are not reachable to mechanical removal by hand or motorized instruments.[9,11] The most important goal is the prolonged obtainability of the drug in sufficient minimum inhibitory concentrations over a required period of time. Drugs used in LDD are summarized in Table 1.[12,13] The advantages and disadvantages are summarized in Table 2.[13,14]

Parameters include site of action, sufficient drug concentration available for ample duration of time, slower periodontal clearance and property of substantivity.[12] Local drugs exert its action on bacteria present within periodontal pocket, soft tissue wall of pocket and on exposed cementum and 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 which can be managed using intraoral irrigation devices. Substantivity pertaining to LDD refers to its ability to bind in the surrounding areas thereby creating a drug reservoir with slow release rate which can be attained by incorporating drug into various devices prior to placement in pocket.[12] Indications and contraindications of LDD are depicted on Table 3.[15]

Ideal requisites of locally delivered drug

Basic and important factors that need to be fulfilled prior to usage of any antimicrobial recommended for periodontal disease management include:[15]

1. Drug should demonstrate *in-vitro* activity against microbes considered important for etiopathogenesis of the disease.
2. Within the subgingival environment the drug should be able to attain the desired dose concentration sufficient to eradicate microorganism.
3. That particular concentration of the drug should not have side effects and need to be specific for organisms causing periodontal disease.

Dental applications of pharmacotherapeutic agents used in LDD:

Tetracycline: It was first available LDD in fiber form. Made up of ethylene/vinyl acetate copolymer fiber with diameter of 0.5 mm, containing tetracycline12.7mg per 9 inches.[16] Antibacterial property of Tetracycline is due to a tetracyclic naphthacene carboxamide ring system with a dimethylamine group at carbon 4 (C4) in ring "A". Marketed under the name Actisite and have been approved by FDA. They are safe, inert, non resorbable copolymer with 25% w/w tetracycline HCI. It maintains persistent concentrations more than 1000 μg/mL for a period of 10 days.[17] Other properties include collagenase inhibition, anti -bone resorption effect, anti-inflammatory actions and fibroblast attachment are of importance in management of periodontal diseases.[18] Periodontal Plus AB is recently developed bioresorbable tetracycline fiber which degrades within 7 days and requires single appointment. Study done by Newman *et al*. on adjunctive tetracycline fiber therapy showed that fiber markedly improved the success of scaling and root planing in the treatment of localized recurrent periodontal cases and in supportive periodontal therapy.[19] For subgingival delivery, tetracycline impregnated fibres of 0.5mm in diameter made up of copolymer of ethylene vinyl acetate and tetracycline hydrochloride are used. It has been noted that a sustained high level of tetracycline averaging 1590 μg/ml delivering up to 25% of available tetracycline was observed following 10-days post placement in gingival crevicular fluid.[20] Periodontal gel formulations containing tetracycline-serratiopeptidase has shown better results along with non-surgical therapy.[21] In summary, the studies reported that tetracycline fibers used as a monotherapy without non- surgical therapy were effective at decreasing probing depths, in gaining clinical attachment and reducing bacterial load.[22,23]

Doxycycline: Doxycycline is bacteriostatic synthetically prepared from oxytetracycline, acts by inhibiting bacterial protein synthesis.[24] Major benefit of this drug over tetracycline is better patient acceptance as it given once a day. It can downregulate MMP enzyme, reducing collagenase activity that are capable of degrading a variety extracellular matrix.[25] Controlled clinical trials have shown low dose of doxycycline was found to be effective in markedly decreasing the gingival inflammation and collagenase activity in the gingival crevicular fluid.[25] Following 7 days post placement of doxycycline; levels were 6.0 μg/mL, which exceeding the minimum inhibitory concentrations for periodontal microorganisms. After 28 days around 95% of polymer is bio absorbed.[26] Doxycline hyclate 10% as a local drug delivery was effective in reducing probing depth and gain in clinical attachment level.[27,28]

- ATRIDOX is the only FDA approved 10% doxycycline in a gel system can reach to a level ranging 1,500-2000 μ/ml in 2 h. ATRIDOX is supplied in two separate plastic syringes, one contains 42.5 mg of doxycycline the other contains 450 mg of the ATRIGEL Delivery System, which is a flowable polymeric preparation that is a mixture of 36.7% poly- DL-lactide dissolved in 63.3% N-methyl-2-pyrrolidone. The fillings of the two syringes are mixed and locally applied by placing it gently inside the periodontal pocket, which then literally flows to the bottom of the pocket and fills the gap between tooth and the gums. When applied, the gel hardens on contact with saliva to wax like consistency and is slowly released for 21 days. Studies have shown that bacteria including P. gingivalis and Fusobacterium nucleatum which are main causative agents, are vulnerable to doxycycline at concentrations of 6 mcg/ml.[29]

Sub gingival Minocycline: Bacteriostatic antibiotic available in three form: film, microspheres and ointment.[30] Mechanism of action of Minocycline is by interfering with protein synthesis in the bacterial cell wall.[31] Reduction in the bacterial number, complete eradication of spirochaetes for a period of 60 days with improvement in clinical parameters was noticed when minocycline was administered in a dosage of 200mg per day for 7 days[32] Repeated use of minocycline as an adjunct to the mechanical treatment of peri-implantitis showed positive results in probing depth reduction and was significantly different form the controls.[33]

- ***Film:*** Ethyl cellulose film contains 30% of Minocycline may cause complete elimination of pathogenic flora after 14 days.[34]
- ***Microsphere:*** ARESTIN is a FDA approved sustained-release form of 2% minocycline microspheres. The each syringe contains

Table 1: Local Drug delivery in Periodontics

Based on the application Personally applied (in patient home self-care)	**Non-sustained subgingival drug delivery** Traditional jet tips Home oral irrigation Home oral irrigation jet tips Oral irrigation (water pick) Soft cone rubber tips **Sustained sub-gingival drug delivery**
Based on the application Professionally applied (in dental office)	**Non-sustained sub gingival drug delivery** Professional pocket irrigation **Sustained subgingival drug delivery** Controlled release devices Hollow fibres Dialysis tubing Strips Films
Based on the duration of medicament release	Sustained release devices – Designed to provide drug delivery for less than 24 hours Controlled release devices –drug release that at least exceeds 1 day - 3 days following application
Depending on degradability	Nondegradable devices (first generation) Degradable devices (second generation)
Others	Vehicles for supragingival drug delivery are mouth rinses, irrigation agents, chewing gums; and those used for subgingival drug delivery are controlled release system, monolithic fiber, hollow fiber acrylic strips and gels.

Table 2: Advantages and Disadvantages of local drug delivery

Advantages	Disadvantages
Delivers drug in an optimal concentration that can be maintained long enough for the anticipated effect to be achieved without causing any side effect.	Time consuming and labour -intensive
Patient compliance better compared to systemic antibiotics	Effect of local applied antimicrobials within the pockets will not be effective in adjacent areas like tongue, tonsils, buccal mucosa, which increases the chance of later infection
Alternative for management of individuals having high propensity for gastro intestinal complications and for females with a propensity for vaginal superinfections or other adverse reactions, from systemic administration.	Inaccessible areas in multirooted teeth like furcation cannot be dealt with local drug delivery.
Concentration of antimicrobial within subgingival environment can be 100 fold higher compared to systemic.	
Antibiotic resistance and superinfection are uncommon.	
As a part home self-care certain forms of LDD can be applied by the patient.	

Table3: Indications and Contraindications of LDD in periodontics

Indications	Contraindications
In sites where instrumentation accessibility for scaling and root planning difficult in case of deep periodontal pockets	Pregnant or Lactating patients if drug shows harmful effects
In refractory periodontitis	In aggressive form of periodontal disease where systemic antibiotics is more effective
Failure to respond following repeated scaling and root planning in case of localized pockets.	Patients who are allergic to components of LDD
As an alternative to antibiotics in areas having acute periodontal abscess.	

microspheres of volume of equivalent to 4 mg, which is corresponding to 1 mg of minocycline base., Prevotella intermedia, F. nucleatum, P. gingivalis A. Actinomycetemcomitans, and Eikenella corrodens are susceptible to Arestin.Once introduced subgingivally, the microspheres adhere to the walls of the pocket , where the polymer is hydrolyzed by the GCF causing water-filled channels to form inside the microspheres providing areas for the encapsulated antibiotic to be released.[35] The minocycline diffuse from the microspheres over a 2-week period and end result is a level of 340 mcg/ml attained in the pocket. Having a advantage of ease of application and the drawback is it's a single-use product.

- ***Ointment***: Dentomycin, Periocline are 2% Minocycline gel reaches a concentration of 1300µ/ml within I hour after application and reduced to 90µ/ml after 7hrs.[36] It was shown that combination of minocycline ointment with non-surgical therapy like scaling and root planing showed significantly better results than debridement done alone.

Metronidazole: widely used as monotherapy and in combination with other antibiotics for the management for gingivitis, acute necrotizing ulcerative gingivitis, chronic periodontitis and Aggressive periodontitis

- ***ELYZOL*** is an oil based gel form contains 25% metronidazole. Once applied the gel acquires more flow and fills pocket. Highly effective against obligate anaerobes, acts by inhibiting DNA synthesis. Studies reported for at least 8 hours concentrations of above 100µ/ml were measurable in periodontal pocket and above 1µ/ml after 36 hours[37] Effective in management of recurrent cases of chronic periodontitis as a supporting aid to conventional therapy. Gel is applied twice a week for a period of 14 day, where the dosage is dependent upon the number of teeth to be treated. For treating of pockets for around 6-8 teeth, 0.3g of gel will be enough.

Subgingival Chlorhexidine: Commonly used as mouth rinses being highly recommended as an adjunct to tooth brushing and for the control of dental plaque . It reduces pellicle formation, altering the attachment of bacteria to tooth and affects the bacterial cell walls causing lysis. It acts by increasing the cellular membrane permeability of the bacteria resulting in coagulation of cytoplasmic macromolecules. Chlorhexidine exhibits high substantivity being cationic in nature. Available in the form of mouth rinses, Gels, varnishes and chip. Positively charged chlorhexidine molecule is enticed to the surface of the biologic membranes of bacterial and epithelial cells which is negatively charged. Mechanism of action includes adherence to bacterial cell wall, disrupting and entering the cell. Upon entry it disrupts the cytoplasm which drifts out of the damaged cell resulting in death of bacteria.[10,38] Studies stated it to be self-retentive and gets degraded over the following 7 to 10 days.[35,39] Around 40% of chlorhexidine is released over a period of 7 -10 days from its carrier with a mean concentration of 125mcg/ml and 480mcg/ml in 3 days.[35,40] Following therapy with Periochip literature have shown suppression of the pocket flora for up to 11 weeks.[41]

Periochip: The Periochip was first launched in US dental market in1998 weighing about 7.4mg and need to be refrigerated at 20-28 degree Celsius. Later in 2002 room temperature periochip was introduced with an advantage being simple to use and relatively easy to store with a longer shelf life 2 years. It consist of 10 chips per box. It's an orange brown colored biodegradable, rectangular chip form of 2.5 mg of chlorhexidine gluconate that is released in a biphasic manner, initially releasing 40% within 24 hours and remaining over a time span of 7-10 days within the pocket. The polymer is made from 3.4 mg of cross-linked hydrolyzed gelatin, 0.5 mg of gelatin and 0.96 mg of purified water, and contains 2.5 mg chlorhexidine.[25] Once the chip is placed within the confines of the pocket, its antiseptic property begin to kills microbes by slowly releasing the contents thereby shallowing of pocket occurs and inflammation get subsided. Hence promoting healing process and preventing further soft tissue or bone loss. Based on pharmacokinetic studies, release pattern of periochip into gingival sulcus after 10 days reflected that chlorhexidine levels in the gingival crevicular fluid were clinically effective for over one week period within the periodontal pockets with no signs of systemic absorption detected.

Periocol-C- Periocol chip is small orange-brown local drug delivery which is rectangular in shape; with one end rounded meant for ease of insertion into the periodontal pockets. Prepared by incorporating 2.5mg chlorhexidine from 20% chlorhexidine solution in type I biodegradable collagen membrane derived from fish sources. Within 24 hours Periocol releases approximately 40-45% chlorhexidine followed which in a rectilinear mode of dispersion for 7-8 days. This pattern of release may be described by initial burst effect due to diffusion of chlorhexidine from the local drug delivery system followed by release of the medication because of enzymatic degradation. Adjunctive usage of Periocol was regarded safe and delivered substantial improvement in both plaque development levels as shown by plaque indices and gingival bleeding levels as evidenced by scores of gingival bleeding index with the gain in clinical attachment level.[42]

- ***Chlosite*** -contains 1.5% chlorhexidine gel which is xanthan based preparation manufactured by Ghimas, Italy. Xanthan is saccharidic, biocompatible, naturally occurring polymer with a definite cross linkage pattern which controls the release of the drug.[43] Formation of three –dimensional pseudoplastic reticulum by xanthan when contact in water, gives the ability to hold and maintain various substances in suspension.[44] Sustained release of the drug is due to swelling –controlled erosional process which also goes through a progressive process of imbibition and following injection it is engrossed from the pocket within 10-30 days. It consist of blend of two preparations: Chlorhexidine dihydrochloride - 1% which is slow releasing and Chlorhexidine digluconate - 0.5% with faster release.[45] Following microorganisms are susceptible to chlorhexidine which includes P. gingivalis, F. nucleatum, P. intermedia, T. forsythia, C. rectus, H. aphrophilus.[46] A concentration greater than 100 ug/mL of chlorhexidine digluconate is achieved on the first day which is then maintained for an average of 6-9 days reaching a level greater than the minimum inhibitory concentration for chlorhexidine (0.10 ug/mL). It's a gel form which degrades rapidly and is well tolerated and efficient in the management of periodontal pockets and peri implantitis.[47]

Other local drug delivery systems-Future trends

1. Clarithromycin gel: Subgingival delivery of 0.5% clarithromycin for management of chronic periodontitis in smoking patients along with conventional scaling and root planing have shown enhanced clinical outcome. Following 6 months all the clinical parameters such as probing pocket depth, clinical attachment level for clarithromycin group demonstrated marked improvement. The drug is yet tobe patented and under analysis.[48]
2. Herbal products- An abundant source of biologically active compounds are derived from natural products which have been the foundation for the advance of new lead substances for pharmaceuticals. Herbal medicines have better patient acceptance and tolerance. Various formulations like aloe vera, neem, tulsi, propolis, cocoa husk, pomegranate, cranberry etc. are being used widely these days.[49,50]
3. Colloidal drug carriers include micelles, emulsions, liposomes and nanoparticles.
4. PT-01 a sub gingival release delivery system containing Ofloxacin.[51]

CONCLUSION

Currently due to lack of sufficient data it's difficult to substantiate one particular local drug delivery system is superior over the others. However local drug deliveries reduce the potential of developing antibiotic resistance and have greater range of success in refractory lesions which is localized with desired characteristics such as ease of placement, controlled release of drugs and resorbablity. Though the efficacy and practicality of local drug delivery have been confirmed by many clinical trials and have been approved by FDA for the management of periodontal disease, yet the risk/benefit ratio concerning to the usage of these drugs has yet to be established. Furthermore, continuous research in this field ensures and enables effective usage.

CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATIONS USED

LDD: Local Drug Delivery; **MMPs:** Matrix metalloproteinase; **GCF:** Gingival Crevicular Fluid.

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