Local Drug Delivery in periodontal diseases.A Review

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Abstract

Periodontitis is an immuno-inflammatory disease of the tissues surrounding the teeth. Various treatment modalities like mechanical debridement and use of antimicrobials have been followed in the treatment of such conditions. Introduction of local drug delivery system in the periodontal pocket is a promising therapeutic modality for achieving better clinical outcomes when used as an adjunct to conventional non surgical periodontal therapy. Intensive research efforts are now focussed on the development of new strategies for more effective treatment.

Keywords : Periodontitis, local drug delivery, scaling and root planning, antimicrobial agent.

Introduction

The inflammation in the periodontal tissue is initiated by microbial plaque and bacterial infection. In the periodontal pocket the bacteria form a highly structured and complex biofilm. As this continues, the biofilm reach far subgingivally and it becomes difficult for the patient to reach it during oral hygiene practices.¹ Traditional treatment options for such conditions includes mechanical debridement aimed at removing the subgingival flora and providing a clean, smooth and compatible root surfaces. But, in several instances, the complex anatomy of the root and the location of the lesion may hamper the treatment and prevent sufficient reduction of the bacterial load.²

Antibacterial agents have been used along with mechanical debridement in the management of periodontal infection. The effectiveness of all the methods are limited due to the

lack of accessibility in the periodontal pocket.³

Periodontal pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria such as *Actinobacillus*

actinomycetem comitans, *Porphyromonas gingivalis* and *Prevotella intermedia*. For the effective treatment, the antibiotic must reach the depth of the pocket and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.⁴ Recent advance in science and technology has revolutionized the basic outlook and approach to the problems of periodontal disease. Earlier it was assumed that periodontal problems were invariably progressive and the morbid effects increase with passage of time. A thorough understanding of the etiopathogenesis of periodontal disease has provided the clinicians and researchers with a number of diagnostic tools and technique that has widened the treatment options.⁵

History

Ever since the introduction of systemic antibiotics, various drugs have been used in the treatment of periodontitis. The disadvantages of systemic antibiotics like bacterial resistance, superimposed infections, uncertain patient compliance, nausea, vomiting and gastrointestinal disturbances⁶ led to the introduction of local drug delivery as the treatment option. It was in the year 1979, Dr. Max Goodson et al first proposed the concept of controlled delivery in the treatment of periodontitis.⁷ Since then, a number of studies have been carried out over the years

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with different antimicrobial agents and in different clinical situations.

Classification

Various classification systems were evolved.

I Based on the application [Rams and Slots] 1996

1. Personally applied (in patient home self-care)

A. Nonsustained subgingival drug delivery

Home oral irrigation

Home oral irrigation jet tips

Traditional jet tips

Oral irrigation (water pick)

Soft cone rubber tips (pick pocket)

B. Sustained subgingival drug delivery

2. Professionally applied (in dental office)

A. Nonsustained subgingival drug delivery

Professional pocket irrigation

B. Sustained subgingival drug delivery

Controlled release devices

Hollow fibres

Dialysis tubing

Strips

Films⁸

II Based on the duration of medicament release

(Greenstein and Tonetti 2000)⁹

A. Sustained release devices – *Designed to provide drug delivery for less than 24 hours*

B. Controlled release devices – *Designed to provide drug release that at least exceeds 1 day or for at least 3 days following application* (Kornman 1993)

III Depending on degradability.

1. Nondegradable devices (first generation)

2. Degradable devices (second generation)⁵

Various drug delivery systems for treating periodontitis are fibres, films, injectable systems, gels, strips, compacts, vesicular system, microparticles and nanoparticles.³

Currently available locally delivered antimicrobials in periodontal therapy,

Tetracycline: containing fibers are the first available local drug. It had ethylene/vinyl acetate copolymer fiber with diameter of 0.5 mm, containing tetracycline 12.7mg per 9 inches.¹ 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. These are non-resorbable, safe, inert copolymer loaded with 25% w/w tetracycline HCl. It maintains constant concentrations more than 1000 µg/mL for a period of 10 days. Follow up showed reduction in the subgingival microbiota.² Bioresorbable tetracycline fibre 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 degrades within 7 days.¹⁰ Tetracycline seratiopeptidase containing gels were evaluated in a study by Maheshwari et al 2005. This combination containing thermoreversible gel was clinically effective along with scaling and root planing.¹¹ 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.¹²

Doxycycline : Atridox is a FDA approved 10% doxycycline in a gel system using a syringe.¹ GCF levels reached its peak to 1,500-2,000 in 2 hours following treatment with Atridox. These levels remained above 1000 µg/mL through 18 hours, and then levels gradually declined.² 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.¹³

Minocycline - Arestin is a FDA approved locally delivered, sustained release form of minocycline microspheres for subgingival placement. The 2% minocycline is

encapsulated into bioresorbable microspheres in gel carrier.¹

Stefan Renvert et al 2008, conducted a study to compare

Various agents available in market ^{2,25}:

Agent	Product available	Dosage form
Tetracycline	Actisite (25%w/v tetracycline Hcl)	Non resorbable fiber
	Periodontal plus AB(2mg of Tetracycline in 25mg of collagen)	Resorbable fiber
Doxycycline	Atridox (10% Doxycycline)	Bio degradable mix in syringe.
Minocycline	Dentomycin gel (2% Minocycline)	Biodegradable gel
	Arestin (2% Minocycline)	Biodegradable mix in syringe
	Perioline (2.1%w/v Minocycline)	Ointment
Metronidazole	Elyzol (25% Metronidazole)	biodegradable gel
Chlorhexidine	Periochip (2.5mg Chlorhexidine)	Biodegradable chip
	Pericol CG (2.5mg Chlorhexidine)	Biodegradable chip
	Chlosite (1.5% Chlorhexidine)	

Recently various newer drugs have been tried to determine their efficacy.

Authors	Aim of the study	Major outcome
Vijay Kumar Chava et al ¹⁷	develop a thermo-reversible sustained-release green tea gel and effects on patients with chronic periodontitis.	use of local application of green tea gel along with conventional therapy showed greater reduction of pocket and inflammation.
A R Pradeep et al 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 attachment level was greater in metformin group than the placebo group. The greatest reduction was found in 1% metformin group.
A R Pradeep et al ¹⁹	to evaluate the efficacy of subgingivally delivered 1.2 % Atorvastatin in patients with chronic periodontitis	mean pocket depth , clinical attachment level gain was greater in patients with Atorvastatin than the placebo.
Ray C Williams et al ²⁰	Minocycline spheres in chronic periodontitis	mean reduction of probing depth was improved in group receiving minocycline spheres along with scaling root planing when compared to group with Scaling and root planing alone.
Amitha Ramesh et al ²¹	evaluation of subgingival application of chlorhexidine varnish and chlorhexidine gel as an adjunct to full mouth scaling and root planing in case of moderate to deep periodontal pocket subjects.	combination of varnish and gel with scaling and root planing had better clinical outcome.
Esha Agarwal et al ²²	Efficacy of 0.5 % Clarithromycin gel with and without scaling root planing	improved clinical outcomes in Clarythromycin gel and scaling and root planing when compared to group that received scaling and root planing alone
A R Pradeep et al ²³	Efficacy of 1 % Alendronate gel in intrabony defects.	greater mean percentage of bone fill, probing depth reduction and clinical attachment gain was seen in the group receiving alendronate gel than placebo.
A R Pradeep et al ²⁴	Efficacy of 1% Alendronate gel in class II Furcation defects	mean probing depth reduction, mean relative vertical and horizontal clinical attachment level in group that received gel in class II furcation defects compared to placebo.
Renvert et al ¹⁵	local minocycline microspheres or chlorhexidine gel following debridement in periimplantitis cases.	use of minocycline resulted in Significant reduction in mean probing pocket depths.

25%w/v tetracycline HCl

10% Doxycycline

25% Metronidazole

2% Minocycline

2.5mg Chlorhexidine

minocycline on probing depths with chlorhexidine at days 30, 90, and 180 ($P = 0.5$, $P = 0.01$, and $P = 0.04$, respectively). The use of repeated local antibiotic as an adjunct to the mechanical treatment of peri-implantitis lesions demonstrated improvements in probing depths that were significantly different from controls and were sustained for 6 months. It was concluded that for greater benefit the treatment may have to be repeated.¹⁴

Metronidazole : Elyzol is a topical medication containing an oil-based metronidazole 25% dental gel, applied in viscous consistency to the pocket.¹ YealShifrovitch et al 2009 in a study enabled the understanding of metronidazole-release kinetics from bioabsorbable polymeric films and demonstrated good biocompatibility and the ability to inhibit *Bacteroides fragilis* growth; therefore, they may be useful in the treatment of periodontal diseases.¹⁵

Chlorhexidine : Periochip is a small chip composed of biodegradable hydrolysed gelatin matrix, cross-linked with glutaraldehyde and also containing glycerine and water, into which 2.5 mg of chlorhexidine gluconate has been incorporated per chip.¹ It is a FDA approved small, orange brown, chip measuring 4.0x 0.5x 0.35mm in a biodegradable matrix of hydrolysed gelatin.

Studies showed reduction in the numbers of the putative periodontopathic organisms *Porphyromonas gingivalis*,

Prevotella intermedia, *Bacteroides forsythus*, and *Campylobacter rectus* after placement of the chip.² Study by Soskolne W.A in 1999 showed that there was an initial peak concentration of chlorhexidine in gingival crevicular fluid at 2 hour after the chip was introduced. Slightly lower concentrations being maintained over next 96 hrs. Total degradation occurred between 7-10 days after insertion.¹⁶

Conclusion

Based on the available evidence, the local drug delivery into the periodontal pocket can improve the periodontal health. However these drugs fail to completely replace the conventional scaling and root planning. Thus the benefit of these drugs as a mono therapy is questionable. When compared to systemic antimicrobials, the local drug delivery will reduce the developing drug resistant bacterial strain which is of current worldwide concern. Also, the controlled release properties can be applied as a therapeutic component in the effective management of localised persisting lesions. Local drug administration should be based on patient clinical findings, scientific evidence and proper diagnosis.

Thus, it can be concluded that local drug delivery though not a substitute for the conventional therapy, can be of added benefit if used as an adjunct with the conventional scaling and root planning.

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