

LOCAL DRUG DELIVERY IN PERIODONTICS: A STRATEGIC INTERVENTION**DR. VIDYA DODWAD*, DR. SHUBHRA VAISH, DR. AAKRITI MAHAJAN, DR. MEHAK CHHOKRA***Received: 15 Jun 2012, Revised and Accepted: 1 July 2012***ABSTRACT**

Periodontitis is an inflammatory disease involving supportive structures of the teeth which is seen universally in all groups, ethnicities, races and both genders. Various antibacterial agents have been used effectively in the management of periodontal infection. The effectiveness of mechanical debridement of plaque and repeated topical and systemic administration of antibacterial agents are limited due to the lack of accessibility to periodontopathic organisms in the periodontal pocket. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of conventional therapy. These products provide a long-term, effective treatment at the site of infection at much smaller doses. Prospective multicentre studies considering risk factors for disease progression have to be designed to identify patients who may benefit the most from Local drug delivery.

INTRODUCTION

Periodontal disease is a general term which encompasses several pathological conditions affecting the tooth supporting structures. It includes conditions such as chronic periodontitis, aggressive periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis.¹ It has been well-established that periodontal disease is the result of a local bacterial infection with a pathogenic microflora within the periodontal pocket. The microflora found in periodontitis is complex and composed mainly of gram negative anaerobic bacteria.² Moreover; studies have shown that the various clinical forms of periodontitis are associated with different microbiota.³

Traditional therapies for periodontal disease have included mechanical debridement to disrupt the subgingival flora and provide clean, smooth and biologically compatible root surfaces. Unfortunately, in some instances, the complex anatomy of the root and the contours of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load to make the tooth surface biologically acceptable. In addition, control of supragingival plaque is essential in order to prevent recolonization of the subgingival area by periodontal pathogens.⁴ Indeed, several clinical studies have clearly indicated that scaling and root planing, in combination with optimal oral hygiene, result in an alteration of the subgingival plaque which is sufficient to stop periodontal destruction in most cases.⁵ It also has been shown that patients who fail to achieve acceptable plaque control during or after subgingival treatment frequently suffer from recurrent periodontitis. Thus, oral hygiene is of the utmost importance for the clinical outcome of non-surgical as well as surgical treatment.

However, severe or aggressive forms of periodontitis in young subjects often cannot be arrested by mechanical treatment alone. Furthermore, there are some patients or sites where even repeated treatment fails to stop the disease. These are referred to as refractory subjects or non-responding sites.⁶ This could be related to the persistence of pathogens in the pocket after treatment or to the production by the bacteria of specific virulence factors interfering with the host defense (e.g. leukotoxin production, encapsulation, etc.). It also could be due to the recolonization of treated sites from bacterial reservoirs such as dentinal tubules and soft tissues.⁷ In this context, it is evident that antimicrobial agents are of great interest and may be valuable as adjuncts to mechanical therapy.⁸

Systemic Therapy - Drawbacks?

Systemically applied antimicrobials have been advocated for the treatment of severe forms of periodontitis. Early approaches to systemic antibiotics in periodontal therapy included mainly single drug therapies with Tetracyclines, Penicillins, Metronidazole or Clindamycin.⁹ However, in the early 1970s, concern emerged with respect to systemic antibiotic therapy for chronic infections such as

periodontal disease. Indeed, side effects including hypersensitivity, gastrointestinal intolerance and the development of bacterial resistance have been described.¹⁰ Some studies also reported poor results due to the fact that the active product could not achieve an adequate concentration at the site of action and/or due to the inability of the active product to be retained locally for a sufficient period of time.

These drawbacks would be markedly reduced if antimicrobial agents applied locally could be used, although unwanted effects such as gastrointestinal disturbances and development of antibiotic resistance cannot be totally ruled out.¹¹ The local tissue concentration of a drug can be enhanced by incorporating the active agent into controlled release delivery systems to be placed directly in the periodontal pocket. Such systems may have applications where systemic drugs are currently used, for instance localized juvenile periodontitis, refractory periodontitis and periodontitis with secondary systemic involvement, e.g. HIV periodontitis.

Sustained local delivery systems might also be recommended for sites considered as difficult to instrument because of depth or anatomical complexity, for example in the case of furcation defects.¹²

However, studies suggest that these systems, used as adjuncts to scaling and root planing, give a slight advantage over mechanical treatment alone. On the other hand, few studies have shown promising results with local drug delivery systems on sites that responded poorly or showed recurrence after scaling and root planing.¹³ If such improvements are maintained for a long-term period, then these systems would be an interesting tool in the management of localized periodontal lesions.

Local Delivery Agents

The choice of the antimicrobial agents in periodontal diseases must be based on the bacterial etiology of the infection. Several antibiotics have been tested for their clinical and microbiological efficacy in periodontal diseases. It can be noted that only a limited number of antimicrobial agents have been used so far in formulations of local delivery systems.

There are distinct phases in a periodontal treatment plan where a dental practitioner can use a sustained release device. It can be used as an adjunct to scaling and root planing and for periodontal maintenance therapy. It can be safely used in medically compromised patients for whom surgery is not an option or those who refuse surgical treatment. It is highly contraindicated in patients with known hypersensitivity to the antimicrobial used as local drug and the delivery of antimicrobial using ultrasonic devices is contraindicated in asthmatics and infective conditions such as AIDS, Tuberculosis.

It has been observed that the local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent in

subgingival sites compared with a systemic drug regimen. This reduces the total patient dose by over 400 fold thereby reducing the potential problems with the use of systemic antibiotic drug regimens and development of drug-resistant microbial populations at non oral body sites.¹⁴ The only problem faced while using local drug delivery is the difficulty in placing therapeutic concentrations of the antimicrobial agent into deeper parts of periodontal pockets and furcation lesions. Lack of adequate manual dexterity, limited understanding of periodontal anatomy, and poor compliance limits the use of antimicrobial agents by patients as a part of their home self-care procedures. It also does

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 re-infection.

Various antimicrobial agents have been used and investigated as local drug delivery in the treatment of periodontal disease. These devices may be sustained release (drug delivery for less than 24 hrs) or controlled release (drug delivery for more than 24 hrs).¹⁵ Most important local drug delivery agents along with their commercial names have been listed in Table 1.

Table 1:

Agent	Type of delivery	Product available	Dosage form and concentration
Metronidazole Dental Gel	Sustained	Elyzol (25%)	biodegradable gel
Minocycline	Sustained	Dentomycin gel (2%) Arestin (2%)	Biodegradable gel Biodegradable mix in syringe
Tetracycline Fiber	Controlled	Actisite (25% w/v tetracycline HCL) Periodontal plus AB	Nonresorbable fiber Resorbable fiber
Chlorhexidine Chip	Controlled	Periochip (2.5mg) Periocol (2.5mg) Chlosite (1.5% CHX)	Biodegradable device Biodegradable Gel
Doxycycline Polymer	Controlled	Atridox (10%)	Bio degradable powder in syringe

Various agents used are

1. Tetracycline

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The first delivery devices involved hollow fibers of cellulose acetate filled with tetracycline.¹⁶ Tetracyclines are a group of closely related bacteriostatic antimicrobials. They have been frequently used in treating refractory periodontitis, including localized aggressive periodontitis.¹⁵

Fibers: The ACTISITE tetracycline fibres have been approved for the treatment of adult periodontitis both by the United States Food and Drug Administration (FDA) and by the European Union's regulatory agencies. These are non-resorbable biologically inert, generally considered as safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25% w/w tetracycline HCl powder packaged as a thread of 0.5 mm in diameter and 23 cm in length. It maintains constant concentrations of active drug in the crevicular fluid in excess of 1000 µg/mL for a period of 10 days.¹⁷ Following application of tetracycline fibres a definite reduction in the subgingival microbiota has been observed.²⁰

Recently bioresorbable tetracycline fiber has been developed with base of collagen film, which is commercially available as PERIODONTAL PLUS AB. It offers the advantage of no second appointment for removal as it biodegrades within 7 days.

Gel

Tetracycline-Serratiopeptidase-Containing Periodontal Gel Formulation has shown statistically significant results along with scaling and root planing.¹⁸

Bioerodible Injectable Poly (ortho ester) for Tetracycline Controlled Delivery formulations loaded with tetracycline 10% or 20% showed complete in vitro degradation concomitant with drug release.¹⁹

In general, the data indicates that tetracycline fibers used as a monotherapy without adjunctive scaling and root planing were effective at reducing probing depths, in gaining clinical attachment and reducing monitored bacteria^{21,22}, though the results of monotherapy were not significantly different when compared to scaling and root planing.²³

Tetracycline fibers have shown a better result when used as an adjunct to scaling and root planing in patients with refractory periodontitis than in patients with adult periodontitis.²⁴ Similarly, other investigations²² and several case reports²⁵ have indicated better results when combined therapy was used at non-responsive sites.

2. Subgingival Doxycycline

Doxycycline is a bacteriostatic agent and has the ability to downregulate MMP's a family of zinc dependent enzymes that are capable of degrading a variety extracellular matrix molecules including collagens.²⁸

The only FDA approved 10% doxycycline in a gel system ATRIDOX (42.5 mg doxycycline) is a subgingival controlled-release product composed of a 2 syringe mixing system.

Doxycycline levels in GCF peaked to 1,500 - 2000 µg/mL in 2 hours following treatment with ATRIDOX. These levels remained above 1000 µg/mL through 18 hours, at which time the levels began to decline gradually. Local levels of doxycycline have been found to remain well above the minimum inhibitory concentration for periodontal pathogens (6.0 µg/mL) through Day 7. Approximately 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days.²⁹

Several studies have reported the efficacy of 10% doxycycline hyclate as a local delivery antimicrobial agent for attaining probing depth reduction and gaining clinical attachment.^{30,31}

3. Subgingival Minocycline

Local delivery of minocycline, a bacteriostatic antibiotic¹⁵ has been tried clinically via in three different modes i.e. film, microspheres, and ointment.^{32,33}

Film

Ethyl cellulose film containing 30% of Minocycline were tested as sustained release devices. The results of this study indicated that the use of this device may cause complete eradication of pathogenic flora from the pocket after 14 days.³⁵

Microsphere

The FDA recently approved a new, locally delivered, sustained-release form of minocycline microspheres (ARESTIN) for subgingival placement. The 2% minocycline is encapsulated into bioresorbable microspheres (20-60µm in diameter) in a gel carrier and has resorption time of 21 days. Gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely.³⁵

Ointment

Minocycline ointment is a bioabsorbable sustained delivery system consisting of 2% minocycline hydrochloride in a matrix of

hydroxyethyl-cellulose, aminoalkyl-methacrylate, triacetin and glycerine. Dentomycin (2% Minocycline gel) has received regulatory approval for the treatment of periodontitis in the European Union. The same product is available in Japan with the name Perioline. The concentration of minocycline in the periodontal pocket is about 1300µg/ml, 1 hr after single topical application of 0.05 ml ointment (1mg of minocycline) and is reduced to 90µg/ml after 7 hrs.³⁴

Results have shown that the combination of ointment with scaling and root planing was significantly better than scaling and root planing alone in pockets > 7mm.³⁴

4. Subgingival Chlorhexidine

The use of chlorhexidine as an antifungal and antibacterial agent has been well established. Chlorhexidine is being used in mouth rinses and is highly recommended in the hygiene phase of treatment as an adjunct to tooth brushing. The major application has been for the control of dental plaque and gingivitis. Its mechanism of action relates to reduction in pellicle formation, alteration of bacterial adherence to teeth and an alteration of bacterial cell walls causing lysis. Its antibacterial action is due to an increase of the cellular membrane permeability followed by the coagulation of intracellular cytoplasmic macromolecules. Because chlorhexidine is highly cationic, it exhibits high substantivity. The long term efficacy of chlorhexidine on the periodontal pocket flora is dependent on the duration of exposure. However, intracrevicular irrigation of the periodontal pocket with chlorhexidine has only a short lived effect on the pocket flora.⁶

Chlorhexidine is available in the form of mouthrinses, Gels, varnishes, and chip to be used as a local drug delivery agent for the treatment of periodontal diseases.

Periochip

2.5 mg Chlorhexidine Gluconate PerioChip, the controlled subgingival delivery of chlorhexidine gluconate, is a small, orange-brown, tombstone-shaped chip (4.0x 0.5x 0.35mm) in a biodegradable matrix of hydrolyzed gelatin and has been approved by FDA. Studies with PerioChip showed reduction in the numbers of the putative periodontopathic organisms *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, and *Campylobacter rectus* after placement of the chip. No overgrowth of opportunistic organisms or other adverse changes in the oral microbial ecosystem were noted.

PerioChip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days.

Several large clinical trials were completed which compared the efficacy of scaling/root planing and combined therapy employing Chlorhexidine chips. The differences between therapies were statistically significant, but may not be clinically relevant. Furthermore, the number of sites with probing depth reduction was greater with combined therapy.^{36,37}

Pericol-CG

Pericol CG is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip is 4x5 mm and thickness is 0.25 - 0.32 mm and 10 mg wt.

Collagen is a natural protein, which is chemotactic for fibroblasts, enhances fibroblast attachment via its scaffold like fibrillar structure and stimulates platelet degranulation, thereby accelerating fibers and clot attachment. It has been shown to resorb after 30 days; however their coronal edge degrades within 10 days.³⁸

Chlo-Site

Chlo-Site is an agent containing 1.5% chlorhexidine of xanthan type (Ghimas Company, Italy). Xanthan gel is a saccharide polymer, which constitutes of a three-dimensional mesh mechanism, which is biocompatible with chlorhexidine.

The gel gets vanished from the pocket within 10-30 days of injection and effective concentration of chlorhexidine against microorganisms is established for at least 15 days in the region. Both chlorhexidine and gel matrix are mucoadhesive so that they stick inside the pockets and are not easily washed out by gingival fluid or saliva. It degrades spontaneously at the site of application, is well tolerated and is efficient in treatment of periodontal pockets & peri-implantitis.³⁸

5. Subgingival Metronidazole

Among the antibiotics that have been considered for periodontal treatment, Metronidazole has often been chosen because of its selective efficacy against obligate anaerobes. It acts by inhibiting DNA synthesis. It is known to convert into a reactive reduced form and affects specifically anaerobic rods and spirochetes in subgingival microflora. After application of Elyzol 25% dental gel, Metronidazole concentrations of above 100 µ/ml were measurable in the periodontal pocket for at least 8 hours and concentrations above 1 µ/ml were found at 36 hours.³⁹

A topical medication ELYZOL contains an oil-based metronidazole 25% dental gel (glyceryl mono-oleate and sesame oil). It is applied in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, forming crystals in contact with water. When metronidazole gel plus scaling and root planing were compared to root planing alone, the results have not been consistent.³⁹ One investigation suggested that there was a better result over a 9-month observation period when combined therapy was employed for probing depth reduction.⁴⁰

Future trends in local drug delivery

Eradication of microorganisms from the periodontal pocket is the most important step in treating periodontitis. The limitations of mouth rinsing and irrigation have prompted research for the development of alternative delivery systems. The requirements for treating periodontal disease include a means for targeting an anti-infective agent to infection sites and sustaining its localized concentration at effective levels for a sufficient time while concurrently evoking minimal or no side effects.⁴⁴ Various newer agents are being investigated in the field of local drug delivery to ensure maximum benefit.

1. Clarithromycin gel

A study has been conducted to investigate the adjunctive effects of subgingivally delivered 0.5 % clarithromycin as an adjunct to scaling and root planing for treating chronic periodontitis smoker subjects. It was observed that the adjunctive use of 0.5% clarithromycin as a controlled drug delivery system enhanced the clinical outcome. At the end of 6 months, the mean GI, PI, SBI, PPD, CAL for the clarithromycin group was significantly reduced. This product is still under investigation and yet to be patented.⁴⁵

2. Herbal products

Various herbal formulations like aloe vera, neem, tulsi, propolis, cocoa husk, pomegranate, cranberry etc. are being used widely these days.^{46,47} These products have shown promising results with no side effects and are economical as well.

3. Okade and co-workers developed a new sub gingival release delivery system (PT-01) containing Ofloxacin for sub gingival therapy. The PT-01 was found to be effective in the reduction of supra gingival plaque, reduction in the plaque index, reduction in bleeding on probing.⁴⁸

4. Fibroblast growth factor would be a very efficacious introduction in local drug delivery. To regenerate periodontal tissues, a sandwich membrane composed of a collagen sponge scaffold and gelatin microspheres containing basic fibroblast growth factor (bFGF) in a controlled-release system was developed. This sandwich membrane induced successful regeneration of the periodontal tissues in a short period of time (4weeks).⁴⁹

5. Colloidal drug carriers include micelles, emulsions, liposomes and nanoparticles (nanospheres and nanocapsules). It is noteworthy

that only liposomes and nanoparticles have been largely exploited for drug delivery because the methods of preparation are generally simple and easy to scale-up. The aim of using colloidal carriers is generally, to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes and/or to protect them against enzyme inactivation.⁵⁰

Nanoparticles, owing to their small size, penetrate regions that may be inaccessible to other delivery systems. These systems reduce the frequency of administration and further provide a uniform distribution of the active agent over an extended period of time. Three preliminary studies have been conducted to assess the efficacy of nanoparticles in periodontal drug delivery.

a) Dung et al used Antisense oligonucleotide- loaded chitosan-tripolyphosphate (TPP) nanoparticles and showed the sustained release of oligonucleotides which is suitable for the local therapeutic application in periodontal diseases.³⁵

b) Pinon et al conducted a preliminary in vivo study in dogs with induced periodontal defects using Triclosan-loaded polymeric (PLGA, PLA and cellulose acetate phthalate) nanoparticles and suggested that triclosan-loaded nanoparticles penetrate through the junctional epithelium.³⁵

c) Moulari et. al, investigated the in vitro bactericidal activity of the Harungana madagascariensis leaf extract (HLE) on the oral bacterial strains largely implicated in dental caries and gingivitis infections. HLE-loaded PLGA nanoparticles were prepared using interfacial polymer deposition following the solvent diffusion method. Incorporation of the HLE into a colloidal carrier improved its antibacterial performance and diminution of the bactericidal concentration was observed.³⁵

CONCLUSION

Current data suggest that local delivery of antimicrobials into a periodontal pocket can improve the periodontal health. However these drug systems do not provide a superior result when compared to scaling and root planing. Thus the benefits of using these systems as a monotherapy are questionable. In conjunction with scaling and root planing, the adjunctive use of local drug delivery may enhance the results in sites that don't respond to conventional therapy. A few localised persistent lesions in otherwise well controlled patients may offer the greatest potential for success with this treatment modality. Prudent administration of antimicrobial agents following judicious pharmacologic principles will preclude the abuse of chemotherapeutic agents and reduce the potential of developing or selecting drug resistant bacterial strains. Local drug delivery systems with controlled release properties have the potential to be used as a therapeutic component in the management of periodontal diseases. However, additional randomized, controlled studies are needed to help delineate the types of lesions, periodontal diseases, or specific situations where local delivery systems would be most beneficial.

It can be concluded that the adjunctive use of local drug delivery may provide a defined but limited beneficial response. However the magnitude of change anticipated by combined therapy must be interpreted in light of the severity of the defects being treated. Therefore the clinician will need to make decisions based on the desired outcomes of the therapy.

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