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Local Drug Delivery System: A Prospect's To the Non-Surgical Periodontal Therapy.

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Abstract

Periodontitis is an inflammatory disease involving supportive structures of the teeth seen universally in all groups, ethnicities, races and genders. Various antibacterial agents have been used effectively for the management of periodontal infection. The effectiveness of mechanical debridement of plaque and repeated topical and systemic administration of antibacterial agents are limited due to the lack of accessibility to periodontopathic organisms in the periodontal pocket. These products provide a long-term, effective treatment at the site of infection at much smaller doses. Prospective studies considering risk factors for disease progression have to be designed to identify patients who may benefit from local drug delivery.

Keywords: Anti-bacterial agents, local drug delivery, periodontitis,

Introduction

Periodontal diseases are one of the most widespread oral diseases, where 80% of American adults and more than 50% of Indian community suffers from this chronic inflammatory disease demonstrating the severity of disease.[1] According to **World Health Organization (WHO),** advanced disease with deep periodontal pockets (≥ 6 mm) affects 10 to 15% of the adult population all over world.[2]

Periodontal disease is caused by gram negative bacteria, facultative anaerobic bacterial species like B. intermedius and B. gingivalis; fusiform organisms, Actinobacillus actinomycetemcomitans, Wolinella recta and Eikenella species; and various bacilli and cocci; spirochetes; amoebas and trichomonas causing subgingival plaque, inflammation and degeneration of alveolar bone, teeth, dental cementum and periodontal ligaments. At severe phase of disease, there occurs a degeneration of collagen and periodontal ligament along with resorption of the alveolar bone and gingival epithelium, leading to the formation of periodontal pocket.[1]

The dental community assumed that bacteria were directly responsible for release of enzymes and toxins that destroyed the periodontium. In addition, other proinflammatory mediators (for example, interleukin-1β and tumor necrosis factor-α) are involved in degradation of the periodontium. Therefore, we can conclude that the host response can be both protective and destructive.[3]

Bacterial plaque that coats the teeth is the main etiological factor in the development of periodontal disease. Calculus does not directly contribute to inflammation of gingiva but it also provides a fixed nidus for the accumulation of plaque and its retention to gingiva. Removal of subgingival plaque and calculus constitutes to the cornerstone therapy of periodontal health.[4]

Antimicrobial agents are of great interest and may be valuable as adjuncts to mechanical therapy.[5] Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics. Inability to achieve and maintain therapeutic concentration of the drug in the periodontal pocket, risk of adverse drug reactions and dependence of patient's compliance are some of the disadvantages reported.[6]

Many chemical agents have been tested as an adjuncts to mechanical methods reducing plaque-associated gingivitis. Chlorhexidine, triclosan, povidone-iodine and various phenolic compounds have been used successfully as an anti-plaque agents. However, side effects such as allergy, discolouration of teeth and unpleasant taste occurs when these chemicals are used for an extended time period.[7]

Herbal medicines have been used for thousands of years in developing countries and more than 80% of population does rely on their use for healthcare needs. Neem, cinnamom, turmeric, aloe vera, clove are amongst the most common herbal products, amongst which turmeric is a dietary spice, with curcuma as its most active ingredient having an antioxidant, anti-inflammatory, anti-carcinogenic, anti-microbial and anti-parasitic properties.[8]

For non-surgical therapy, there are multiple options of antimicrobials which are locally delivered into the mucosa, such as metronidazole, chlorhexidine, minocycline, doxycycline and tetracycline.These drugs helps to modulate the inflammatory response of the tissues and inhibit the periodontal microorganisms when placed in the periodontal pockets. Antibacterial agents are used along with mechanical debridement for the management of periodontal infection. Their effectiveness is limited due to the lack of accessibility to the periodontal pocket.[9]

Local administration provides an answer to these problems. However, the important factor in this treatment

is its ability to control and prolong the release rate of therapeutic agent from the device. Because the periodontal pocket is inaccessible, various techniques are developed to be administered as an antibacterial agents into the periodontal pocket, such as intra-pocket irrigation and intra-pocket sustained release delivery systems.[10]

Locally delivered antimicrobials are designed along with the concerned drugs which are impregnated as a vehicle and are available as gels, fibers, chips, polymers or ointments. Success in any drug delivery system are designed to target the periodontal infection depending on its ability to deliver the antimicrobial agent to the base of the pocket at either a bacteriostatic or bactericidal concentration. It also facilitates the retention of medicament for a longer duration to ensure an efficacious result.[10]

According to ***Michael G Jorgensen et al 2000***[11], a multifaceted yet straight forward approach is presented for management of destructive periodontal disease.

According ***ADA Journal of American Dental Association 2000***[11], emphases the importance of use of antimicrobial rinses as a part of daily oral care regimen to control the accumulation of dental plaque.

These locally applied antimicrobial agents into the periodontal pockets may further suppress the periodontal pathogens thereby augment the effect of conventional mechanical therapy.

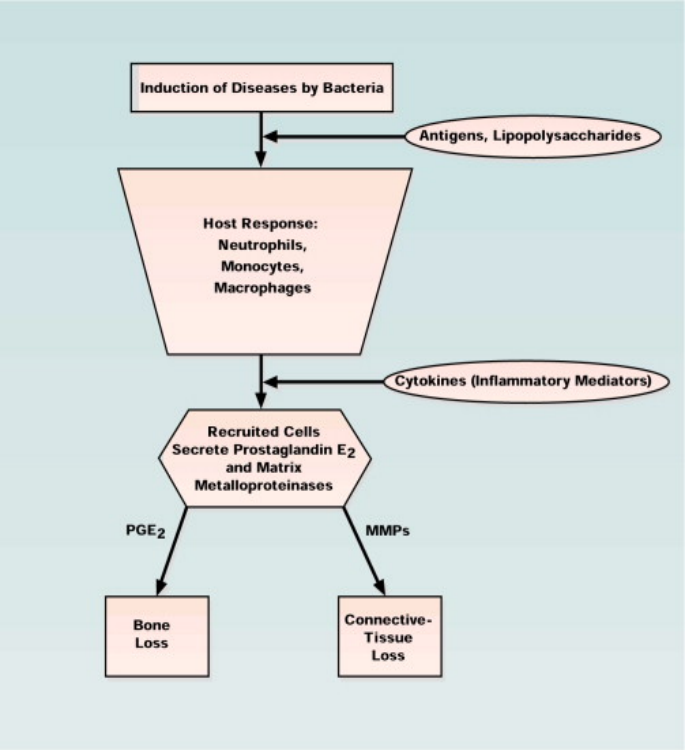

Figure:1 Greenstein G And Lamster I. Disease Pathogenesis From Changing Periodontal Paradigms: Therapeutic Implications. Int J Periodontics Restorative Dent 2000; 14:337-57.[12]

Historical Perspective of Locally Delivered Antimicrobials

During early days the resolution of inflammation was either by spontaneous in nature by exfoliation or by extraction. By the turn of 20th century, it was considered that calculus was a mechanical irritant & its removal by scaling & root planning was practiced. Modern era of periodontal therapy began roughly 40 years ago, where surgical pocket elimination & osseous surgery was performed. Prior to the 1950s, periodontitis was treated mostly by tooth exfoliation and is still the predominant treatment in world's population.[11]

In 1960 and 1970 the nature of periodontitis became apparent and it was the time for new knowledge and approaches for the therapy. During 1980, data was collected evaluating the thoroughness of root debridement and subgingival infection control, as it was one of the

major determinant for a successful periodontal therapy with this being non-surgical treatment as a commonly used treatment modality.[13,14]

The first antibiotic was mainly systemically administered **penicillin.** Metronidazole was initially introduced for treating trichomoniasis in the 1950s. Then its therapeutic use has subsequently been expanded to include anaerobic bacterial infections affecting specifically the obligate anaerobic part of oral flora including Porphyromonas gingivalis and other black pigmenting gram negative organisms but not Actinobacillus actinomycetemcomitans, a facultative anaerobe.[15,16,17]

In 1970 tetracycline became popular due to its broad spectrum antimicrobial activity and low toxicity. Literature stated that tetracycline, clindamycin, erythromycin are capable of inhibiting collagenase which interferes with breakdown of tissues in periodontal disease.[10]

Also, it became widely recognised that the early allergic problems with topical antibiotics were almost uniquely a phenomenon of penicillin, with minimal problems resulting from the topical application of antibiotics. At the same time concern emerged relative to growing problems with the use of systemic antibiotics including allergies, gastrointestinal disorders and development of resistant bacterial strains.[10]

Furthermore, when a chemical agent is applied topically instead of systemically, a lower dose is required to reach the optimal concentration at the site of infection and at the same time to minimize any adverse side effects. Consequently, interest in topical antimicrobials has increased in recent years.[13]

Pihlstrom et al in 1983[13] reviewed current studies to compare surgical and non-surgical treatment of periodontal diseases and found loss of clinical attachment following flap procedure or shallow pockets and no clinically significant loss after scaling and root planning.

Goodson et al, 1979[4] was the first who proposed the concept of controlled delivery for the treating periodontitis.

Terminologies[18]

At present one may find several different terms applied to antimicrobial therapy placed directly in the subgingival regions having different therapeutic implications.[18]

The concept of **targeted drug delivery** originated in the 1970s, based on this theory that if one could substantially improve the cellular specificity of a drug there would be an accompanying significant improvement in its therapeutic index. Recent advances in the surface receptor biology and genetic regulation as well as technical breakthrough such as monoclonal antibody technology have now provided new approaches to targeted drug delivery such that individual cells of interest may be treated with minimal effect on other cells. With such technology targeted drug delivery referred to delivery of agents of specific cells.

The term **local delivery** and **site specific delivery** are synonymously used with targeted delivery. The term local and site specific do not imply the same specificity at a cellular level as the term targeted delivery. In periodontics, the application of currently available drugs to the subgingival area may be approximately described as local delivery or site specific delivery.[18]

A second term of importance is **controlled delivery or controlled release**. Controlled delivery systems are as such designed to release a drug slowly for more prolonged availability and sustained drug action. It should be emphasized that controlled delivery system such as timed release cold capsules are not necessarily local delivery systems.[12].

Local delivery devices systems are designed to deliver agents locally into periodontal pocke without any mechanism to retain its therapeutic level for a long time period. Such devices generally exhibit exponential increase and decrease in drug concentration at the site. Although some agents delivered by subgingival irrigation such as chlorhexidine or tetracycline may as a result of innate chemical structure retained in an area and detachable for several hours.

Controlled release local delivery devices employ the controlled release technologies described above or other similar technologies to assure therapeutic concentrations of the antimicrobial in the subgingival area for atleast 3 days following a single application. Controlled release delivery of antimicrobial into periodontal pocket received great interest and appears to be promising in periodontal therapy.[18]

Pharmacokinetic Parameters In The Periodontal Pockets

Goodson in 1989[19] pointed out that the pharmacological agent must reach its site of action and must be maintained there at a sufficient concentration for the intended pharmacological effect to occur.

Pharmacokinetics describe what the body does to the drug, as opposed to pharmacodynamics which describe what the drug does to the body.[20]

The three criteria are site, concentration and time which are strictly correlated.

Site of Action

The targets of the pharmacological agents locally delivered for the treatment of periodontitis include the bacteria residing in the periodontal pocket and possibly the bacteria invading both the soft and hard tissue walls of the pocket; the junctional epithelium, the exposed cementum or radicular dentin. Substantial evidence indicates that not all forms of the local application allows delivery of an agent into the periodontal pocket. Agents in mouthrinses or supragingival irrigating solutions have been shown to be unable to reach the deepest portion of the pocket.[19,21,22]

However gaining access to the antimicrobial boundaries of the pocket does not necessarily mean gaining access to the target bacteria. Subgingival bacteria include highly organised aggregates of adherent bacteria; a biofilm. Highly complex extracellular polysaccharides contribute to form the matrix of the bacterial biofilm; they may impair diffusion of the applied active agents as a scavenger and thus protects the biofilm bacteria from the action of antimicrobials.[19,21,22]

Concentration[19]

An intrinsically efficacious pharmacological agent should reach the site of action at a concentration higher than its minimal efficacious concentration.

a. **Concentration and efficacy:** The minimum inhibitory concentration to minimium bactericidal concentration varies when the susceptibility of different bacteria isolates are tested. As a target for in vivo concentration, the in vitro concentration inhibiting or killing 905 of the tested isolates is frequently selected. High levels of variability are frequently observed in estimates of both minimum inhibitory concentration and minimum bactericidal concentration.[13]

b. **Concentration and unwanted effect:**Adverse effects of antibiotic therapy are also associated with local concentration of the drug. The most important concentration dependent side effect following local drug delivery of antimicrobials in the periodontal pocket is the overgrowth of the non- susceptible organisms. After the exposure of the marginally effective antibiotic concentration, resistant bacteria may repopulate the whole ecological niche: overgrowth of intrinsically non-susceptible organisms such as yeast may be more likely

seen. In periodontal disease the issue is further complicated by the fact that the subgingival microbiota comprises of variety of microorganisms with different levels of susceptibility to various antibiotics.

Time

Once a drug reaches the site of action at an effective concentration it must remain at the site long enough for its pharmacological effect to occur. Different classes of antimicrobial agents inhibit or kill infecting microorganisms by specific mechanisms, e.g: inhibition of protein synthesis, interference with cell wall growth or DNA synthesis. Bacterial inhibition or killing by these different specific mechanisms have been shown to require in vitro different durations of exposure to effective concentrations of antimicrobial drugs. The duration of antibacterial levels of the drug at the site of infection is therefore considered to be off critical importance. Also, an organised biofilm, however, most of the bacteria display a very slow growth rate which seriously limits the effect of antimicrobials.[19,21,22]

Periodontal Clearance

Periodontal pockets are clearly flushed with flow of the inflammatory exudate and the crevicular fluid. GCF flow into the periodontal pockets markedly increase with the gingival tissue inflammation. Goodson (1989) estimated that the fluid present in a 5mm periodontal pocket is replaced about 40 times an hour, such high clearance is the result of a low resting volume (0.5ul) and a comparatively high flow rate is seen (20ul). It becomes apparent that following intracrevicular placement, an antimicrobial will be rapidly removed from the pocket according to an exponential decay equation.

C(t) = C0 e-kt

Where t is the time and k (rate constant of the process) is equal to F/V (F- gingival fluid flow rate, V= Volume of distribution of a drug i.e, the volume of periodontal pocket.

Substituting **GOODSON'S** estimates of the gingival flow rate and resting volume of the periodontal pocket in equation, the half time of elimination of a drug can also be theoretically calculated as:

T1/2 = Ln(2) V/F = Ln(2) 0.5ul/ 20ul/hour =0.017 hours= 1.04 minutes.

The expected half time of elimination of an intracrevicularly placed pharmacological agents is about 1 minute. It becomes apparent that the following intracrevicular placement, an antimicrobial will be rapidly removed from the periodontal pocket.

Similarly **oosterwal et al (1996)** found a nearly 2-log decrease in gingival crevicular fluid levels of an injected sodium fluroscent dye within 5 minutes of subgingival placement. The rapid clearance of substances from the periodontal pocket limits the efficacy of locally applied non- bonding antimicrobial agents in the periodontitis treatment.

From equation 1, it is possible to calculate that the total antibacterial time expected of a highly potent antimicrobial (MIC/ minimum inhibitory concentration of 3mg/L)delivered of a highly concentration solution(100mg/ml) is about 15 minutes.[19,21,22]

Substantivity

Substantivity refers to the property of a substance to bind soft or hard tissue walls of pocket by establishing a drug reservoir. Some medications have this intrinsic ability to bind to the soft or hard tissue walls of the pocket. Drug half life is thereby prolonged and treatment duration becomes a function of how a drug is stored in the reservoir.[19,21,22]

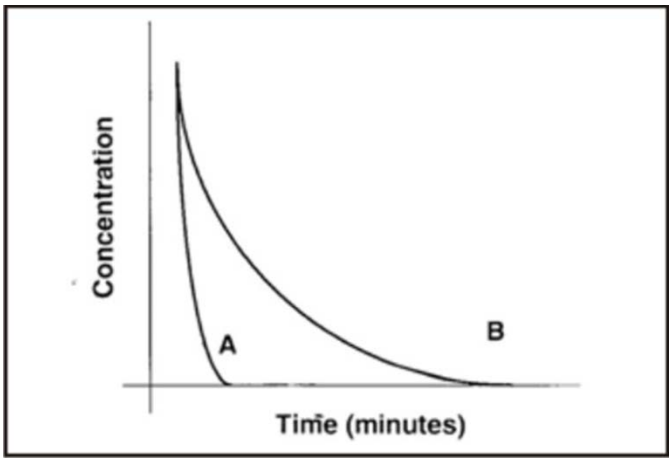

Figure:2 Clearance Of An Intracrevicularly Placed Antimicrobial Without Substantivity(A) And With Substantivity(B).

Chinna K, Bhatnagar R. Local drug delivery. Int J Den Sci, 2012:1(4).[19]

In the subgingival environment, tetracyclines and clindamycin have demonstrated substantivity and it has been noted that high concentrations are necessary to increase the duration of antibacterial activity.[14]

It has also became clear that the property can be influenced by a series of parameters such as:

1. Concentration of the medication
2. Length of time of contact of the solution with oral structures
3. Ph
4. Temperature
5. Inter-individual variations were also observed.

Classification of Local Antimicrobial Agent Therapy In Periodontics[1,7,13,23-31]

1. According To The Duration Of Medicament Release:

Greenstein G, Tonetti M, 2000[24]

A. Sustained release of formulation

B. Controlled release of local delivery

Local Antimicrobial Agents As:

Sebastian, 1995

1. Personally applied[25]

a. Non sustained subgingival drug delivery (home oral irrigation): Provides high pocket concentration of the antimicrobial agent for only short period of time.

b. Sustained subgingival drug delivery (none developed till date): Provides retention of the antimicrobial agents for less than 24 hours.

2. Professionally applied in dental office:

a. **Non sustained subgingival drug delivery (professional pocket irrigation)-**Professional subgingival irrigation device include wide array of powered and manually operated irrigation. Irrigation using a syringe with blund end needle end has been tried which can penetrate 71.5% of pocket depth in pockets 3.5-6 mm deep.

Some of the commonly used local drug delivery devices are:

1. A conventional pulsed oral irrigator (water pik) at a high pressure setting may deliver aqueous solution to approximately 50% of the distance between the free gingival margin and the most coronal connective tissue attachment. The standard blunt jet tip is directed at either a 450 or 900 application angle to the tooth gingival tissue margins.
2. A recently developed soft cone rubber tip (Pik Pocket) may enhance local pocket placement and delivery of antimicrobial agents in the pocket. These tips are reported to provide subgingival aqueous penetration to 90% depth of sites less than or equal to 6mm, and 64% to the depth of pocket less than or equal to 7mm. The irrigating tip of a hand held syringe is atleast 3mm below the gingival margins to attain full pocket penetration of aqueous solution into shallow and deep periodontal sites. Blunt ended cannulas attached to oral irrigators and professionally advanced to one half of the probing

depth providing 80% subgingival fluid penetration into pocket more than or equal to 6mm.

3. Ultrasonic scaling devices have been used professionally to deliver antimicrobial agents into the periodontal pocket during mechanical root debridement procedures. An irrigant delivered through ultrasonic scaling tips has shown complete penetration in 86% sites ranging from 3-9mm pocket depth.

b. **Sustained subgingival drug delivery**

This may be attained with drugs possessing a high intrinsic substantivity for tooth root surfaces or with the use of slow release and controlled release drug delivery system.

Vehicles tested for sustained periodontal pocket delivery of antimicrobial agents include solutions, pastes, hollow fibres, acrylic strips, monolithic fibers, resorbable cellulose, collagen and biodegradable gels.

3. Controlled Release Local Delivery System As:

Kornman 1993

1. Reservoirs without rate controlling system[18]

a. Dialysis tubing

b. Gels

2. Reservoirs with rate controlling system

a. Monolithic devices

b. Acrylic strips

c. Cellulose strips

d. Ethyl vinyl acetate fibers

A. Reservoirs Without Rate Controlling System

1. **Dialysis tubing-** This group includes dialysis tubing containing a core of drug solution. A 3-5 mm in length and 0.2 mm internal diameter tubing is the usual quantity required for each pocket.
2. **Gels:** Gels tested include polyethylene oxide and white petroleum. The advantages of this gel is its syringeability and thereby ease of placement. Gels containing 2% minocycline are marked as dentomycin and 25% metronidazole as elyzol. These gels allow antibiotics to be syringed into the pocket.

B. Reservoirs With Rate Controlling Systems:

1. **Monolithic matrices or devices:** Examples include: acrylic strips, ethylene vinyl acetate, ethyl cellulose strips and cross linked collagen films.
2. **Acrylic strips:**They are typically 0.2 mm thick and cut to be about 1mm more than the probing depth. Treatment is carried out over 2-4 weeks with new strips inserted every week.
3. **Ethyl cellulose strips:** contains chlorhexidine or metronidazole for 6 days.
4. **Ethylene vinyl acetate fibres**: 0.5mm diameter have been tested in a similar way as that of acrylic strips.

A formulation of 25% tetracycline in EVA (Ethylene vinyl acetate fibers/ Actisite) has been developed as a 0.5mm non biogradable fibres.

5. Depending On Degradability, Intra Pocket Devices Can Be Divided Into:

A. Non- degradable devices

B. Degradable devices

6. Controlled Drug Release Polymeric Systems As:

Langer And Peppas 1981

1. Diffusion controlled system[26]

a. Reservoirs (membrane device)

b. Matrices (monolithic devices)

2. Chemically controlled systems

a. Bioerodible systems

b. Pendant chain systems

3. Swelling controlled system

In swelling controlled system, the polymer swells in a dissolution medium usually water allowing release of drug.

4. Magnetically controlled systems

In magnetically controlled system, drug and magnetic beads are uniformly dispersed in polymer by external magnetic field.

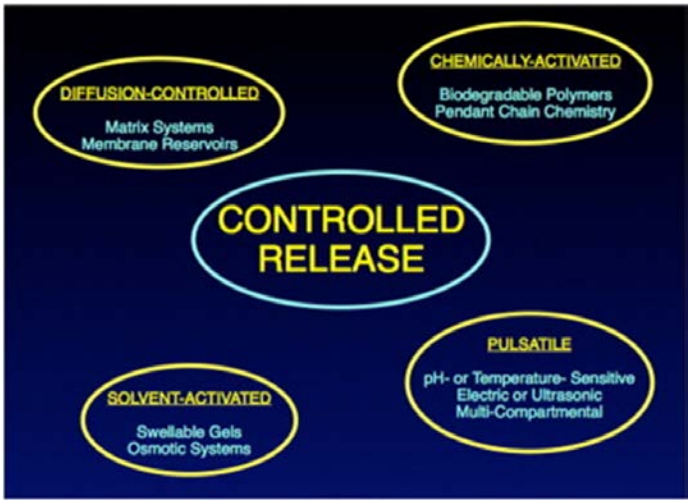

Figure:3 Langer And Peppas, 1981[27]

Advantages Of Local Drug Delivery[28,30,32,33]

1. A local route of drug delivery attains 100 fold higher concentration of an antimicrobial agent at subgingival areas when compared with a systemic drug regime, thus helps in reducing the total patient dose by around 400 folds. For example, local placement of tetracycline releasing ethylene vinyl acetate monolithic fiber yields tetracycline concentrations in excess of 1300 ug/ml in gingival crevicular fluid in 10 days. In comparison repeated systemic doses of tetracycline- HCL can provide tetracycline levels of 4-8ug/ml in GCF.
2. Local pocket deliver employs an antimicrobial agentswhich is not suitable for systemic administration such as various broad spectrum antiseptic solution.
3. Personally applied antimicrobials regimes offers potential use of daily drug placement into periodontal pocket as a part of home self-care procedure.
4. Professional pocket application of local antimicrobial agent reduces potential problems with the use of systemic antibiotic drug regimens.
5. Local antibiotic placement also reduces the risk of developing drug resistant microbial population at non oral body sites.Potential problems with patient compliance are eliminated by professional application of local antimicrobial agents in periodontal pockets.[20]
6. Local antibiotic delivery is an alternative treatment for women having vaginal infection, and for individuals predisposed to gastrointestinal tract complications (ulcerative colitis) or other adverse reaction.
7. The risk of developing drug resistant microbial populations at normal body sites is also diminished.
8. It inhibits or kills the putative pathogens by reaching the site of infection, the specific site.
9. Local drug therapy has three potential advantages :

1. Decrease drug dose
2. Increase drug concentration
3. Reduced systemic side effect such as G.I.T distress

Disadvantages Of Local Drug Delivery[28,30]

1. Difficulty in placing therapeutic concentration of the antimicrobial agent into deeper parts of periodontal pocket and furcation lesions
2. Personal application of antimicrobial agents by patients as a part of their home self-care procedures is frequently compromised by patient's lack of adequate manual dexterity with limited understanding of periodontal anatomy and poor patients compliance and performance with recommended procedures.
3. Time consuming and labor-intensive.
4. Non sustained subgingival drug delivery is limited only by a brief exposure of target microorganisms to the applied antimicrobial agent.
5. Antimicrobial agents when locally applied into periodontal pockets do not affect periodontal

pathogens residing within gingival connective tissues and on extra-pocket oral surfaces such as tongue, tonsils and buccal mucosa finally increasing the risk of reinfection and recurrence in treated areas.

6. Connective tissue associated plaque and extrapocket oral surfaces don‘t get affected by local drug delivery which may be responsible for recurrence of disease in treated areas.

Conclusion

Current data suggested that local delivery of antimicrobials into a periodontal pocket improves the periodontal health.

Various drug delivery and targeting systems are under development to obtain increased dissolution velocity, increased saturation solubility, improved bioadhesivity and versatility in surface modification so that better and effective administration of desired and newer drug can be done through the best possible system.

Kalsi R et al [2011] and Pe´rez PM et al [2013] in their respective systematic review and meta analysis stated that local drug delivery has an added advantage over scaling and root planning alone

The herbal remedies have an edge over conventional antibiotic treatment which suffer the limitation of low benefit to high risk as compared to herbal treatment which possess high benefit to low risk ratio. Standardization and quality assurance of these herbal remedies is also a key area to be focused in future and efforts have been initialized towards this target. There are much more opportunities for further research in the utility of herbal remedies for periodontal diseases.

The herbal medicines have shown to possess a wide array of biological properties such as antimicrobial, antioxidant, and anti-inflammatory effects. The natural phytochemicals present in these herbs aid in suppressing the alveolar bone loss, which is the striking feature in periodontitis. Since herbal therapies aids in effectiveness, safety, accessibility and control over treatment hence can be tried in dentistry as they are used in medical disorders. Although many studies , have shown the potency of herbal medicines as an alternative to conventional therapy, there still lies a void in research with respect to the clinical application of these agents in periodontics. Future targeted trials in learning the mechanism of action of these herbal remedies are warranted.

Long-term research has been carried out to support the use of established remedies. Development of novel drug delivery systems for all herbal ingredients are likely to be one of the thrust-hold area of research in future perspective.

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