A REVIEW ON LOCAL DRUG DELIVERY

Noorul Aneesa. N[1*], Arvina Rajasekar[2]

[1*] Intern, Saveetha Dental College and Hospitals, Chennai-600077, Tamil Nadu, India
[2] Senior Lecturer, Department of Periodontology, Saveetha Dental College and Hospitals, Chennai-600077, Tamil Nadu, India

Corresponding Author:
Noorul Aneesa. N
Intern,
Saveetha Dental College and Hospitals,
Saveetha Institute of Medical and Technical Sciences,
Chennai - 600077.

Type of Manuscript: Review Article
Running Title: A review on local drug delivery

***Abstract*: Periodontitis is an inflammatory disease of the supporting tissues of the teeth, caused by a group of specific microorganisms. Aggressive forms of periodontitis can be localized or generalized. The concept that localized problem sites may be treated by local drug delivery appears attractive as the antimicrobial agent is delivered within periodontal pockets and the therapy is targeted on specific pathogenic microorganisms. Periodontitis can result in bone resorption creating bony defects, which may cause tooth loss. Various drugs have been studied using local delivery to improve the periodontal health and to achieve periodontal regeneration. Local delivery of antimicrobial agents using controlled release systems should be considered as adjunctive to mechanical debridement for the treatment of localized forms of periodontal destruction.**

***Keywords*: Drug Delivery, Micro Organisms, Antimicrobial**

1. Introduction

Periodontitis is an infectious disease of microbial origin, modified by a host response and resulting in loss of attachment and alveolar bone in a susceptible host. There are 3 aspects to periodontal disease, the microbial etiology, a hyper responsive immune system and a susceptible host. At present, the treatment of periodontal disease consists of controlling the microbial etiology. But research in controlling the immune response and identification of a susceptible host is ongoing.(1)

The gold standard for periodontal therapy is SRP and all other methods are compared to it. However, antimicrobial agents have been used in periodontal disease, owing to its microbial etiology.The purpose of antibiotic chemotherapy is to aid the host defenses in controlling and eliminating microbes that temporarily have overwhelmed the protective host mechanisms.(2)

The use of locally delivered antimicrobials is relatively new addition in the management of periodontitis. This treatment method is primarily the result of more than 20 years of research pioneered by Goodson by the Forsyth Dental Research Centre. All local delivery systems have the goal of delivering high concentrations of an antibiotic or antimicrobial directly to the site of periodontal infection. Concentrations of medication can be achieved considerably higher than could be obtained with systemic administration, whereas the systemic uptake of the medication is minimal.(3,4)

Pharmacokinetic parameters in the periodontal pocket

Pharmacological agents applied locally for the treatment of Periodontics are targeted to several areas. These include bacteria residing in the periodontal pocket, soft tissue walls of the pocket and the exposed cementum or radicular dentin.

Experimental evidence suggests that many forms of local drug delivery are not able to deliver medications to all those locations. For example agents in mouth rinses and those used during supragingival irrigation do not predictably reach beyond 5 mm into the periodontal pocket.(4)

However, irrigation solutions delivered intracrevicularly, via a cannula on other device, can predictably be projected into deep periodontal pockets. On the other hand, gaining access to the anatomical boundaries of the pocket does not necessarily mean penetration to the target bacteria because highly organized aggregates of adherent bacteria (biofilms) may impair diffusion or inactivate pharmacologic agents. Therefore antimicrobial action on biofilm bacteria may require higher concentrations of the active agent.(5,6)

Once a drug reaches the site of action at an effective concentration, it must remain at the site long enough for the pharmacological effects to occur. The duration of exposure required is dependent upon the mechanism by which the antimicrobial agent inhibits or destroys target bacteria. For example chlorhexidine a bacterial agent kills microorganisms by compromising the

integrity to the cell membrane and required a shorter exposure time than a bacteriostatic agent, such as tetracycline, which inhibits protein synthesis. (7)

Metronidazole and microcycline dental gels provide increased drug concentrations for 24 hours, which subsequently decrease rapidly. They are categorized as sustained local drug delivery systems and the antibiotic level in the pocket decreases exponentially at a rate directly proportional to their pocket concentration, this is referred to as first order kinetics. In contrast the other drug devices maintain a high drug concentration for a prolonged period of time and are referred to as controlled delivery systems. The maintenance of a steady drug concentration for the duration of treatment is called zero order kinetics.(8)

Periodontal clearance

GCF is an altered serum Transudate found in the gingival sulcus. GCF flow into periodontal pockets averages 20 µl/hour and markedly increased with gingival tissue inflammation. Total pocket fluid volume thus may turn over 40 times an hour in a moderate sized periodontal pocket of 5 mm (0.5 µl volume), which is more frequent than the oral cavity salivary turnover rate of about 28 times an hour (Goodson, 1989).(9)

The expected half-life of a pharmacological agent in the gingival crevice (i.e., the time necessary for the concentration to become half the original is about 1 minute. The high rate of clearance represents the major obstacle to maintaining effective concentrations of antimicrobial agent within the pocket. Longer therapeutic duration required the use of a subgingival drug reservoir that can release medication to counteract its continuous loss due to crevicular fluid flow. (10)

Substantivity

It refers to the property of a substance to bind to the soft and /or hard tissue walls of the pocket, thereby establishing a drug reservoir. Equilibrium between the bound and the free drug in the pocket is established and as the concentration of free antimicrobial agent decrease through crevicular fluid clearance the bound medicament is gradually released in a biologically active form. Drug half-life is thereby prolonged and treatment duration becomes a function of how much drug is stored in the reservoir. In dentistry, this property was first described for chlorhexidine, for which it was established at the drug reservoir offset salivary clearance. In the subgingival environment tetracyclins and clindamycin have demonstrated substantivity, and it has been noted that high concentrations are necessary to increase the duration of antibacterial activity. The size of the drug reservoir that can be established following irrigation of a periodontal pocket represents the major limitations to prolonging the half life of a substantive drug and thus the duration of the desired antibacterial effect.(11,12)

Personally applied Local Drug Delivery

Non sustained antimicrobial agents (Home irrigation). Home irrigation devices allow the patient to deliver medicaments into the periodontal pocket at home on a more frequent basis. This is ineffective against subgingival microflora, as medicaments cannot reach subgingival area. All methods offer only a sustained pocket delivery.

Agents used are Chlorhexidine, Listerine, Saline, Stannous fluoride, Diluted iodine solution. Oral irrigation devices designed for home use include blunt tipped irrigating cannula e.g. Water pipe.(13)

Resorbable sustained release chemotherapeutic devices

Locally applied antimicrobial gels

Bray et al (1993) investigated the efficacy of subgingival application with 0.5% and 0.2% chlorhexidine gel as an adjunct to scaling and root planning. Statistically significant reduction in probing pocket depth and bleeding on probing occurred with 0.2% chlorhexidine gel form baseline to 12 weeks. Metronidazole gel (25%) is available in Europe as Elizol. The advantages of Metronidazole is its selective efficacy against obligate anaerobes. 5% Metronidazole collagen devices supplied in the form of square pieces have been developed. When inserted into the pocket in contact with GCF it forms a resorbable gel.(14,15)

Triclosan gel

Triclosan is a bisphenolic compound which has not only antimicrobial but also anti-inflammatory properties. Furuichi et al (1997) evaluated short-term effects of trichlosan containing dentifrice/gel combination when applied at periodontal sites treated with scaling and root planning and results showed marked improvement in clinical parameters.916)

Atrigel gel (Sanguinarine gel)

Dunn et al (1991) evaluated the efficacy of a biodegradable controlled release gel designed to deliver Sanguinarine gel in concentration of 2.5%, 5% and 10%. The results showed marked reduction of pocket depth by 1.2 mm often 3 months of follow up.(17)

Clindamycin gel

It is effective against most of the periodontal pathogens except for A.actinomycetemcomitans and E.corrodens. Savetre et al (1993) reported that use of a small amount of clindamycin HCL inserted into periodontal pocket for 2 weeks enhanced the effect of scaling and roots planning an subgingival microflora of adult periodontitis.(18)

Locally delivered antimicrobial ointments

Microcycline HCl (Periocline) has a longer serum half-life and lower urinary excretion rate than other tetracyclins. This permits the use of smaller and less frequent doses. According to Van Steamberghe et al (1993) microcycline HCl ointment applied every 2 weeks and for 6 weeks (total 4 applications) significantly reduced periodontal pockets by 1.7 mm compared to vehicle control of 1.4 mm. Tetracycline HCl (40%) in a white petrolatum is as potential as a sustained release auto dissipating system. Eckler et al (1990) reported that it enhances the effect of scaling and root planning.(17)

Controlled released devices

The controlled release local delivery systems that have been used in Periodontics and are currently under investigation may be classified as either reservoir without a rate controlling system. The reservoirs without rate controlling delivery include devices such as hollow fibers filled with a therapeutic agent in which the agent is released simply by diffusion. Reservoirs with rate controlling systems may take many forms. The most common forms included solvent action on coated drug particles, microporous polymer membrane on monolithic matrices or erodible polymeric matrices.

The resorbable devices would not require a second visit for removal and they avoid the possible undesirable effects of a non resorbable device left in place. The various drugs used in these devices are oflaxacin, Doxycycline, Tetracycline, chlorhexidine, methylene blue.(18,19,20)

Description of different devices

Tetracycline fibre (actisite)

The actisite delivery system consists of a polymer, ethylene vinyl acetate, 25% saturated with tetracycline hydrochloride. In the marketed form, it is 23 cm in length and 0.5mm in diameter and contains 12.7 mg of tetracycline hydrochloride. The fibre releases tetracycline at a constant rate for 14 days.

Comparing tetracycline fibre with systemic tetracycline, the gingival tissue fluid concentration is 1590 μg/ml versus 4 to 8 μg/ml, whereas the serum concentration is 0.4 μg/ml. The total dose of tetracycline after 10 days of fibre treatment is 12.7 mg versus 10,000 mg for systemic delivery. At a concentration more than 150 times that achieved by systemic delivery, the tetracycline fibre provides bactericidal concentrations of tetracycline.(21,22,23)

Technique

The tetracycline fibre comes as a flexible cord on fibre. Its yellow color is from the impregnated tetracycline hydrochloride. Although the fibre has a slight amount of memory, it can be bent easily and is relatively user friendly. The optimal sites for use of fibres are periodontal pockets 5 mm or more in depth that bleed on probing and had not responded to mechanical therapy. An individual tooth on several teeth may be treated at one time. The fibre technique itself does not require local anaesthesia, however because scaling and root planning is often redone at this time, anaesthesia may be helpful.

It is advisable to take short lengths of fibre 2 to 3 inches, in a cotton forceps and place the fibre at the opening of the pocket to be treated. A gingival retraction cord packing pocket gently. Deeper pockets require more fibre than shallow pockets; therefore, the fibre should be folded on it and packed into the pocket until the pocket is filled to slightly below the gingival margin. Because gingival shrinkage is anticipated the dentist should not completely fill the pocket but stay approximately 1 mm apical to the gingival margin. Inter proximal pockets should be packed from both the facial and lingual sides. Passing fibre around the tooth does help retention during the treatment period.(24,25)

Once the fibre placement is complete, the dentist isolates the area with cotton rolls and gauze, dries the tooth with the air, syringe and applies a drop of tissue adhesive at each interdental area as well as facially and lingually. This can be done most effectively with the use of a squeezett. Vaseline can be placed over the adhesive to prevent the cheek and tongue from sticking to the adhesive.

To avoid dislodging the fibre and adhesive the patient is instructed not to brush or floss the treated areas until fibres are removed. The patient is placed on twice a day chlorhexidine mouth rinse while the fibres are in place and for 1 week after their removal.(26)

Fibres should be kept in place for 7 to 14 days. If fibres are lost the patient should return for replacement.

Chlorhexidine chip (Periochip)

The chlorhexidine chip is a small biodegradable film of hydrolyzed gelatin into which has been incorporated 2.5 mg of chlorhexidine gluconate. The chip resembles a body's fingernail measuring approximately 4 x 5 mm and 0.35 mm in thickness. Beneficial properties of the chip are its biodegradability and ease of use.

The chip is easily placed into periodontal pockets that are 5 mm or more. It is self-retentive and delivers chlorhexidine to the side at the concentration of 125 μg/ml for atleast 7 days.(27)

Technique

The chip is placed immediately after scaling and root planning. The chip is grasped in a cotton forceps and gently inserted into the pocket. Because the chip is 4x5 mm, the pocket must be that large to accept a full chip. If the chip gets too wet it may become soft and even start to disintegrate. It is therefore advisable to dry the area. Because a burning sensation is occasionally reported after chip placement, the placement of multiple chips around a single tooth may result in discomfort.

The chip required no retentive system and biodegrades in 7 to 10 days. No postoperative appointed is required. The patient can be seen for his or her next regular appointment or next recall appointment. To avoid dislodging the chip, the patient is instructed not to brush or floss the treated areas for 7 days.

The most effective use of the chip has occurred when the chip is place in pockets 5 mm or greater every 3 months. Not only has this resulted in a reduction in actual probing depth, but also there are fewer residual pockets 5 mm or greater.(28,29)

Doxycycline polymer (Atridox)

A liquid biodegradable drug delivery system has been developed that hardens in the periodontal pocket and give a controlled release of the incorporated agent. This delivery system has been modified to incorporate and release doxycycline.

Two multicentre clinical trials were conducted to test the safety and efficacy of this product. In each trial 10 research centres completed a randomized modified double blind study of 41 adults with moderate to severe periodontitis. At baseline, subjects were randomized to one of four treatment groups and qualifying sites were treated. These groups included Doxycycline, Vehicle control, Oral hygiene only and Scaling and root planning.(31,32,33)

Types of disease treated with local drug delivery systems

All drug delivery systems were used to treat patients with adult periodontitis. Only tetracycline fibres were used to treat aggressive periodontitis. But Mandell (1986) et al, suggested that the tetracycline fibres were not efficient at suppressing A. actinomycetemcomitans tissue invasiveness. Despite the invitro susceptibility of A.a to tetracycline, the data indicated that evaluated levels of A.a were found after therapy. This was attributed to reduction of antagonistic organisms, which permitted the A.a to return to the pocket from the connective tissue and proliferate. Riep et al (1996) also reported that local delivery with metronidazole was not effective at suppressing A.a infections. On the other hand, Mombelli et al (1997) reported that tetracycline fibres were able to suppress, but not eliminate A.a or P. g. However, Bernimonlin et al (1996) successfully treated patients with rapidly progressive periodontitis using tetracycline fibres in conjunction with root planning.(34,35)

CONCLUSION

Based on the available evidence, the local drug delivery into the periodontal pocket can improve the periodontal health. , the controlled release properties can be applied as a therapeutic component in the effective management of localised persisting lesions. Local drug administration should be based on patient clinical findings, scientific evidence and proper diagnosis. Thus, it can be concluded that local drug delivery though not a substitute for the conventional therapy, can be of added benefit if used as an adjunct with the conventional scaling and root planning.

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