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Local Drug Delivery –A Targeted Approach

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Abstract

Successful periodontal treatment is dependent on anti-inflammatory procedure which includes both mechanical and chemotherapeutic approach. Chemotherapeutic approach includes local application or sustained release of local drug delivery agents and systemic approaches. Locally delivered antimicrobial agents are administered to prevent plaque accumulation and to disinfect the root surface and adjacent periodontal tissues. They are designed to enhance the healing following periodontal therapy. This paper summarizes the principles of local intra pocket delivery of antimicrobial agents and their mechanism of delivery and it also addresses the use of systems in clinical practice and its efficacy in the management of periodontal disease.

Keywords: Local drug delivery, Periodontal Pocket, Periodontitis

Introduction

Periodontitis is considered as an infection because of its bacterial etiology and altered immune response [1]. Unbalanced host response can result in destruction of the periodontium [2]. To attain periodontal health by suppressing bacterial pathogens, scaling and root planing and ultrasonic debridement are routinely done. The sites which are not responsive to conventional periodontal therapy can be achieved by adjunctive chemotherapy [3]. The decision of the local drug delivery during active treatment or maintenance should be based on clinical findings, responses to therapy, desired clinical outcome and the patient's medical history [4]. Success of any drug delivery system depends upon its ability to deliver the antimicrobial agents to the base of the pocket at a bacteriostatic or bactericidal concentration [5]. This paper addresses the principle of local delivery of antibacterial agents and their clinical applications.

Progression of periodontal disease

In the current paradigm of periodontal disease, periodontal pathogens are essential for disease initiation. However, the extent and severity of tissue destruction are largely dependent on the nature of the host-microbial interactions. These interactions are dynamic, since the microbial composition of the dental biofilm and host immune competency can vary widely between individuals resulting in differences in host responses and subsequent alveolar bone loss. Systemic diseases, hormones and other risk factors have also been found to influence the progress of periodontal diseases. Diabetic patients are at increased risk because of the vascular abnormalities, change in the crevicular fluid and altered collagen activity. Increased levels of estrogen will modify the host response and may influence the development of gingival inflammation [6]. Smokers account for the majority of the refractory periodontitis and for poor response following periodontal treatment [7].

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Treatment of periodontal disease

The goals of periodontal treatment include elimination of periodontal pocket, halting disease progression, enabling host recovery and gaining clinical attachment level. Non- surgical scaling and root planing are considered as basic standard treatment for periodontal disease. Due to the physical difficulties imposed by pocket morphology instrumentation may fail to instrument the base of deep pockets adequately in 75% of root surfaces [8].

Limitations of mechanical therapy

1. Failure of instrument to reach base of deep pockets
2. Higher levels of pathogens found in deep pockets
3. Bio film and microbial retention in grooves and pockets.
4. Microbial retention in dentinal tubules
5. Diffusion of bacteria into soft tissue
6. Migration of periodontal pathogens from other sites.

Chemotherapy in treatment of periodontal diseases

The use of antimicrobials offers a method to overcome limitations of mechanical therapy for the periodontal diseases. Products that are used to prevent and treat periodontal disease include mouth rinses, dentifrices, systemic antimicrobials and locally delivered antimicrobials. Antioxidative actions of chlorhexidine, tetracycline, doxycycline and essential oils may be a part of the mechanism of actions of chemotherapeutics used in the treatment of periodontal disease [9]. Chemotherapeutic rinses will penetrate the outer layer of mature biofilm and at the same time the mouth rinses may not reach deep into periodontal pockets. In shallow or moderate pockets the use of irrigators with blunt-ended cannulae or syringes are used and it may improve the ability of the drug to reach the site. The crevicular flow volume is increased during infection resulting in further dilution and displacement of locally delivered chemotherapeutics.

Local drug delivery

Both topical drug delivery and controlled drug delivery are known as local drug delivery / site specific

drug delivery. Local drug delivery system successfully satisfies 3 needs. They are

1. The device must deliver the drug to the base of the pocket.
2. It should deliver the drug at microbiologically effective concentration
3. The device must sustain the concentration of the drug in the pocket for sufficient length of time and at sufficient concentration to be clinically effective.

Advantages of LDD [10]

1. Improve patient compliance
2. Improve pharmacokinetics
3. Improve drug access to the site of disease
4. Lowers the total drug dosage
5. No risk of emergence of resistant microorganism
6. Drug can reach the site of action in adequate concentration
7. Maintain the drug level for a sufficient period of time

Disadvantages

1. Time consuming and laborious
2. Difficulty in placing therapeutic concentration of antimicrobial agent into deeper periodontal pockets and furcation lesions
3. Personal application of antimicrobial agents by patients as a part of their home self-care procedure is compromised.

Ideal requisites of Local Delivery System

1. Device must deliver drug to the base of the pocket.
2. Must deliver drug at microbiologically efficacious concentration.
3. Must sustain the concentration of drug in the pocket for sufficient length of time.
4. Ease of placement.
5. Retention after placement.
6. Biodegradable.
7. No emergence of bacterial resistance.
8. Safe with minimal side effects.
9. Should be effective only against periodontal pathogens and not on commensal microflora.

Classification of Local Delivery Systems

- I. Depending on usage
 - A) Personally applied
 - B) Professionally applied
- II. Depending on area of maximum concentration
 - A) Supragingival sustained release
 - B) Subgingival sustained release
 chemotherapeutic devices
- III. Based on degradability of the device
 - 1) Resorbable
 - 2) Non-Resorbable
- IV. Based on duration of action [11]
 - A. Sustained released devices - These are delivery systems whose action lasts less than 24 hours therefore require multiple applications. It follows the first order kinetics.
 - B. Controlled delivery devices – These are the devices which follows zero order kinetics and the actions last longer than 24 hours, thereby decreasing the number applications.

Comparison of LDD and systemic antibiotics

Systemic medications advantages

1. Ensure drug delivery to the base of the pocket via serum
2. Treat potential reservoirs of bacterial reinfection
3. Alter tissue invasive organisms
4. Take less time
5. Less cooperation
6. Treat multiple sites simultaneously
7. Different types of drugs available

Disadvantages

1. Development of resistant bacterial strains.
2. Superimposed infections.
3. Uncertain patient compliance.

In contrast LDD provides

1. High drug concentration
2. Minimal side effects
3. Less reliance on patient compliance for taking the medication

Drugs used for Local drug delivery

Tetracycline

These are broad spectrum antibiotics that affect anaerobic and facultative organisms. They are bacteriostatic on systemic administration and bactericidal at high concentration when applied locally. Disadvantages include increased drug resistance, ability to kill commensal organisms associated with health along with pathogens. They are substantive, potent, non-toxic at prescribed dosages and detected in epithelial tissue at 1 to 20 μm on local delivery. They have been frequently used in treating refractory periodontitis and localized aggressive periodontitis [11]. Following subgingival irrigation for 5 minutes, concentration of 50% tetracycline HCL solution retains its activity for 16 days. 40% mixture of tetracycline in petrolatum in the periodontal pocket was used, however no adjunctive clinical benefits was seen.

Tetracycline containing fibers

The Actisite tetracycline fibers have been approved for the treatment of aggressive periodontitis. Periodontal plus AB is a bio-resorbable tetracycline fiber which offers the advantage of no second appointment for removal. Tetracycline containing periodontal gel formulation has shown statistically significant result after SRP or along with SRP [12].

Subgingival Doxycycline

Atridox 42.5 mg doxycycline is a subgingival product. Its level in GCF peaked to 1500-2000 $\mu\text{g}/\text{ml}$ in 2 hours and its level remained above 1000 $\mu\text{g}/\text{ml}$ for 18 hours.

Subgingival Minocycline

There are 3 modes of local application-film, microspheres and ointment [13].

1. Film of ethyl-cellulose containing 30% of minocycline cause complete eradication of pathogenic flora in 14 days.
2. Microspheres: It is sustained release forms of minocycline microspheres (Arestin) for subgingival delivery. GCF hydrolyses the polymer and 14 days the minocycline release and bioresorb completely.

- Ointment: The concentration of minocycline in the pocket is about 1300µg/ ml after single application of 0.05 ml ointment and decreased to 90µg/ ml after 7 hours. Commercially available as Dentocmycin (2% gel) in European Union and Periocline in Japan.

Metronidazole

Elyzol contain an oil bound metronidazole 25% dental gel. It is equivalent to SRP but not adjunctive to SRP. After application, metronidazole concentration of above 100 µg/ ml are measurable in periodontal pocket for at least 8 hours and in 36 hours the concentration above 1 µg/ ml was found.

Subgingival chlorhexidine

Periocol

It is prepared by incorporating 2.5 mg CHX from a 20% CHX solution in collagen membrane. They resorb after 30 days but coronal edges degrade within 10 days.

Periochip: (2.5 mg of CHX gluconate)

Use of periochip showed reduction in periodontopathogens. It release CHX invitro in a biphasic manner. Within 24 hours 40% of CHX is released and the remaining CHX is released for 7-10 days in linear fashion.

Chlosite

It is an agent containing 1.5% CHX of Xanthon type. It is efficient in the treatment of periimplantitis and periodontal pocket. Chlorhexidine and gel matrix are muco-adhesive so that they stick inside the pockets and not easily washed off. It is well tolerated and the effective concentration of chlorhexidine against microorganisms is established for at least 15 days in the region.

Role of sustained local delivery antimicrobial agents

Several pharmaceutical agents suppress or eradicate pathogenic microbiota, improve attachment levels, pocket probing depth and bleeding on probing [14]. The rationale for using an antimicrobial is to chemically kill or decrease the plaques. In diseased site that are more difficult to control local drug delivery devices such as chlorhexidine chips or 10 % doxycycline gel can be placed in direct contact with the roots surface,

pathogenic organism that were not accessible to mechanical removal.

Type of drug delivery devices

Various local drug delivery system for treating periodontitis-Fibers, Film, Injectable systems, Gels, Micro particle system, Nanoparticle system etc. Intra pocket devices can be divided in to degradable and non-degradable [15]. In non-degradable devices the advantage is the therapist can control the time of exposure of the pocket environment to the drug. The non-degradable device left in sites beyond the period of therapeutic efficacy may result in foreign body response. Degradable devices help the patient to minimize multiple visits. Different forms of degradable devices are there and this includes fibers, film / slabs and injectable system

Fibers

Fibers are non-degradable dosage form and fiber like devices to deliver the drugs to the periodontal pocket was first introduced by Goodson *et al.*, 1983 using cellulose acetate dialysis tubing [16]. Treatment of commercially available delivery system results in significant reduction in pocket probing depth, bleeding on probing and significant increase in attachment levels. It is similar to application of retraction card prior to the impression taking after crown preparation. The fiber can be placed around the circumference of the tooth to the depth of the pocket and folded back on itself repeatedly to fill the pocket completely.

Disadvantages

- Time needed for fiber placement (5 to 10 minutes for tooth)
- Need for use of either a periodontal pack or a cyanoacrylate glue to retain the device with the pocket
- High risk for extrusion of the fibers from the pockets during the 10 days of treatment [17].
- Multiple visit (one for insertion and one for removal)

Films and slabs

Types – Both degradable and non- degradable films are available. It is more widely used intrapocket delivery device

Advantages

1. The dimension and shape of the film can be easily controlled to correspond to the dimension of the pocket to be treated
2. Can be easily inserted
3. Minimal discomfort to the patient
4. Approximate size of the film is 400 µm.
5. Sufficient adhesiveness is present

Non degradable films

Addy et al., in 1982[18] described the film or slab form intrapocket delivery devices. They described the use of slabs of methyl methacrylate for the intrapocket delivery of tetracycline, metronidazole and Chlorhexidine and this system has not been used for clinical cases.

Degradable films

Many degradable devices in the form of a film have been tested experimentally. *Periochip* has been developed for the controlled subgingival delivery of Chlorhexidine. This is a 5 mm x 4 mm x 0.3 mm film containing 2.5 mg Chlorhexidine gluconate. Subgingival placement of this chip releases its CHX and the gingival crevicular fluid level of ≥ 100 ppm for over 7 to 10 days period. The gain in attachment was also greater in the periochip treated pockets. Degradable delivery systems of tetracycline increase the intra pocket levels of tetracycline greater than 8 µg / ml within 10 days. Significant improvement in bleeding on probing and a reduction in the percentage of spirochetes and black pigmented bacteroides species were noticed after that last application. A collagen film containing 5 % metronidazole as a local metronidazole therapy as an adjunct to SRP showed significant adjunctive effect for the local metronidazole therapy on gingival index, BOP, PPD and CAL.

Injectable system

Injectable systems are particularly attractive for the delivery of antibiotic agents into the periodontal pocket. It is considered as degradable system. It is relatively simple procedure with number of advantages. The fluid nature of the formulations would allow the drug to gain access to the entire pocket. The formulation need to undergo a change in to a sticky semisolid or solid phase so as to prevent it from being washed out. Commercially available 2 % minocycline containing

ointment and 2% metronidazole (Elyzol) are the examples for injectable systems.

Conclusion

Knowledge of the etiology of periodontal disease has provided a foundation for the use of antimicrobials in the treatment of periodontal diseases. Since the late 1970s, a variety of LDD have been specifically designed for the use in periodontal pocket. The main objective is to establish a drug reservoir within periodontal pocket that could maintain effective concentration for a longer period. Local drug delivery agents are designed to prevent plaque accumulation to disinfect the root surface and adjacent periodontal tissue [19]. Local administration of drugs provides a useful answer to the problem like resistant strains and superimposed infection. The efficacy of LDD depends upon the penetration, concentration and duration after drug in place. The use of antibiotics for the treatment of periodontal disease should be highly sensitive. Study lengths and sample sizes must be increased to get concrete conclusion for the benefit of LDD systems.

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