Review Article

Local Drug Delivery in the Treatment of Periodontal Diseases

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ABSTRACT

Periodontitis is a multifactorial, immunomodulatory disease primarily affecting the supporting tissues of the teeth. Various treatment modalities such as mechanical debridement and use of antimicrobial drugs have been used in the treatment of periodontal diseases. Introduction of the local drug delivery (LDD) system is one of the promising approaches in the management of periodontal diseases. It shows better clinical outcomes, when used as an adjunct to scaling and root planning; hence, it cannot be used as a monotherapy. Research efforts have been focused on developing new agents to use in the LDD system.

KEYWORDS: *Antimicrobials, local drug delivery, periodontitis*

INTRODUCTION

Periodontitis is defined as a chronic, multifactorial, inflammatory disease affecting the supporting tissues of the teeth, while pathogenic microorganisms play a primary role in the progression of periodontal disease.[1] Periodontal disease starts with the inflammatory reaction involving the gingiva, which when untreated progresses to the supporting tissues of the teeth (i.e., periodontal ligament, cementum, and the alveolar bone) and leads to pocket formation.[2] Various therapeutic approaches have been made to eliminate the pathogenic microorganisms, including mechanical instrumentation or with electronic instrumentation alone or along with the use of chemical therapeutic agents either systemically or locally.[3]

To overcome the certain disadvantages of systemic antimicrobial therapy, the concept of local drug delivery (LDD) was introduced.[4]

LOCAL DRUG DELIVERY

The concept of LDD was introduced by Dr. Max Goodson in 1979.[5] The main rationale for LDD is to place an antimicrobial or antiseptic agent directly into the periodontal pocket, in contact with the root surface, thus eliminating the pathogenic microorganisms, which is not accessible with hand- or power-driven instruments.[6]

Classification

I. Based on application (RAMs and slots)[7]
   A. Personally applied at home by the patient
      - Nonsustained (e.g., home oral irrigation)
      - Sustained.
   B. Professionally applied at dental office
      - Nonsustained (e.g., pocket irrigation)
      - Sustained (controlled drug delivery devices such as films, strips, chips, fibers, and gels).

II. Based on duration of drug release[8]
   A. Sustained release devices
      These devices provide drug delivery less than or within 24 h
   B. Controlled release devices
      These devices provide drug release with a minimum of 1 day and a maximum of up to 3 days.

III. Based on degradation[9]
   A. Degradable
   B. Nondegradable.

IV. Based on physical form[10]
   A. Films (e.g., tetracycline)
   B. Fibers (e.g., minocycline)
   C. Chips (e.g., chlorhexidine)
   D. Injectable forms (e.g., metronidazole, chlorhexidine).

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Available forms of local drug delivery[9]

- Films
- Fibers
- Chips
- Strips and compact
- Injectable gels
- Ointment
- Vesicular system
- Microparticle system.

Ideal requirements for a local drug delivery system[7,11]

- It should be biodegradable
- It should be effective on pathogenic microflora, not on commensal microflora
- Ease of placement
- The drug delivery system should deliver the drug directly to the base of the pocket
- It should maintain the ideal concentration of the drug for a sufficient duration of time
- Cost-effective
- It should prevent drug resistance
- It must be retained in place after placement.

Indications[7]

- Pockets that are >5 mm, patients with Grade A/B periodontitis
- Patients showing poor compliance with oral hygiene therapy[12]
- Medically compromised patients
- Patients in whom surgical therapy is contraindicated
- Refractory periodontitis
- In conditions such as peri-implantitis
- Grade II furcation involvements.

Contraindications[5,7]

- When there is an allergy to the particular drug to be used
- Pregnant and lactating patients
- Without scaling and root planing
- In cases of Grade III periodontitis
- As a replacement for surgical periodontal therapy
- As a replacement for systemic antimicrobial therapy
- Patients with a history of infective endocarditis and who have a risk for infective endocarditis[12].

Advantages[14]

- A higher concentration of drug (up to 100-fold compared to systemic therapy) is attained at the gingival crevicular fluid (GCF) compared to the systemic antimicrobial therapy
- Drug resistance and superinfection are reduced
- Painless and less invasive procedure
- The technique is suitable for certain agents, which cannot be given through systemic route (e.g., chlorhexidine)
- Drug dosage is less compared to systemic therapy[13].

Disadvantages[7,14]

- This can be applied only by dental professionals, and it is time-consuming
- Main action of the drug is only on the periodontal pathogens residing in the pocket. Thus, action of drug is not seen on extra pocket sites such as tongue, tonsils, and buccal mucosa
- Technique sensitive, difficult to place in deep periodontal pockets or furcations
- Second appointment is required for nondegradable LDD systems.

Commonly used local drug delivery agents

Tetracycline

Tetracyclines are bacteriostatic antimicrobials used as LDD device. It was the first LDD system used by Goodson in 1979.[11] *In vitro* studies have shown that tetracycline shows excellent substantivity to dentin tooth surfaces.[15] It is available in the form of actisite and Periodontal Plus AB.[14]

Actisite is available in the form of fibers that are 23 cm long and 0.5 cm in diameter, which is nonresorbable, inert, and safe.[1] It is loaded with 25% tetracycline hydrochloride (HCl). The fibers are placed inside the pocket layer by layer and secured with periodontal dressing. It maintains a constant concentration in the GCF for up to 10 days. As it is nonresorbable, it should be removed after 10 days.[16,17] The resorbable form of tetracycline fibers is commercially available as Periodontal Plus AB; it biodegrades in the pocket within 7 days. Hence, there is no need of second appointment.[2]

Kataria *et al.* and Panwar *et al*. applied tetracycline fibers in the periodontal pocket as an adjunct to scaling and root planing, stating that there are significant improvement in clinical parameters and reduction in microbial count in chronic periodontitis.[18,19]

Doxycycline

It is a bacteriostatic agent commercially available in the form of LDD system as Atridox.[3] It is an FDA-approved 10% gel system comprising 42.5% of doxycycline, and it is composed of 2-syringe delivery system. The subgingival concentration maintains the minimum inhibitory concentration for up to 7 days. Moreover, about 95% biodegrade within 28 days.[16] Garret *et al.* conducted a randomized clinical trial on patients with chronic periodontitis. The control group received SRP + placebo gel, and the test group received SRP + doxycycline gel. The clinical attachment level

was increased in the test group compared to the control group over the mean period of 9 months.[20]

Minocycline

It belongs to the tetracycline group of drugs. It is bacteriostatic in nature, and it has superior substantivity compared to tetracycline. It is available in the form of films, microspheres, and ointment.[21] It is commercially available in the market as Arestin is in the form of microspheres. The 2% gel is encapsulated in the microspheres (20–60 μm). The microspheres gradually release minocycline in the pocket for up to 14 days, and then it resorbs.[22]

Dentomycin is a 2% minocycline HCl gel embedded in a matrix of hydroxyethyl cellulose. Graça *et al*. conducted a randomized clinical trial using 2% minocycline gel. The trial showed that compared to the SRP group, the SRP + minocycline group shows improvement in clinical parameters.[23]

Chlorhexidine

Chlorhexidine is the second-generation plaque control agent. It plays a primary role in the control of dental plaque and gingivitis. The mechanism of action of chlorhexdine is by reducing pellicle formation, altering bacterial adherence to teeth, and causing cell lysis. It is bacteriostatic at lower concentrations and bactericidal at higher concentrations.[16] Chlorhexidine is available as varnish, gel, and chip to be used as an LDD agent.[1]

Periochip

It is an orange-brown chip of 4.0 mm × 0.5 mm × 0.25 mm in size consisting of 2.5 mg of chlorhexidine, in a biodegradable matrix of hydrolyzed gelatin, which is approved by the FDA. The chip is placed deep into the periodontal pocket; initially, it releases 45% chlorhexidine in the first 24 h; then, it releases constantly in the linear fashion for the next 7–10 days; hence, it is referred to as biphasic manner.[16]

Periocol CG

It is a chip of 4 mm × 5 mm in size with a thickness ranging from 0.25 to 0.32 mm. It consists of 2.5 mg of chlorhexidine derived from 20% chlorhexidine which is embedded in collagen membrane. It degrades within 30 days.

Chlosite

It is a gel system containing 1.5% chlorhexidine of xanthene type. As both chlorhexidine and xanthene are mucoadhesive, it adheres firmly to the pocket, and it easily washes out on GCF or saliva. It degrades within 10–30 days inside the pocket while maintaining a maximum concentration for up to 15 days.

Jeffcoat *et al*. conducted a study with two groups of SRP and placebo chip and other group received both SRP and chlorhexidine chip as an adjunct. The clinical parameters were improved in SRP + chlorhexidine chip group compared to the SRP + placebo group.[24] In another study by Soskolne, he evaluated the safety and efficacy of SRP alone and SRP + chlorhexidine chip. The mean probing depth reduction was greater in SRP + chlorhexidine group compared to the control group.[10]

Metronidazole

It is a bactericidal agent, primarily effective against obligate anaerobes. Its mechanism of action is by disrupting the DNA synthesis. Metronidazole is commercially available in the form of LDD as Elyzol. It is 25% oil-based metronidazole gel.[25] Ainamo *et al*. compared the effect of subgingival scaling and subgingival scaling with 25% metronidazole in patients with chronic periodontitis. It is found that the probing pocket depth and bleeding on probing are reduced in metronidazole group.[26] Noyan *et al*. compared the effects of scaling and root planing, systemic metronidazole, and scaling and root planing along with local administration of 25% metronidazole gel. The results of the study have shown that the scaling and root planing along with local administration of metronidazole gel has shown better clinical and microbiological parameters compared to the other groups.[27]

Clarithromycin

It is used as LDD system in the form of 0.5% gel. Agarwal *et al*. evaluated the efficacy of subgingivally delivered 0.5% clarithromycin gel as an adjunct to scaling and root planing in chronic periodontitis smoking subjects, and it shows significant result in improving clinical parameters.[28]

Drugs for Osseous Defects

Alendronate

It belongs to the bisphosphonate group of drugs. The mechanism of action is by inhibiting the action of osteoclasts, thus reducing bone resorption. As systemic administration of bisphosphonate causes gastrointestinal disturbances, to minimize the adverse effects, it is limited to local delivery and it can attain higher concentration in the GCF compared to the systemic route.[29]

Rocha *et al*. in their study evaluated the effect of 1% alendronate gel as a LDD agent as an adjunct to scaling and root planing in type 2 diabetes mellitus patients with chronic periodontitis. It is found to be effective in reducing bleeding on probing, improving clinical attachment level, and increasing bone fill when compared to placebo gel.[30]

Simvastatin

Simvastatin is a potent inhibitor of HMG–CoA reductase enzyme, which is a key enzyme in cholesterol synthesis. It stimulates bone formation by increasing the expression of bone morphogenic protein-2 and endothelial growth factor.[31] Pradeep *et al*. in their study evaluated the bone fill by radiographic assessment by using computer-aided software and found significant bone fill in sites treated with simvastatin along with LDD.[32]

Newer Trends

Local delivery of growth factors

Growth factors such as platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen are introduced in LDD. They effectively involved in mitogenesis, angiogenesis, bone turnover, and wound regeneration.[33,34]

Colloidal drug carriers

It includes vesicles, liposomes, nanoparticles, emulsions, and micelles which are largely used as LDD agents because of their ease of placement. Colloidal drug carriers increase the bioavailability of the drug in the pocket and increase their specificity of action toward the tissue.[16]

Herbal extracts

Herbal agents individually or with a combination of several herbal agents are also used as an LDD.[4]

Conclusion

Advancement in the medical field leads to newer therapeutic agents and different modes of controlled drug delivery systems. One of the problems faced is to attain a sufficient concentration of drug at the target site. Hence, LDD system was introduced as it attains sufficient concentration of target site, and it has certain advantages over systemic mode of admissions such as less dosage, less side effects, and drug resistance. Thus, LDD is used as adjunct to scaling and root planing in treating periodontal diseases.

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Conflicts of interest

There are no conflicts of interest.

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