Local Drug Delivery in Periodontics : An Update

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Abstract

Periodontitis is an inflammatory disease of the supporting tissues of teeth caused by a group of specific microorganisms. The microbial etiology of human periodontitis suggests antimicrobial agents along with mechanical therapy as one of the effective treatment options. Systemic administration of antibiotics agents is limited due to the lack of accessibility of periodontopathic organisms in periodontal pocket. Local delivery of antimicrobial agents using controlled/ sustained release systems have been investigated for the possibility of overcoming the limitation of systemic therapy. This article reviews the various local drug delivery systems available in periodontics.

Keywords : Chlorhexidine, Local drug delivery, Metronidazole, Minocycline Periodontitis, Tetracycline.

Introduction

Periodontitis is inflammation of gingival and the adjacent attachment apparatus and is characterized by loss of connective tissue attachment and alveolar bone. The appearance of periodontal pocket is the first clinical manifestation of periodontal disease which offers a favorable environment for growth of anaerobic pathogenic bacteria such as Actinobacillus actinomycetemcomitans, Bacteroid gingivalis, Bacteroid melanogenicus sub species intermedius, Porphyromonas gingivalis and Prevotella intermedia. Suspected periodontal pathogens have been shown to produce a large number of biological molecules that may act directly on host tissues and destroy its integrity.[1]

Conventional therapy for periodontal disease consists of mechanical debridement to disrupt subgingival flora, usually performed by scaling and root planning. However, the mechanical therapy itself may not always reduce or eliminate anaerobic infection at the base of the pocket, within the gingival tissues, and in both structures inaccessible to periodontal instruments.[2] To overcome this, systemic and local antibiotics as an adjunct to mechanical therapy were introduced. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short period of time, forcing repeated dosing for longer periods. Another often overlooked factor is that systemic antibiotics do not penetrate sub gingival bio film to kill the bacteria. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of systemic antibiotic therapy. The concept of controlled delivery of drug therapy in the treatment of periodontitis was introduced by Dr. Max Goodson in early 1980[3]. Local administration of anti microbial drugs directly into the periodontal pocket achieves much higher concentration of the drug at the target site and there is no dependence on patient compliance for success of the therapy. The fact that periodontal diseases are localized to the immediate environment of the pocket make the periodontal pocket a natural site for treatment with local sustained- delivery systems. This forms the basis of local drug delivery (LDD) devices in the treatment of periodontitis.

Indications of Local Drug Delivery

1. As an adjunct to mechanical therapy and regenerative procedures.
2. In case of patients who are systemically compromised and cannot undergo periodontal flap surgery.
3. In case of patients with refractory periodontitis.

Contradictions

Patients who are allergic to drug and vehicle component.

Advantages

1. Less invasive, Painless and a Simple Procedure.
2. Cost effective
3. Drug dosage required is lesser as compared to systemic administration.
4. Dose of antimicrobial drug available sub-gingivally is 100 fold higher as compared to systemic drug therapy[4].
5. LDD reduces the total patient dose by over 400 fold thereby reducing the potential side effects with the use of systemic antibiotic drug regimen and development of drug-resistant microbial populations at non-oral body sites.[4]
6. LDD can favour better patient acceptance and compliance.

Limitations

1. The main limitation associated with LDD is the placement of drug into deep periodontal pockets and furcation lesions.
2. Drug is not available to the periodontal pathogens residing within adjacent gingival connective tissue and on extra pocket oral surfaces viz. tongue, tonsils and buccal mucosa which may lead to recurrence of periodontal infection.

Vehicles

Various local drug delivery vehicles are: Fibers, Films, Injectable systems (gels and Injectable gels), Strips, Vesicular systems, Microparticle system, Nanoparticulate system.

Fibers: Fibers are hollow type systems commonly made up of polymers such as poly caprolactone (PCL), polyurethanes, polypropylene, and cellulose acetate propionate and ethyl vinyl acetates (EVA). Among these monolithic EVA fibers used in vitro and in vivo studies are found to be effective in controlled release of encapsulated drugs.[5] The major drawback of hollow fibers was that they permit rapid eradication of drugs. To overcome this limitation, drug impregnated monolithic fibers were developed. These fibers are placed circumferentially into the pockets with an applicator and the pocket is sealed with cyanoacrylate adhesive.

Films: are widely used forms of intra-pocket delivery device prepared either by solvent casting or direct milling. Films are usually composed of cross - linked fish gelatin (bycoprotein), synthetic biodegradable polymers such as poly (lactide-co-glycolide) and non biodegradable include ethyl cellulose. Newer distinguishable films composed of poly (vinyl alcohol) (PVA) and carboxy methyl- chitosan (CMCS) are prepared by blending / casting methods and are found to be biocompatible, show pH responsive swelling, have good retention at application site and maintain high drug concentration at least for five

days.[6]

Injectable Systems: These systems allow easy application of agents into periodontal pocket using a syringe and later on the pocket is sealed using adhesive. Commonly used are gels and injectable gels.

Gels: Gels are MTZ containing gel systems based on hydroxyl ethyl cellulose, corbopol 974 & polycarbophil and are applied sub ligually with the help of blunt cannula and syringe. The first gel system was teteracycline based loaded into the micro tubular excepient halloysite coated with chitosan to further retard drug release.[7]

Injectable Gels: These are semi solid formulations composed of oleogels like glyceryl mono- oleate, cellulose derivatives such as hydroxyl propyl methyl cellulose and hydroxyl ethyl cellulose, hydro gels.

Strips: Acrylic strips are fabricated using a mixture of monomers; polymers either by solvent casting or pressure melt method.

Vesicular Systems: Commonly used vesicular systems for targeting periodontal biofilm are lectin bearing liposomes (proteoliposomes) which are retained by bacteria eventually delivering triclosan into the cellular interiors.[8]

Microparticle System: Usually available as non- biodegradable and biodegradable. These materials include natural polymers, modified natural substances and synthetic polymers and are usually available in the form of chip or dental paste formulation or directly injected into the periodontal cavity.

Nanoparticulate System: Nano-particulate system is a modern drug delivery system with high dispersibility in an aqueous medium, controlled release rate and increased stability and bio compatibility. Nano particles usually used as a drug delivery system for dental application are composed of 2-hydroxyethyl meth acrylate (HEMA) and polyethyleneglycoldimethacrylate (PEGDMA).[9]

Drugs Used as Local Delivery Agents in Periodontics

Tetracyclines: Tetracyclines are broad spectrum antibiotics produced naturally from certain species of streptomyces or derieved semi synthetically. These have been frequently used in treating refractory periodontitis including localized aggressive periodontitis as they have the ability to concentrate in the periodontal tissues and inhibit the growth of Aggregatibacter actinomycetem-comitans. Tetracyclines are available as non resorbable, cylindrical, 0.5mm diameter monolithic ethylene vinyl acetate fibres which when inserted into periodontal pocket provides concentration of more than 1300µg/ ml for 7 days (Actisite®, Corporation, Palo Alto, CA). Actisite was the first commercially available controlled release anti microbial product and was introduced in 1994. Recently, bioresorbable tetracycline fibers (periodontal plus AB®) have been developed .

Minocycline: minocycline belongs to Group III tetracyclines. It is available as films, microspheres, ointment.

Films: It is composed of ethyl cellulose film containing 30% of minocycline.

Microsphere: It is available as sustained release form of 2% minocycline microspheres with a diameter of 20-60µm with a resorption time of 21 days (Arestin®)

Ointment: It is a sustained delivery system consisting of 2% minocycline hydrochloride in a matrix of hydroxyl ethyl cellulose, aminoalkyl-methacrylate, triacetine and glycerine (Dentomycin®, Periocline®)

Doxycycline: Doxycycline belongs to Group III teracyclines. It is available as sub gingival controlled- release broad spectrum 10% Doxycycline hyclate gel composed of a two syringe mixing system(Atridox®). It is the only FDA approved drug for local delivery and has the ability to down regulate MMPs a family of zinc dependent enzymes that are capable of degrading a variety of extracellular matrix molecules including collagen.

Chlorhexidine: CHX belongs to Biguanide group. It binds electro statically to the acidic groups in the surface proteins. It is available as resorbable chip, collagen membrane and gel to be used for sub gingival application.

Periochip: Periochip® (Perio Products Ltd, Jerusalem, Israel) is a resorbable small chip of size 4.0×5.0× 0.35mm. It is composed of bio-degradable hydrolysed gelatin matrix, cross linked with glutaraldehyde, glycerine and water into which 2.5mg of chlorhexidine gluconate has been in corporated per chip. It releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the CHX within first 24 hours and then releasing the remaining CHX in an almost linear fashion for 7-10 days.[15]

Periocol: Periocol® (Eucare Pharmaceuticals, Chennai) is a new sustained release CHX system composed of CHX and collagen obtained from the air bladder of fresh water fishes. It is prepared by in corporating 2.5 mg CHX from a 20% CHX solution in collagen membrane. The size of chip is 4×5mm and thickness is 0.25-0.32mm and 10 mg weight.

Chlo-site: Chlo-site® (Ghimas Company, Italy) is an agent composed of 1.5% CHX of xanthan type consisting of saccharide three dimensional mesh type polymers. The resorption time of gel is within 30 days and attains effective sub gingival concentration for at least 15 days.[16]

Metronidazole: Metronidazole belongs to Nitroimidazoles. It is selectively toxic to anaerobic micro-organisms and exerts cytotoxicity by damaging DNA and other critical biomolecules. The most commonly used is Elyzol® (gel which is a biodegradable oil based delivery device containing 25% of metronidazole benzoate in a matrix consisting of glyceryl mono-oleate and sesame oil.

Conclusion

Major problem associated with periodontal pocket is that many drugs do not reach the target sites in the therapeutic concentrations. Local drug delivery systems provide a safe, easily applied, more site-specified and controlled drug delivery into the periodontal pocket and proves to be a viable adjunct to conventional therapy. However long term clinical studies in human subjects are required to evaluate the potential benefits of local drug delivery agents in periodontal regenerative therapy.

References

1. Ahuja A, Rehman S, Ali J, Chaudhary R. Effects of dental films containing amoxicillin and metronidazole on periodontal pathogens: microbial response. Pharmazie 2003;58:716-20.
2. Dodwad V, Vaish S, Mahajan A, Chhokra M. Local drug delivery in periodontics : A strategic intervention.Int JPharm Pharm Sci 2012;4:30-4.
3. Divya PV, Nandakumar K. Local drug delivery Periocol in periodontics.Trends iomater . Artif Organs 2006; 19: 74-80.
4. Goodson J. Antimicrobial strategies for treatment of periodontal diseases. Periodontol 2000:1994;

5:142-68.
5. Goodson JM et al. Monolithic tetracycline containing fibres for controlled delivery to periodontal pockets. J Periodontol 1983; 54:575-79.
6. Vyas SP,Sihorkar V,Mishra V. Controlled and targeted drug delivery strategy towards intra periodontal pocket disease. J Clin Pharm Ther 2000; 25:21-42.
7. Kelly HM, Deasy PB, Ziaka E, Cleffey N. Formulation and preliminary in vivo dog studies of a novel drug delivery for the treatment of periodontitis. Int J Pharm 2004;15:167-83.
8. Vyas SP et. al. Preparation, characterization and in vitro anti microbial activity of metronidazole bearing lctinized liposomes for intra periodontal pocket delivery. Pharmazie 2001;56:554-60.
9. Dung TH et al. Chitosan- TPP nano particle as a release system of antisense oligonucleotide in the oral environment. J Nanosci Nanotechnol 2007;7:3695-99.
10. Aimetti M, Romano F, Torta I, Cirillo D, Caposio P, Romagnoli R. Debridement and local application of tetracycline- loaded fibres in the management of persistent periodontitis: results after 12 months.J Clin Periodontol. 2004;31:166-72.
11. Gupta R, Pandit N, Aggarwal S, Verma A. Comparative evaluation of sub gingivally delivered 10% doxycycline hyclate and xanthan- based chlorhexidine gels in the treatment of chronic periodontitis. J Contemp Dent Pract. 2008;9:25-32.
12. Grover V, Kapoor A, Malhotra R, Battu VS, Bhatia A, Sachdeva S.To assess the effectiveness of a chlorhexidine chip in the treatment of chronic peridodontitis: A clinical and radiographic study. J Indian Soc Periodontol 2011;15:139-46.
13. Jain R, Mohamed F, Hemalatha M. Minocycline containing local drug delivery system in the management of chronic periodontitis. A randomized controlled trial. J Indian Soc Periodontol. 2012; 16: 179-83.
14. Chaturvedi TP, Srivastava R, Srivastava AK, Gupta V, Verma P. Evaluation of metronidazole nanofibres in patients with chronic periodontitis.A clinical study.Int J Pharma Investig 2012;2:213-7.
15. Ciancio SG. Local delivery of chlorhexidine .Compend Contin Educ Dent 1999;20:427- 32.
16. Nandakumar P.K. Local drug delivery Periocol in Periodontics. Trends Biomater Artif Organs 2006;19:74-80.

Table - I : Clinical Studies of Local Drug Delivery Systems

Drug	Reference	Form of drug	Type of drug	Sample size	Results
Tetracycline	Aimetti M et al 2004[10]	Tetracycline loaded fibres	Controlled release	19 patients with atleast 4 bilateral pockets	**In test group:** Reduction in P.D- 2.05 mm Gain in CAL- 1.79 mm Reduction in B.O.P- 23.68%
Doxycycline	Gupta R et al 2008[11]	10% doxycycline hyclate gel	Controlled release	90 sites in 30 patients	**Test group:** At 3 months Reduction in P.D- 0.86±1.0 mm C.A.L gain- 0.80±0.92 mm
Chlorhexidine	Gupta R et al 2008[11]	CHX gel	Controlled release	90 sites in 30 patients	**Test group:** At 3 months Reduction in P.D- 0.66±1.58 mm C.A.L gain- 0.63±1.47 mm
Chlorhexidine	Grover V et al 2013[12]	CHX chip	Controlled release	40 patients	**Test group:** At 3 months Reduction in P.D- 5.68±1.60 mm C.A.L gain- 8.86±1.53 mm
Minocycline	Jain R et al 2012[13]	2% Minocycline gel	Sustained release	22 pairs of sites	**Test group:** At 9 months Reduction in P.D- 3.8±0.79 mm No. of non motile bacilli - 21.65±3.74 And were significantly less than control group
Metronidazole	Chaturvedi TP et al 2012[14]	Metronidazole nano fibres	Controlled release	40 bleeding sites were selected	**Reduction in:** P.D- 68% PI- 85% B.O.P- 90%

Legend for Table 1: P.D- Probing Depth; C.A.L- Clinical Attachment Level; PI- Plaque Index; B.O.P-Bleeding On Probing.

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EVENT ALERT

NATIONAL EVENT

World Dental Show
4-5-6 October 2013
Mumbai (Maharashtra)

Expodent Bengaluru
26-27 October 2013
Bengaluru

Expodent International India
27-28-29 December 2013
New Delhi

46th Kerala State Dental Conference 2014
17, 18, 19 January 2014
C. Kesavan Memorial Town Hall, Kollam

67th Indian Dental Conference
21, 22, 23 February 2014
Hitex, Hyderabad

Annual World Dental Congress (FDI) 2014
11, 12, 13, 14 September 2014
New Delhi, India

INTERNATIONAL EVENT

International Association of Paediatric Dentistry
12-15 June 2013
Seoul, Korea

American Dental Hygienists Association
19-25 June 2013
Boston, USA

SLDA 80 Anniversary Annual Scientific Sessions
27 June to 1 July 2013
Srilanka

European Organisation for Caries Research
60th ORCA Congress
3-6 July 2013
Liverpool, UK

International Federation of Dental Hygienist
19th International Symposium
on Dental Hygiene
14-17 August 2013
Cape Town, South Africa

The British Society of Paediatric Dentistry
Annual Meeting 2013
17-20 September 2013
East Scotland, UK

American Academy of Periodontology
99th Annual Meeting
28 September-1 October 2013
Philadelphia, USA

World Congress on Preventive Dentistry
9-12 October 2013
Budapest, Hungary

American Dental Association
154th Annual Session
31 October-3 November 2013
New Orleans, USA

Greater New York Dental Meeting
29 November-4 December 2013
New York, USA

European Organisation for Caries Research
61st ORCA Congress
25 July 2014
Greifswald, Germany