Local Drug Delivery Modalities in Treatment of Periodontitis: A Review

Jyoti I Pattanshetti, Ila Tiwari, Guljot Singh, Fatima Tazyeen, Anuj Singh Parihar, Neha Khare

Abstract:
Periodontitis is an inflammatory disease that causes destruction of tooth supporting tissues, characterized by multifactorial etiology with pathogenic bacteria being the primary etiologic agents that swell the subgingival area. Local drug delivery system consists of antimicrobial dosages that produces more constant and prolonged concentration profiles within the subgingival tissue and provides better access into the periodontal pockets. It addresses the critical distress of exposing the patient to adverse effects of systemic administration. This article reviews the literature and presents novel trends such as osteoblast activators, growth factors, and herbal products in the local drug delivery system.

Key Words: Antimicrobial, growth factors, herbal extracts, periodontal pockets, sustained delivery

Introduction
Periodontitis is an inflammatory disease that causes destruction of tooth supporting tissues and is characterized by multifactorial etiology with pathogenic bacteria being the primary etiologic agents that swell the subgingival area. The clinical signs include changes in the morphology of gingival tissues, gingival bleeding as well as periodontal pocket formation. This pocket provides an ideal environment for the growth and proliferation of anaerobic pathogenic bacteria. The periodontal treatment aims to eradicate gingival inflammation, eliminate bleeding, reduce periodontal pocket depth, arrest destruction of soft tissue, and bone. Therapeutic approach for periodontitis is to eliminate the bacteria, either with hand instrumentation or with electronic instrumentation along with use of chemotherapeutic agents systemically or locally.

Topical administration of antibacterial agents in the form of mouth washes, dentifrice or gels is an effective measure in controlling supragingival plaque. Irrigation systems or devices can deliver agents into deep pockets but clinically not effective to stop the progression of periodontal attachment loss. Recent novel trend is delivery of antimicrobial dosages using topical delivery and controlled release system at the target site which produces more constant and prolonged concentration profiles. These devices utilizes the control release technologies to deliver therapeutic concentrations for at least three or more number of days following a single application. The drug will be released over time either by degradation of the polymer backbone or diffusion through polymer matrix or by a combination of the any two mechanisms, i.e., pure diffusion, chemical reactions, counter current diffusion or externally imposed controls.

Local Drug Delivery
The treatment method was pioneered by Goodson of Forsyth’s Dental Research Center. The effectiveness of this therapy is that, it reaches the base of periodontal pocket and it maintains the antimicrobial concentration for an adequate time for effect to occur. Periodontal pocket provides a natural reservoir bathed by gingival crevicular fluid that is easily accessible for the insertion of a delivery device.

There are distinct phases in a periodontal treatment plan where a dental practitioner can use a sustained release device. It can be used as an adjunct to scaling and root planning and for periodontal maintenance therapy. Microbiological analysis is required for proper selection of antibiotics before commencement of treatment as disease exhibits a diverse anti-microbial susceptibility. It can be safely used in medically compromised patients for whom surgery is not an option or those who refuse surgical treatment. Various formulations are available in the form of fibers, film, injectable systems, gels, strips and compacts, vesicular systems, micro particle system and nanoparticle (NP) system.

The commonly used antimicrobial delivery systems are:
- Tetracycline fiber
- Metronidazole gel
- Chlorhexidine chip
- Minocycline gel
- Doxycycline polymer.

Tetracycline
Historically, tetracyclines are classified into first, second and third generation. Those obtained by biosynthesis...
i.e., tetracycline; chlortetacycline; oxytetracycline; demeclocycline are first generation; if they are derivatives of semisynthesis: Doxycycline; lymeccycline; meclocycline; methacycline; minocycline; rolitetracycline are classified as second generation and if they are obtained from total synthesis i.e., tigecycline are categorized as third generation.9

Tetracycline fibers are commercially available as Actisite® (tetracycline periodontal) periodontal fiber for periodontal pocket placement consists of a 23 cm (9 inch) monofilament of ethylene/vinylacetate copolymer, 0.5 mm in diameter, containing 12.7 mg of evenly dispersed tetracycline hydrochloride, USP Actisite® (tetracycline periodontal) fiber provides continuous release of tetracycline for 10 days.10 The other commercially available formulation is periodontal plus AB. It is a sustained drug delivery system with multimodal delivery kinetics for specific use in periodontal disease sites. A collagen fibril based formulation contains tetracycline hydrochloride (2 mg of tetracycline) in which 25 mg are collagen fibrils that can be directly applied for all levels of periodontal infections.11

Sachdeva and Agarwal12 applied tetracycline in the form of modified collagen matrix following scaling and root planning and found beneficial role in treatment of chronic periodontitis. Similarly Kataria et al.,13 Panwar and Gupta14 applied tetracycline fibers as an adjunct to scaling and root planing and found it to be more effective in reducing inflammation. Pavia et al.,15 showed that tetracycline and its derivatives minocycline, oxytetracycline and chlorotetracycline strongly adsorb to tooth surfaces retaining their antibacterial activity and are quite effective in treating chronic periodontitis.

**Minocycline**

Minocycline is available in the form of microspheres, film and ointment for local delivery system and exhibits bacteriostatic action at the target site.16 Moreover out of all the tetracyclines, minocycline has the most marked substantivity and greater lipid solubility.17 It is available commercially under the trade name of Arestin™. Technology employs microencapsulated minocycline hydrochloride in a bioabsorbable polymer as the vehicle (polyglycolide-co-dl-lactide [PLG]). The administration causes sustained local release of the antibiotic.18

Graça et al.,19 evaluated topical locally delivered minocycline as an adjunctive to non-surgical periodontal treatment and suggested that adjunctive minocycline gel provides a more advantageous outcome for nonsurgical periodontal treatment in terms of probing attachment level and bleeding on deep probing. Similarly, Lu and Chei20 carried out a clinical trial and suggested that scaling and root planning with adjunctive sub gingival administration of minocycline ointment has a significantly better and prolonged effect as compared to scaling and root planning alone on the reduction of probing depth, clinical attachment loss, gingival index and interleukin-1β content, but in contrary Graça et al.,19 does not found beneficial effect on bleeding on probing.

**Doxycycline**

Doxycycline is available commercially by the trade name Atridox. The product is a subgingival controlled-release product composed of a two syringe mixing system.21 Abdaly et al.,22 evaluated local delivery of Atridox as an adjunctive in management of chronic periodontitis and found reduction in subgingival microbiological count. Javali and Vandana23 carried out a study to evaluate and compare the efficacy of local delivery of 10% doxycycline hylcate in adjunct to scaling and root planing in the treatment of Periodontitis and found that on comparison, scaling and root planning in adjunct with doxycycline group showed better results. Salvi et al.,24 revealed significant reduction in clinical and microbiological parameters after application of atridox.

**Metronidazole**

Metronidazole is available commercially by the trade name of Elyzol. This local drug delivery system utilizes a semi-solid suspension of metronidazole benzoate in a mixture of glyceryl mono-oleate and triglyceride. It is advantageous to use it in the treatment of chronic periodontitis as anaerobic bacteria are believed to be the predominant causative factor in periodontitis and metronidazole is a member of nitroimidazole class of antibiotics that specifically targets anaerobic microorganisms.25 Among the various locally delivered chemotherapeutic agents metronidazole, has bactericidal action against anaerobes, such as *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythia*, Fusobacterium species and spirochetes like *Treponema denticola*, *Treponema vincentii*, which are generally believed to be the main pathogens associated with periodontitis.26

Stolzel studied systemic absorption of metronidazole and concluded that the systemic load after single application of metronidazole 25% dental gel is less in comparison to one metronidazole 250 mg tablet.27 Ainamo et al.,28 compared the effect of metronidazole 25% gel with subgingival scaling in adult Periodontitis and found that both periodontal pocket depth and bleeding on probing were significantly reduced in both groups. Noyan et al.,29 observed that local metronidazole in combination with scaling and root planning seems to be more effective in terms of producing both clinical and microbial improvements.

**Azithromycin (AZM)**

A AZM has a wide antimicrobial spectrum of action towards anaerobic bacteria as well as Gram-negative bacilli. It is effective against periodontal pathogens such as aggregatibacter actinomycetemcomitans and *P. gingivalis*. 

---

297
Tyagi et al.,30 investigated the clinical effectiveness of AZM at a concentration of 0.5% in an indigenously prepared bioabsorbable controlled release gel as an adjunct to non-surgical mechanical therapy in the treatment of chronic periodontitis. Although both treatment strategies seem to benefit patients, the adjunctive use of 0.5% of AZM showed better results.

**Chlorhexidine**

Chlorhexidine is available in the form of mouth rinses, gels, varnishes, and chip to be used as a local drug delivery agent for the treatment of periodontal diseases. It is commercially available as periochip (2.5 mg), chloste (1.5% CHX), periocol (2.5 mg). Various studies31–33 have demonstrated chlorhexidine as an adjunct to scaling and root planning as an effective measure in improving clinical parameters and reducing microbial load.

**Newer Trends**

**Taurolidine**

Taurolidine is a novel introduction and might be an alternative in periodontitis treatment. Zollinger et al.,34 evaluated in vitro effect via coating the surface with 10 mg/ml taurolidine and found that this concentration prevented completely biofilm formation of P. gingivalis. Thus, it can be used as an adjunct to mechanical removal of biofilms.

**Simvastatin (SMV)**

SMV exhibits bone regeneration properties by participating directly in osteoblast activation via increasing bone morphogenic factor-2 expression, in osteoclast inhibition and indirectly by stimulating neovascularization by increasing the secretion of vascular endothelial growth factor.35 SMV is a specific competitive inhibitor of 3-hydroxy-2-methyl-glutaryl coenzyme A reductase. Pradeep et al.,36 investigated the effectiveness of SMV by carrying out radiologic assessment of intrabony defect fill by using computer-aided software and found significant intrabony defect fill at sites treated with SMV as an adjunct to scaling and root planning.

**Alendronate**

Alendronate (4-amino 1-hydroxybutylidene bisphosphonate), a novel bisphosphonate is a very potent inhibitor of bone resorption. Veena et al.,37 applied 0.1 ml alendronate gel and 0.1 ml placebo gel following surgical flap debridement at the experimental and control sites respectively and found that alendronate was more effective in improving parameters clinically and radio graphically as compared to placebo.

Rocha et al.,38 evaluated effect of local delivery of 1% alendronate gel into periodontal pockets in chronic periodontitis patients with Type 2 diabetes mellitus and revealed alendronate as an effective adjunct to scaling and root planning as it resulted in probing depth reduction, clinical attachment level gain and improved bone fill as compared to placebo gel. Thus, Alendronate is an effective treatment modality in periodontitis associated bone loss.

**Basic Fibroblast Growth Factor (bFGF) (In situ Tissue Engineering)**

Nakahara et al.,39 developed a controlled-release system by using a sandwich membrane consisting of a collagen sponge scaffold and gelatine microspheres containing bFGF in situ on the basis of new concept of in situ tissue engineering and demonstrated regeneration of periodontal tissues in 4 weeks. Thus concluded that sandwich membrane induced successful regeneration of the periodontal tissues in a short period of time. Murakami et al.,40 demonstrated that bFGF can be applied as one of the therapeutic modalities which actively induce periodontal tissue regeneration. The results of in vitro studies suggest that by suppressing the cytodifferentiation of periodontal ligament cells (PDL) cells into mineralized tissue forming cells, bFGF may play important roles in wound healing by promoting angiogenesis and inducing the growth of immature PDL cells, and may in turn accelerate periodontal regeneration.

**Chitosan**

Chitosan is an interesting polymer that has been used extensively in the medical field. It is either partially or fully deacetylated chitin. As chitin occurs naturally in fungal cell walls and crustacean shells, it is a fully biodegradable and biocompatible natural polymer, and can be used as an adhesive and as an antibacterial and antifungal agent.31 It is a versatile hydrophilic polysaccharide derived from chitin, has a broad antimicrobial spectrum to which gram-negative, Gram-positive bacteria and fungi are highly susceptible and has a regenerative effect on periodontia and also accelerates the formation of osteoblasts which are responsible for bone formation.42 ikinci et al.,43 determined the antimicrobial activity of chitosan formulations either in a gel or film form against a periodontal pathogen, P. gingivalis and concluded that this formulation seems to be promising delivery systems for local therapy of periodontal diseases due to its antimicrobial activity and bio adhesive property.

**Ipriflavone**

Ipriflavone (7-isopropoxy iso-flavone) is a synthetic isoflavone derivative that acts primarily to suppress bone resorption. Other in vitro studies have shown that ipriflavone can stimulate osteoblasts to form new bone.44 Min et al.,45 evaluated effect of ipriflavone on periodontal reorganization and revealed that it shows more rapid effect. Perugini et al.,46 designed a film dosage form for sustained delivery of ipriflavone into the periodontal pocket. A monolayer composite systems made of ipriflavone loaded poly micromatrices in a chitosan film form, were obtained by emulsification/evaporation/casting technique. In vitro experiments demonstrated that the composite micromatrical films represent a suitable dosage form to prolong ipriflavone release for 20 days.
Herbal Extracts

Harungana madagascariensis (Hypericaceae) is known to have biological properties with mainly antibacterial, antifungal and antiviral effects. Moulari et al.,47 investigated the in vitro bactericidal effect of the ethyl acetate H. madagascariensis leaf extract using the PLG-NP and found significant bactericidal effects against the bacterial strains tested. However the study observed diminution of the bactericidal concentration on in corporatation of H. madagascariensis into PLG-NP as incorporation of the HLE into a colloidal carrier optimized its antibacterial performance.

Aloe vera possess certain active components such as saponins, anthraquinones, amino acids, lignin, salicylic acid, etc., in which anthraquinones have the strong anti-bacterial, anti-viral and anti-neoplastic properties.48 Virdi et al.,49 evaluated the effect of A. vera gel in patients with chronic periodontitis and found that group in which A. vera gel was applied as an adjunct to scaling and root planning showed significantly better results than scaling and root alone. Thus, the study encourages the use of A. vera in the treatment of periodontitis.

Eucalyptus,50 neem leaf51 and bloodroot also possess antibacterial and anti-inflammatory properties and can help in improving oral health status. Other than individual herbs, herbal combinations such as mixture of menthol, chamomile, peppermint oil, sage oil, clove oil, caraway oil, echinacea extract and myrrh tincture exhibit properties to reduce severity of periodontitis symptoms and can improve the oral hygiene.52

Conclusion

Advancements in the field of medicine have led to delivery of safe and efficient medicine into periodontal pockets bypassing the systemic metabolism. High gingival crevicular fluid concentration and access to periodontal pockets can be achieved without exposing the individual to systemic complications. The local application provides a better opportunity to deal patients with non-responding and recurrent periodontal pockets and results in better patient compliance and satisfaction. General dentists should promote local drug delivery systems in chronic periodontitis patients as this therapeutic intervention protect patients from risk of systemic overload or drug over dosage.

References


