Localy Delivery of Antimicrobials in Periodontics : A Compresive Review

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Abstract

Periodontal disease is a general term encompassing several pathological conditions such as chronic periodontitis, aggressive periodontitis, and necrotizing periodontitis. The primary etiology of periodontal disease is bacterial plaque however environment,behavioral and genetic factors acts as a risk, which influence host response and disease progresion.Most periodontal therapy remains focused on eradication of bacterial plaque and modification of risk factors. Chemotherapy may be directed at subgingival plaque, using antimicrobials, or at the host response using anti-inflammatory agents. Antimicrobials can be locally or systemically delivered; however in most cases antimicrobial chemotherapy should be considered adjunctive to mechanical debridement. Local delivery means introduction of materials into the periodontal pocket designed to positively affect the treatment of periodontal diseases. These systems have provided the profession with a new tool which,in clinical trials, has shown to alter the subgingival flora and influence the healing of the marginal attachment appartus. This review article evaluates the efficacy, limitation and future perspectives of local drug delivery of antimicrobials in Periodontics.

Key Words: Local Delivery Antimicrobial Agents; Periodontitis; Systemic Antimicrobial; Tetracycline.

Introduction

Periodontal diseases are bacterial in origin.**Moore** detected over 300 different bacterial species in the oral cavity[1].It is well documented that bacteria play a decisive role in the etiology of periodontal disease.Most periodontal therapy remain focused on eradication of bacterial plaque and modification of risk factors. Both systemic and local delivery of antimicrobials have been used in treament of periodontal disease. Local delivery means introduction of materials into the periodontal pocket designed to positively affect the treatment of inflammatory periodontal diseases. Local delivery alleviates many concerns associated with systemic antimicrobial therapy,such as bacterial resistance,adverse effects,lack of compliance and the fact that periodontal destruction is often localized to a few sites or teeth. Methods employed to convey antimicrobial agents into periodontal pockets have included rinsing, irrigation, systemic administeration and local application using sustained and controlled delivery devices.

These systems have provided the profession with a new tool which,in clinical trials,has shown to alter the subgingival flora and influence the healing of the marginal attachment appartus. This review article evaluates the efficacy, limitation and future perspectives of local drug delivery of antimicrobials in Periodontics.

Terminology[2]

Different terms are used to explain the local delivery of antimicrobial therapy in Periodontitis. Some of the terms are synonyms while others have different meanings and therapeutic.

Targeted drug delivery: Delivery of agents to specific cells.

Local or site specific are used as synonyms to targeted drug delivery.

Controlled delivery or Controlled release: Release of drug for prolonged drug availability and sustained drug action.

Sustained release/slow release/timed release/ prolonged action or extended action: Are used synonymously to controlled release.

Topical Application: Form of local delivery referring to deliver of an agent to an exposed surface.

Historical Perspective[2]

The concept of local drug delivery had its origins in early 1970s based on the theory that if one could substantially improve the cellular specificity of a drug there would be an accompanying improvement in the therapeutic index. With recent advances in receptor biology, genetic regulation and technical breakthrough has provided new approaches in local drug delivery in periodontal therapy. The local drug delivery in periodontics was championed and developed into a viable concept by Dr.Max Goodson which involved hollow fibers of cellulose acetate filled with tetracycline[3].

Desirable characteristics of locally delivered antimicrobials[4]:

- Researches site of disease activity
- Achieves adequate concentration of drug.
- Effective against causative pathogens.
- Biodegradable.
- Minimal adverse effects and no bacterial resistance.

Indication

1. Patients with periodontitis who are in periodontal maintainance and who are otherwise stable but exihibit limited localized persistent or recurrent deep probing depths.

2. Patients with chronic periodontitis who have completed initial therapy,with localized non responding sites and in whom surgery is ruled out.
3. Where eshetics is concern and surgery may be contraindicated.
4. During periodontal regenerative procedures.
5. Dental phobic patients.

Contra Indication

Should not be used in following areas:

1. As a replacement for scaling and root planing in Initial therapy or Maintainance Phase.
2. As a replacement for surgerical therapy.
3. In patients with multiple areas requiring treatment.
4. As a subsitute for systemic antibiotics, periodontal disease in systemic compromise patients , periodontal abscess and aggressive periodontitis.
5. Patients susceptible to infective endocarditis are contraindication for irrigation devices to avoid the risk of bactermia.
6. Patients with known hypersensitivity to particular antimicrobial used.

Advantages and Limitation of antimicrobial agents employed in local drug delivery system.

The tetracyclines are broad spectrum antibiotics that affect anaerobes and facultative organisms. Local deliver of these agents provides high concentrations that are bactericidal compare to systemic administration which are bacteriostatic. A major disadvantage of tetracyclines is its killing of benign organisms associated with health as well as pathogens. Tetracyclines are substantive, potent, not toxic and have detected at 1 to 20 micro millimeter within epithelial tissue [5].Metronidazole is effective only against anaerobes and this specificity is both an advantage as well as liability[6].Metronidazole is not substantive and its extent that it induces resistant bacterial strains is unclear. This drug is potent, non toxic and not readily absorbed into the tissues[7].Chlohexidine is an antiseptic with no bacterial resistance associated and is substantive, potent, less toxic and does not absorb in the tissues[8].

Mechanical Plaque Removal Versus Local Delivery Antimicrobial Therapy:

Local delivery of antimicrobial is not a supplementary for good mechanical therapy.It may serve as an adjunct to scaling and root planing in very specific situations. Mechanical debridement is essential in removing hard accumulations on the roots, through subgingival scaling and root planning, but it is time-consuming, unpleasant for the patients, and technically difficult to perform[9]. Studies have shown that subgingival debridements in periodontitis patients were followed by profound shifts in the composition of the subgingival microflora which is comparable with the microflora found in healthy sites. However, these changes are transient, especially in residual deep sites (probing pocket depth >6mm) after periodontal therapy. Re-colonization of the subgingival area by motile rods and spirochetes may occur within 2-8 weeks, which seems to be dependent on level of oral hygiene, efficacy of the subgingival debridement and residual probing pocket depth[10]. Mechanical plaque control removes calculus, endotoxin, disruption of biofilm,induction of potentially protective antibody response and increased number of beneficial bacteria.Whereas these benefits are not seen with local delivery of antimicrobial agents alone.but other advantage of local delivery of antimicrobial are easy to perform,takes little time,doesn't remove cementum and well tolerated by patients.

There is no long term evidence that the use of local delivery can reduce the intervals for periodontal maintaince visits.Studies has shown same clinical results between two.Therefore their is no clear advantage for using local delivery,when good clinical results are obtained with scaling and root planning.

Systemic Versa Local Delivery[11,12]

Systemic route treat multiple sites,potential microbial reserviors,organisms at the base of pocket and in the tissues because of systemic absorption,less expensive, and variety of drugs are avalaible.Systemic antibiotics have been proven to be effective and are specially reccommended in the treatment of Aggressive and Refractory periodontitis.

With local application, the antibiotic is inserted directly into the pocket, resulting in much higher concentrations without the adverse effects of systemic antiboiotics,improved compliance of the patients,less propensity for bacterial resistance and minimal side effects.Local delivery in case of Aggressive forms of periodontiis has not shown successful results,may be because of tissue invasive bacteria and limited tissue concentration of the medicaments.Compare to systemic administration it is time consuming and labour intensive.Local delivery of antimicrobial agents is not a subsitute for systemic antibiotics,when indicated in specific periodontal disease.(Fig 1)

Commonly used local delivery Antmicrobials agents are:[13](Table I)

- Tetracyclines and its derivatives minocycline and doxycycline.
- Metronidazole.
- Ofloxacin.
- Tinidazole.
- Chlorhexidine.

Table-I: Local Delivery Antimicrobial Agents.

Antimicrobial Agents	Product	Company
Tetracycline fibre	Actisite	Alza
Minocycline gel.	Dentomycin	Blackwell Supplies
Minocycline microspeheres.	Arestin	OraPharma
Doxycycline Polymer	Atridox	Atrix Laboratory
Metronidazole Gel	Elyzol	Dumex
Chorhexidine Gel	Perio Chip	Perio products

Various devices avaliable,properties,their handling characteristics and comparison[13]. (Table II,III,IV)

Tetracycline: (Actisite)

Actisite is 9 inch flexible ethylene vinyl acetate fibres loaded with 25% tetracycline hydrochrolide.The fibre is layered back and forth,filling the periodontal pocket,it is then secured in place with a cynaoacrylate adhesive and covered with periodontal dressing.After 10 days the fibre is removed.(Fig 2)

Minocycline Gel: (Dentomycin,PerioCline)

Dentomycine is a lipid gel into which 2% minocycline hydrochloride is incorporated and is expressed into the periodontal pocket using a syringe until the pocket is overfilled.The gel resorbs within 1 day and subsequent application are recommended at 2 weeks and 4 weeks after the first application. Periocline is a subginguival delivery suystem of 2% minocycline HCL.It is a syngingable gel suspension delivery formulations.

Doxycycline Hyclate:(Atridox)

Atridox is a local drug delivery gel system that consists of doxycycline hyclate 10% in a synringable gel form.It is a biodegradable subgingivally controlled release product composed of a two syringe mixing system.(Fig 3.4)

Clinical studies suggest a potential periodontal benefits from the subgingival application of doxycycline. It is a valuable adjunct to scaling and root planing.

Minocycline Microspheres: (Arestin)

Minocycline microspheres one milligram of minocycline is microencapsulated into a bioabsorable polymer and delivered subgingivally as a powder via a syringe. On contact with the gingival fluid it hydrolyses and releases minocycline with minimum inhibitory concentrations, exceeding at required for periodontal pathogens for at least 14 days.

Metronidazole:(Elyzol,Metrogene)

Metronidazole bioabsorbable gel contains 25% metronidazole benzoate in a sesame oil matrix.The gel is delivered with a syringe and a blunt cannula into the periodntal pocket until it is filled.The gel changes into a semisolid state when it contacts the GCF.The activity and resorption occur within 12 to 24 hours.The application is repeated 7 days later.

Metrogene is a 5% metronidazole manufactured by septodont,France.Supplied in the form of sponge square pieces.It is a combination of two known substances bovine collagen into which metronidazole is incorporated at a concentration of 5 %.When it come in contact witrh GCF in the pockets it rapidly forms a resorble gel which is non irritant and virtually devoid of any toxic reaction.

Chlorhexidine: (PerioChip)

The chlorhexidine chip delivers 2.5 mg chlorhexidine gliconate in a bioabsorbable hydrolysed gelatin.The chip (4mmX 5mmX0.35mm) is placed into the pocket with a forceps. Activity is seen for 1 week and resorption occurs shortly thereafter.(Fig 5,6)

Treatment of periodontal pocke twith PerioChip as an adjunct to Scaling Root planing has provided a significant greater improvement in clinical parameters than Scaling Root Planing alone.

Table.II: Properties of Local delivery Antimicrobial Agents.

Antimicrobial Agents.	Delivery	Resorption	Duration	Organism Targeted.	Plasma concentation	Bacterial Resistance
Tetracycline Fibre	Controlled	None	10 Day	Broad spectrum	Minimal	Possible
Minocycline Gel.	Sustained	1Day	1 Day	Broad spectrum	Minimal	Possible
Minocycline Microspeheres	Controlled	>14 Day	>14 Day	Broad spectrum	Minimal	Possible
Doxycycline Polymer	Controlled	27 Day	7 Day	Broad spectrum	Minimal	Possible
Metronidazole Gel	Sustained	12-24 Hr	12-24 Hr	Anaaerobics	Minimal	Possible
Chorhexidine Gel	Controlled	7-10 Day	7 Day	Broad spectrum	Minimal	Possible

Table-III : Handling characteristics of Local Delivery Devices.

Antimicrobial Agents	No of sites treated/unit of product	Treatment Time	Storage/shelf life
Actisite	1-2	10 Minutes	Room Temp/1.5y
Dentomycin	Multiple	Few seconds	Ref/4y
Arestin	1	Few seconds	Room Temp/2y
Atridox	1	Few seconds	Ref/20 mo
Elyzol	Multiple	Few seconds	Room temp/3y
PerioChip	Multiple	Less than 1 Minutes	Ref/3-18 mo

Table.IV:Comparison of Local Drug Delivery Agents.

Devices	GCF Level	Ease of Application	Longest study
Tetracycline Fibres	1500ug/ml	Moderate	12 months
Metronidazoe Dental Gel	24 hrs >1ug/ml	Easy	24 months
Chlorhexidine Gel	150ug/ml	Easy	9 months
Minocycline Dental Gel	Unknown	Easy	18 months
Doxycycline Polymer	420ug/ml	Easy	9 months

Antibiotic resistance associated with local delivery[8,14]

Sublethal amount of administered drug leak out of pocket during therapy and increases the potential to develop drug resistance.Some studies have addressed the detection of resistant strains after use of local drug delivery. All these data suggest that local drug delivery results in a transient selection and increase of drug resistnt organisms,but these are limited data regarding drug resistant after local drug delivery.It should not be lulled into a false sense of security that Local Drug Delivery is without risk of contributing to increase levels of drug resistance.

Summary And Conclusion:

The primary application of local delivery at present is limited to localized sites of chronic periodontiits patients.The effectiveness is not clear in treatments of specific defects such as vertical bone loss,furcation involvement or around implants.Additional,sufficient evidence does not exists to recommend the use of local delivery on specific probing depths, actively progressive sites or specific periodontal procedures.

Local antimicrobial delivery in the treatment of periodontal disease has a definate but limited usefulness.The efficacy of traditional mechanical therapy

targeted toward reduction of the plaque mass remains unquetiond.The benefits of local delivery of antimicrobial agents and other medicaments are appealing, and future research should provide more information regarding the nature of the defects and the types of desease indicated. Local delivery advent as not provided a treatment panacea,it has provided an additional mode of therapy in treatment of periodontitis.

Continued research is needed to clear the use of local delivery of antimicribials in the management of:

- Aggressive periodontitis.

- Peri-implant disease.

- Specific probing depths and specific defects.

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Legands

Fig. 1 Systemic vs Local Delivery.jpg
Fig. 2 Actisite.jpg
Fig. 3 Atridox.jpg
Fig. 4 Atridox Insertion.jpg
Fig. 5 PerioChip.jpg
Fig. 6 PerioChip.jpg

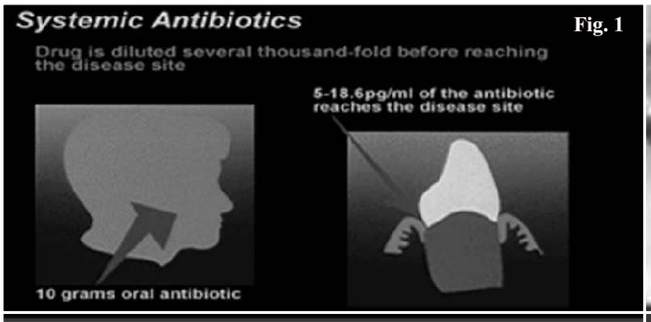

Fig. 1

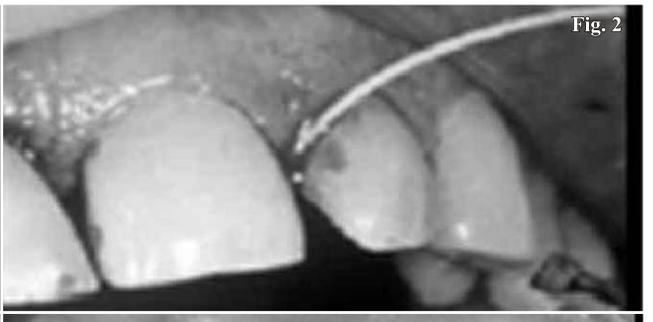
Fig. 2

Fig. 3

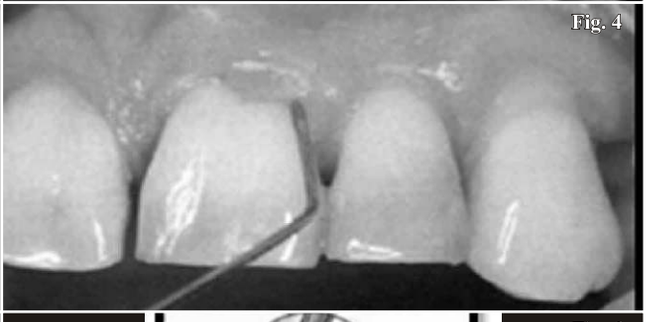
Fig. 4

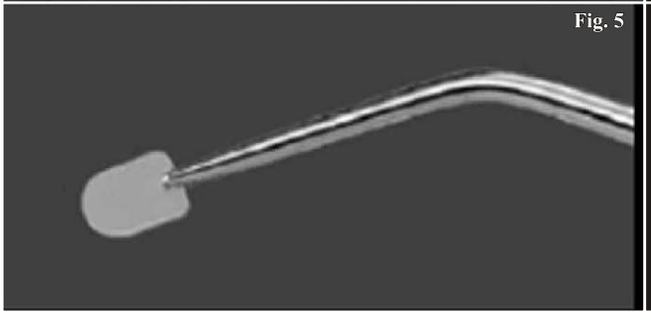
Fig. 5

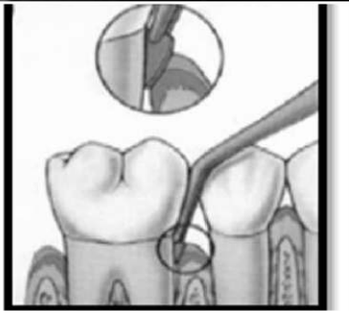
Fig. 6