

LOCAL DRUG DELIVERY IN PERIODONTICS: CURRENT CONCEPTS AND TRENDS

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ABSTRACT

Background: Periodontal disease is a chronic infection of the periodontium affecting the soft and mineralized tissues surrounding the teeth. Numerous therapeutic strategies have been aimed at eradication of the pathogens responsible for periodontal disease, including antimicrobial therapy both systemic and local. **Objectives:** 1. To compare local and systemic delivery of antimicrobial agents 2. To illustrate the rationale, benefits and drawbacks of various antimicrobial agents used as local delivery in periodontal therapy. **Conclusion:** Most research has focussed on the use of locally delivered antimicrobial agents as monotherapy and as adjuncts to scaling and root planing. Further research is required to determine the use of local delivery antimicrobial agents in specific situations as well as the long term benefits.

Key words: antimicrobial agents, local drug delivery, controlled release antimicrobials

INTRODUCTION

Gingival and periodontal diseases in their varied forms have afflicted mankind since the dawn of history. The earliest historical records dealing with human diseases and their treatment make a special mention of periodontal diseases and the need for treating them.¹

The primary role of bacteria in the etiology of periodontal diseases is unequivocal. Treatments have been varied and numerous, yet traditional mechanical debridement to disrupt the sub gingival flora and provide clean, smooth and biologically compatible root surfaces is still the mainstay. In spite of the excellent results achieved, mechanical debridement alone, has shown to leave behind a significant number of pathogenic microorganisms in relatively inaccessible areas.^{1,2}

A microbiological approach to periodontal therapy aims primarily at suppressing specific pathogenic bacteria and permitting subsequent re-colonisation of microbiota compatible with health.¹ Studies conducted, revealed antimicrobial agents to be helpful as adjuncts in treating periodontal disease, hence investigators sought different methods to deliver these antimicrobials to periodontal pockets. The various methods employed, have included rinsing, irrigation, systemic administration and local application using sustained and controlled delivery devices.

For an antibiotic to be effective in periodontal treatment, it must penetrate well into the gingival sulcus and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.² In the last 25 years, reports stating that systemically administered antibiotics are excreted via saliva and gingival fluid, have triggered great interest in antibiotic therapy.³ It has been shown

that systemic administration of antibiotics results in changes in plaque flora, reduction in gingivitis and decrease in the rate of bone resorption.⁴ In systemic administration, however, the drug must be given in high doses in order to maintain effective concentration of the drug in the gingival crevicular fluid.⁵ Systemic administration therefore has potential for adverse side effects such as development of microbial resistance, host hypersensitivity and superimposed infections.⁴

The localized or site-specific administration of chemotherapeutic agents may offer the advantage of treatment of site specific disease sites, possible use of lower total dosage levels, probable avoidance of systemic complications associated with high dosage levels and the possibility of controlling the release and concentration of therapeutic agents if a controlled-release delivery vehicle or device is employed. The relative inaccessibility of periodontal pockets has resulted in the development of various methods of administering the therapeutic agents, such as intrapocket irrigation and various controlled delivery systems.⁶

Sub gingival irrigation systems are available for use by the patient at home, as well as for use in the dental office. Oral irrigation is relatively easy to use and can deliver high concentrations of a drug to the site. Various antimicrobials have been tested as irrigants, including chlorhexidine, iodine, sanguinarine, essential oils and many different antibiotics. Even though irrigation devices can deliver drugs to the base of the pocket, the drug level

declines exponentially and rapidly. This rapid clearance of substances from periodontal pockets, therefore limits the efficacy of locally applied non binding antimicrobial agents in the treatment of periodontitis.⁷

Controlled delivery systems are designed to release a drug slowly for more prolonged drug availability and sustained drug action. These dosage forms or delivery systems are commonly referred to as sustained-release, controlled-release, prolonged release, timed-release, slow release, sustained-action, prolonged action or extended-action.⁸

The use of antimicrobial mouth rinses for plaque and gingivitis control is also a form of local delivery. However the term 'local delivery' is usually used to suggest more specific or targeted delivery of an agent.⁸

Each drug delivery system has its merits and demerits. The success of any drug delivery system designed to target periodontal infections depends upon its ability to deliver the antimicrobial agents to the base of the pocket at a bacteriostatic or bactericidal concentration. It must also facilitate retention of the medicament long enough to ensure an efficacious result.⁵

SYSTEMIC ANTIBIOTIC THERAPY^{1,5,7}

Systemic periodontal antimicrobial therapy is based on the premise that specific microorganisms cause destructive periodontal disease and that the antimicrobial agent in the periodontal pocket can exceed the concentration necessary to kill the pathogen(s). The systemic antimicrobial agents enter periodontal pockets following their intestinal absorption

and passage from the blood stream into oral tissues, gingival crevicular fluid and saliva.

Advantages:

1. Systemic antibiotics can reach microorganisms at the base of deep periodontal pockets and furcation areas, via the serum.
2. Affects tissue invasive organisms – residing within the connective tissues.
3. Eradication of periodontal pathogens colonizing the oral mucosa and other extra dental sites – the potential reservoirs of bacterial reinfection.
4. Multiple sites are treated simultaneously.
5. Less time consuming (when compared to local drug delivery).
6. A variety of drugs are available.

Disadvantages:

1. Development of resistant bacterial strains.
2. Superimposed infections.
3. Uncertain patient compliance.
4. The drug must be given in high doses in order to maintain an effective drug concentration in the gingival crevicular fluid. This may result in various side effects like nausea, vomiting and gastrointestinal disturbances.

LOCAL ANTIBIOTIC THERAPY^{5,7}

Local antibiotic therapy involves the direct placement of an antimicrobial agent into sub gingival sites, minimizing the impact of the agent on non oral body sites.

Advantages:

1. Relatively small amounts of the drug can produce a high concentration in the periodontal pocket.
2. Minimal side effects
3. Less potential of inducing resistant bacterial strains in other parts of the body.
4. Controlled release devices can maintain a high concentration of the drug for an extended period.⁸
5. Reduces potential problems with patient compliance.
6. May employ antimicrobial agents not suitable for systemic administration, such as various broad spectrum antiseptic solutions.

Disadvantages:

1. Difficulty in placing therapeutic concentrations of the antimicrobial agent into deeper parts of periodontal pockets and furcation lesions.
2. Time consuming, if many periodontal sites are to be treated.
3. 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 later re-infection and disease recurrence in treated areas.
4. Locally applied antimicrobial agents appear beneficial if bacteriostatic / bactericidal drug levels can be maintained over extended time periods. Transient applications of relatively low antibiotic concentrations

provide little or no adjunctive effects to mechanical therapy, because the high flow rate of the gingival crevicular fluid will cause a fast evacuation of the already released drug from the pocket to the mouth, thereby depleting the concentration of the drug in the pocket.

The various local delivery antimicrobials available are^{9,10,11,12}

1. Tetracycline – non resorbable fibres
2. Metronidazole gel
3. Minocycline ointment
4. Chlorhexidine chips
5. Doxycycline hyclate in a resorbable polymer
6. Resorbable tetracycline in fibrillar collagen
7. Minocycline microspheres
8. Azithromycin gel

The drug delivery systems have been assessed with regard to their functional characteristics, effectiveness as monotherapy (as compared to scaling and root planing) and as adjuncts to conventional care.

STUDIES USING CONTROLLED RELEASE ANTIMICROBIALS IN PERIODONTAL THERAPY

The concept of controlled-release local delivery of therapeutic agents, either antimicrobials or anti-inflammatory agents, was championed and developed into a viable concept, primarily by Dr. Max Goodson.⁸ Since then, a number of studies have been done over the years with different antimicrobial agents and in different clinical situations.

Feasibility of treating periodontal disease by controlled drug delivery of antimicrobials from within the pocket. They showed the tetracycline filled hollow fibers placed in the gingival sulcus to have a dramatic effect both on the periodontal microflora and the clinical manifestations of the disease. The fibers released the entire drug in the first 2 hours. Thus these devices were with minimal control of drug release. Lindhe et al (1979)¹⁴ studied the effect of local tetracycline delivery using hollow fibre devices for 2 days in 5 patients with periodontitis. They reported an improvement in both microbial and clinical parameters, which were similar to scaling and root planing during the short term evaluation.

Minabe et al (1991)¹⁵ studied the efficacy of tetracycline in patients with adult periodontitis. The selected patients were randomly allocated to the following groups according to the treatment – 1) 4 consecutive administrations of tetracycline immobilized cross linked collagen film (TC film) at intervals of 1 week (TC group); 2) root planing treatment (RP group); 3) combination (TC + RP group); 4) no treatment (control group). Records of plaque index, gingival index, bleeding on probing, probing depth, probing attachment level and microbial counts were obtained at 0,4,6 and 9 weeks. By the end of 9 weeks all the groups showed a reduction in the clinical parameters. In particular, the TC+RP group showed significant reduction in bleeding on probing and an increased attachment gain. The findings demonstrate that root planing is effective and that the effects are

enhanced by the local administration of TC films.

Jones et al (1992)¹⁶ compared the clinical efficacy of 2% minocycline in a sub gingival local delivery system alone, to scaling and root planning (SRP) in adult periodontitis. All patients were given a single sitting of scaling and root planning then divided into experimental and control groups. The experimental group received 2% minocycline while the control group received only SRP. After assessing clinical parameters for 6 months it was concluded that sub gingival minocycline as an adjunct to SRP produced significant clinical benefits over SRP alone in patients with adult periodontitis.

Polson et al (1997)¹⁷ evaluated the clinical safety and effectiveness of a subgingivally delivered biodegradable drug delivery system containing either 10% doxycycline hyclate, 5% sanguinarium chloride or no agent in a 9 month multicenter trial. 10% doxycycline hyclate delivered in a biodegradable delivery system was found to be an effective means of reducing the clinical signs of adult periodontitis.

Jeffcoat et al (2000)¹⁸ in their 9 month study found the chlorhexidine-gelatin chip to significantly reduced alveolar bone loss when used as an adjunct to scaling and root planning.

Eickholz et al (2002)¹⁹ evaluated the clinical effect of sub gingival application of doxycycline adjunctive to non surgical periodontal therapy in 111 patients over a period of 6 months. They concluded that by the adjunctive use of sub gingival

doxycycline the threshold for surgical periodontal therapy might be moved towards deeper pockets.

AN EFFECTIVE TREATMENT MODALITY^{21,22}

Sustained or controlled release local delivery antimicrobial agents are available for use as adjuncts to scaling and root planning in the treatment of periodontitis. These products are placed into periodontal pockets in order to reduce subgingival bacterial flora and clinical signs of periodontitis. A high level of the active agent is deposited in the periodontal pocket and the delivery vehicle facilitates prolonged drug delivery.

Studies assessing the efficacy of local delivery antimicrobial agents generally show statistically significant improvement in clinical and microbial parameters. However, whether they can reduce the need for surgery, improve long-term tooth retention or are cost effective would need to be ascertained in further studies. The use of local delivery antimicrobial agents in special sites (periodontal abscesses, peri-implantitis) and special populations (smokers, aggressive periodontitis) as well as long term benefits would require further evaluation.

Clinicians may consider the use of local delivery antimicrobial agents in chronic periodontitis as an adjunct to scaling and root planning:

- When localized recurrent and/or residual probing depth $\geq 5\text{mm}$ with inflammation is still present following conventional therapies.

Therapies other than local delivery antimicrobial agents should be considered when:

- Multiple sites with probing depth $\geq 5\text{mm}$ exist

in the same quadrant.

- The use of local delivery antimicrobial agents has failed to control periodontitis.
- Anatomical defects are present

Gopinath et al (2009)²⁰ assessed the clinical efficacy and safety of locally administered minocycline microspheres in the treatment of chronic periodontitis over 180 days. The results of the study indicated that treatment with scaling and root planning plus minocycline microspheres was more effective and safer than scaling and root planning alone in reducing the signs of chronic periodontitis.

CONCLUSION

The overall treatment though statistically significant has not found widespread use of these systems in the clinical community.¹² A decision to use local delivery antimicrobial agents should be based on patient history, clinical findings, scientific evidence and the merits and demerits of alternative therapies.

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