



Local Drug Delivery in Periodontics- A review

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ABSTRACT:

Periodontal disease is a multifactorial disease that affects the supporting tissues resulting in the destruction of supporting structure. Non-surgical periodontal treatment has been a cornerstone in the management of periodontitis. However the use of adjuncts along with mechanical debridement have shown better results in the clinical outcome in the management of periodontal disease. Local drug delivery system is the application of antimicrobial or anti-infective agent that would target pathogenic microorganisms by delivering it at the base of the pocket yielding a stable and good clinical outcome along with mechanical debridement. This review aims to focus upon the various local drug delivery systems in the management of periodontitis and its future trends.

Keywords: The Periodontitis, Local Drug Delivery, Non- Surgical Periodontal Therapy

INTRODUCTION:

Periodontitis is an inflammatory disease of the supportive tissues surrounding the teeth caused by specific or a group of specific microorganism resulting in progressive destruction of the periodontal tissues with pocket formation or recession or both.¹The goal of periodontal therapy is to halt the process of the disease by restoring the compatibility of periodontally diseased root surfaces. The aim of non-surgical periodontal therapy is to eliminate the microflora from the tooth surface as well as from

the adjacent soft tissues. In addition it also helps in creating an environment so that recolonization can be prevented using personal oral hygiene methods.²

Non-surgical periodontal therapy is considered as a gold standard and is the first recommended approach to the control of periodontal disease. However conventional mechanical debridement do not remove all the periodontopathic bacteria in certain inaccessible areas. But, mechanical debridement along with adjunctive use of anti-infective agents and other host modulatory agents have shown clinical improvement in the

management of periodontal diseases.² There are even advancement in the use of adjuncts like the use of ablative laser, hyperbaric oxygen, antioxidants, newer host modulatory agents and certain probiotics which is now receiving much attention as it has shown added benefits in suppressing the periodontopathic bacteria.

Local drug delivery system is designed to target periodontal pathogens by delivering the antimicrobial agents to the base of the pocket at a bacteriostatic or bactericidal concentration. This is done in order to disinfect the pathogenic microorganism by delivering the agents directly at the site so that the medicament is retained long enough to yield good result. Local Drug delivery system was pioneered by Dr Max Goodson in 1979 of the Forsyth Dental Research Centre.³ Local drug delivery into periodontal pockets may be further classified as providing either nonsustained or sustained subgingival drug delivery. Nonsustained subgingival drug delivery provides high pocket concentrations of the antimicrobial agent for only short time periods. Subgingival irrigation with antiseptic agents lacking substantivity for oral tissues (povidone-iodine) is examples of nonsustained subgingival drug delivery. Sustained subgingival drug delivery provides retention of the within periodontal pockets. Controlled drug release can be provided with subgingival irrigation of agents intrinsically substantive for tooth root surfaces (aqueous tetracycline) or pocket placement of commercial antimicrobial fibers, gel or films.⁴

Currently available locally delivered antimicrobials in periodontal therapy

TETRACYCLINE:

Tetracycline is the first available local drug composed of polymer ethylene vinyl acetate with 25% saturated tetracycline HCl. It is marketed as

Actisite in the form of flexible yellow fibres of length 23cm and 0.5mm diameter containing 2.7mg of tetracycline HCL which are non-resorbable safe and inert. The Actisite tetracycline fibres have been approved both by the United States Food and Drug Administration (FDA) and by the European Union's regulatory agencies.⁴ Tetracycline can also be available as Periodontal Plus AB with a base of collagen film.⁴ Tetracycline along with seratiopeptidase containing gels were used in non surgical therapy after scaling and root planing which was proved to be clinically effective in the management of periodontal disease⁵ because of the added benefit of anti-inflammatory effect of seratiopeptidase and antimicrobial effect of tetracycline. Various studies were conducted with tetracycline as monotherapy and also as an adjunctive to scaling and root planing. In a 6-month multi-center evaluation of adjunctive tetracycline fiber therapy by Newman et al 1994, showed that fiber therapy significantly enhanced the effectiveness of scaling and root planing in the management of localised recurrent periodontitis sites, in patients receiving regular supportive periodontal therapy.⁶ Disadvantage of using tetracycline is their early degradation and sometimes it also yields in candidal infection

DOXYCYCLINE:

Doxycycline is available as Atridox which is a FDA approved containing 10 % concentration in a syringe. It comes as two syringe that are mixed together back and forth in 100 cycles. A 23 gauge cannula is used to deliver the material in the pocket. GCF level reaches to 1500-2000 in 2 hours following the use of ATRIDOX.⁴ The levels remained for 18 hours thereby gradually declined. Walker et al 2000 in an attempt to determine the effectiveness of sustained-release, biodegradable gel containing 8.5% doxycycline

on the anaerobic flora and on antibiotic susceptibility patterns associated with subgingival plaque and saliva reported that the treatment significantly reduced the anaerobic population in plaque but did not result in change in either number of resistant bacteria or the acquisition of antibiotic resistance.⁷

MINOCYCLINE:

Arestin is available in the form of minocycline microspheres in HCL in a bioabsorbable polymer of polyglycolide-co-dl lactide. With the help of a disposable plastic syringe placed on a stainless steel handle the microspheres are dispensed in the subgingival space. The microspheres are bioadhesive on contact with moisture and does not require additional adhesives or dressings to hold it in place. Once in the pocket the microspheres react with the crevicular fluid which hydrolyzes the polymer causing water-filled channels to form inside the microspheres. These holes become the pathway for the antibiotic for sustained release. The minocycline then diffuses through these portals and permeates the surrounding tissues. Over a period of time, the microspheres themselves get fragmented through polymer hydrolysis and degrade and are ultimately bioresorbed. It is reported that the microspheres are completely biodegraded in about 21 days Renvert et al 2008, conducted a study to compare minocycline with chlorhexidine which showed improvement in the mechanical treatment of periimplant lesion with the use of minocycline and it also sustained for 6 months.⁸ Minocycline is also available as Dentomycin or Periocline

METRONIDAZOLE:

Elyzol is a topical medication containing an oil-based metronidazole 25% dental gel, applied in viscous 1 consistency to the pocket. The gel is

subgingivally placed with a syringe and a blunt cannula. The drug concentration in crevicular fluid follows an exponential pattern which is compatible with sustained drug delivery. Ainamo et al (1992) compared the effect of metronidazole 25% gel with subgingival scaling in adult Periodontitis and found that both periodontal pocket depth and bleeding on probing were significantly reduced in both groups.⁹ Stelzel M et al (1997) compared topical application of a metronidazole 25% dental gel with subgingival scaling and found better results as compared to SRP alone.¹⁰ Thus the effectiveness of metronidazole as an adjunct to SRP in the treatment of chronic adult periodontitis, but clinical significance and dissemination of antibiotics should be taken into account in the evaluation of metronidazole as an alternative to SRP

CHLORHEXIDINE:

Available as Periochip consisting of 34 percent chlorhexidine in a cross linked gelatin matrix .The chip is 5mm long, 4mm wide with a 2.5 mg of chlorhexidine gluconate. The dimensions of the chip prevent placement in small tortuous pockets so that placement into pockets of less than 5mm may be difficult and not recommended. Chlorhexidine concentration is 800-1000 ppm in GCF in the first 48 hours after the placement of periochip .Later on 100-500 ppm of chlorhexidine is present over the next 6 days. The chip is biodegradable and no second appointment is needed to remove it. PerioCol™-CG is a controlled-release chlorhexidine chip. Each PerioCol™-CG contains approximately 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of Type 1 collagen derived from fish sources. It releases chlorhexidine in vitro with a release profile of approximately 40-45% within 24hrs and afterward in linear fashion

for 7-8 days. The release profile may be explained by initial burst effect due to diffusion of the drug from the chip followed by release of the drug due to enzymatic degradation. Chlosite consists of 1.5% chlorhexidine bonded in a xanthan carrier substance. It contains chlorhexidine in two different forms. The first form is 0.5 % highly soluble chlorhexidine digluconate, also called chlorhexidine-bis (D-gluconate). This form of chlorhexidine is used as an antiseptic agent. The second form is a slow-release 1 % chlorhexidine dihydrochloride (a bis-biguanide with bacteriostatic characteristics). Chlosite uses xanthan gel as the carrier. Xanthan in Chlosite provides good subgingival bonding of the local delivery device via mucoadhesion, while the high Chlorhexidine content guarantees a safe bactericidal effect. D. Steinberg et al (1990): Release of Chlorhexidine from a degradable delivery system and the degradation of the matrix is controlled by variation in the formulation. This presented a new dental drug delivery system for sustained

release of chlorhexidine that can be used as an adjunct in the treatment of periodontal diseases.¹¹

OFLOXACIN:

OFLOXACIN INSERTS PT-01 is a soluble insert, with both fast and sustained release parts containing 10% ofloxacin and showed a constant drug level of above 2 mg/ml, (minimum MIC for most pathogenic organisms) which could be sustained for up to 7 days .The controlled release system exhibited a biphasic pattern with a rapid early release phase peaking at approximately 12µg/ml and stabilizing at approximately 2µg/ml from day 3 to 7 following insertion. According to Kinura et al 1991 initial investigations failed to any additional microbiological effect in a split mouth design.¹² But according to Yamagami et al 1992 Four weekly applications of the insert resulted in significant resolution of periodontal inflammation and improvement in other clinical parameters compared to controls.¹³

Table 1: FUTURE TRENDS:

DRUG	AUTHOR	STUDIES
Clarithromycin Gel Available as 0.5% gel	Agarwal E et al 2012 ¹⁴	With the Adjunctive use of the gel the mean Gingival index, Plaque Index, Sulcular Bleeding Index, Probing Pocket Depth, Clinical Attachment Level for the clarithromycin group was significantly reduced compared to the control group.
Azithromycin Gel Available as 0.5% gel	Pradeep AR et al 2013 ¹⁵	Adjunctive effects of subgingivally delivered 0.5% azithromycin as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis showed significant improvement in clinical outcome.
Statins 1.2mg gel	Pradeep AR et al 2010 ¹⁶	Investigated the effectiveness of simvastatin (SMV) 1.2 mg gel into the periodontal pocket using a syringe with blunt cannula. Greater decrease in gingival index and Pocket Depth and more Clinical Attachment level gain with significant intrabony defect fill was observed.

Alendronate 1 % gel form	Pradeep AR 2012 ¹⁷	The efficacy of 1% Alendronate gel used as an adjunct to SRP for the treatment of intrabony defects in patients with chronic periodontitis with type 2 diabetes showed significant increase in the Pocket Depth reduction, CAL gain, and improved bone fill.
Metformin 0.5%-1%	Pradeep AR 2013 ¹⁸	The efficacy of varying concentrations of subgingivally delivered 0.5%, 1%, metformin in the treatment of chronic periodontitis mean reduction of pocket depth and mean clinical in attachment level was greater in metformin group than the placebo group. The greatest reduction was found in 1% metformin group

Local Drug Delivery versus Mechanical Debridement

Hanes *et al.* in their systematic review, stated that as compared to Scaling and Root Planing alone, when Scaling and Root Planing is combined with certain local drug delivery agents, statistically significant adjunctive effects on Pocket Depth reduction or Clinical Attachment Level gain and decreased Bleeding on Probing were observed.¹⁹

Antibiotic Resistance Associated with Local Drug Delivery Systems:

Local drug delivery provides a high drug concentration at a specific site. Sublethal amounts of administered drugs leak out of pockets during therapy. Therefore, the potential exists that local drug delivery may contribute to development of drug resistant organisms in areas other than the treated sites. Exposure to sub inhibitory concentrations of metronidazole or minocycline resulted in development of resistance among *P.gingivalis*, *P.intermedia*, *F.Nucleatum*, *P.Anaerobius*.⁷ this suggests that repeated use of these agents can result in increased levels of drug resistant bacteria.

CONCLUSION:

Traditional periodontal therapy is the gold standard in the treatment of maximum cases of periodontal diseases. Local drug delivery often appears to be as effective as scaling and root planing with regards to reducing signs of

periodontal inflammatory diseases. At present, there are insufficient data to indicate that one local drug delivery service is clearly superior to all the other systems. There is a lack of data to support the impression that local drug delivery in conjunction with root planing reduces the need for periodontal surgery more than scaling and root planing alone.

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