

Local Drug Delivery

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ABSTRACT: *Periodontal diseases are considered infection of the periodontium, because there is bacterial etiology, an immune response, and tissue destruction. Putative pathogens associated with periodontal diseases are susceptible to a variety of antiseptics and antibiotics. Methods employed to convey antimicrobial agents into periodontal pockets have included rinsing, irrigation, systemic administration, and local application using sustained and controlled delivery devices. Mechanical therapy itself may not always reduce or eliminate the anaerobic infection at the base of pocket, with in the gingival tissues and in both structures inaccessible to periodontal instruments.*

To overcome this, addition of antimicrobials both systemic and locally would enhance a treatment protocol and serve as adjuncts to mechanical therapy. Systemic antimicrobial agents may reduce or eliminate bacteria that cannot be removed by scaling and root planning. However, adverse effects such as drug toxicity, acquired bacterial resistance, drug interaction and patient's compliance limit the use of systemic antimicrobials.

Thus to override these short comings, local deliveries of antibacterial agents into periodontal pockets have been extensively studied. This modom of drug delivery limits the drug to its target site and hence achieving a much higher concentration.

Keywords —Antimicrobials, Systemic antibiotics, Delivery agents, Irrigation devices, Drug toxicity.

I. INTRODUCTION

The inflammatory periodontal diseases are widely accepted as being caused by bacteria associated with dental plaque. However, the nature of the periodontal disease resulting from dental plaque appears to depend to a large extent on the interaction among the bacterial agent, the environment, and the response of the host's defense mechanisms to the bacterial assault[1].

Since the early 1970's, the quest to identify bacterial specificity in periodontal disease became the prominent area of investigation. This lead Loesche (1976) to promulgate the specific plaque hypothesis, suggesting that specific bacteria caused specific forms of periodontal diseases. Increasing knowledge of anaerobic bacteria as predominant agents in the development of periodontal disease has led to new treatment strategies, aiming primarily at suppression or elimination of specific periodontal diseases. Non-surgical and surgical therapy is both applicable in the treatment of periodontal disease. However, mechanical therapy itself may not always reduce or eliminate the anaerobic infection at the base of pocket, with in the gingival tissues and in both structures inaccessible to periodontal instruments [2]. Moreover, recolonization of disease associated bacteria occurs from the residual bacterial reservoir in dentinal tubules causing renewal of the inflammatory state[3]. To overcome this, addition of antimicrobials both systemic and locally would enhance a treatment protocol and serve as adjuncts to mechanical therapy. Systemic antimicrobial agents may reduce or eliminate bacteria that cannot be removed by scaling and root planning. However, adverse effects such as drug toxicity, acquired bacterial resistance, drug interaction and patient's compliance limit the use of systemic antimicrobials[4].

Therefore to override these short comings, local deliveries of antibacterial agents into periodontal pockets have been extensively studied. It was Dr. Max Goodson in 1979 that championed and developed local delivery of therapeutic agents into a viable concept. This modom of drug delivery avoids most of the problems associated with systemic therapy, limiting the drug to its target site and hence achieving a much higher concentration[5]. For local delivery in the subgingival areas, various antimicrobials have been tried e.g. tetracycline, chlorhexidine and metronidazole[6]. Similarly, various studies have been conducted on the different modes of local delivery of the antimicrobials subgingivally. Local antimicrobial therapy in periodontitis involves direct placement of an antimicrobial agent(s) into subgingival sites, minimizing the impact of the agent(s) on non oral body sites. Local antimicrobial agents may be personally applied as a part of home oral hygiene regimens, and professionally applied as part of office-based treatment procedures.

Local antimicrobial delivery into periodontal pockets may be further classified as providing either nonsustained or sustained subgingival drug delivery. Nonsustained subgingival drug delivery provides high pocket concentrations of the antimicrobial agent for only short time periods. Subgingival irrigation with antiseptic agents lacking substantivity for oral tissues (povidone-iodine) is examples of nonsustained subgingival drug delivery. Sustained subgingival drug delivery provides retention of the within periodontal pockets. Controlled drug release can be provided with subgingival irrigation of agents intrinsically substantive for tooth root surfaces (aqueous tetracycline) or pocket placement of commercial antimicrobial fibers, gel or films.

Locally applied antimicrobial agents should be safe, stable, substantive, efficacious, cost effective, patient compliant, achieve effective concentrations. Factors affecting the bio-availability of an antimicrobial agent are solubility, pH and ion-binding capacity, delivery vehicle-drug interaction and metabolism.

II. SUPRAGINGIVAL IRRIGATION

Home irrigation devices allow the patient to deliver medicaments into the periodontal pocket at home on more frequent basis than is practical with professional gingival irrigation, the ability of the device to gain access to the depth of periodontal pocket and the manual dexterity of the patients are the limiting factors [7,8]. The mechanism of action of irrigation occurs through the direct application of a pulsed or steady stream of water or other solution. Studies by (Bhasker [9,10] et al and Selting [11] et al) have found pulsation and pressure to be critical components of an irrigation device. The pulsation creates two zones of hydrokinetic activity. The impact zone is where solution initially contacts the surface and flushing zone is where solution reaches into the subgingival sulcus. The outcome of hydrokinetic activity is subgingival penetration [12]. Home irrigation devices include supragingival and subgingival devices. Irrigation with a standard jet tip is generally called supragingival irrigation. Tip is placed coronal to gingival margin. Oral irrigation devices with traditional jet tip results in greater access of medicament to periodontal pocket when compared with rinsing alone. A 90 degree angle of application to the tooth surface provides 71% penetration in shallow pockets [13]. These devices may be useful in delivering of medicaments in cases of gingivitis with shallow pocket depths, they are less useful in delivering medicaments in periodontitis patients with deeper pockets. They are mainly used for full mouth irrigation.

III. SUBGINGIVAL IRRIGATION

Irrigation with the soft, site specific tip is often called subgingival irrigation. This also refers to placement of tip, which is placed slightly below the gingival margin. These devices generally include blunt end metal cannula that the patient inserts into the periodontal pocket, this increases the depth of penetration of fluid but has the potential for injury owing to the metal tip (Greenstein 1992) [14]. The subgingival tip is generally used for the localized irrigation of specific site, such as a deep pocket, furcation, implant, or crown and bridge. Studies have shown that it can deliver solution into a pocket of 6mm or less up to 90% of its depth. In pockets greater than 6mm, the depth of penetration has been shown to 64% [15]. Professional subgingival irrigation device include a wide range of powered and manually operated irrigations. Irrigation using a syringe with blunt end cannula attached to an oral irrigator can penetrate to 71.5% of the pocket depth in pocket 3.5 to 6 mm deep (Hollander 1989) [16]. Vehicles tested for sustained periodontal pocket delivery of antimicrobial agents include solution pastes, hollow fibre, acrylic strips, monolithic fibres, resorbable cellulose, collagen and biodegradable gel [17].

IV. LOCAL ANTIMICROBIAL AGENTS

A local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent in subgingival sites compared with a systemic drug regimen. For example, local placement of a tetracycline-releasing ethylene vinyl acetate monolithic fiber can yield tetracycline concentrations in excess of 1300 Fg/ml in gingival crevicular fluid over 10 days. In comparison, repeated systemic doses of tetracycline- HCl can only provide tetracycline levels of 4-8 pg/ml in gingival crevicular fluid [18]. Disadvantages of local antimicrobial treatment of periodontitis include difficulty in placing therapeutic concentrations of the antimicrobial agent into deeper parts of periodontal pockets and furcation lesions. Personal application of antimicrobial agents by patients as a part of their home self-care procedures is frequently compromised by the patient's lack of adequate manual dexterity, limited understanding of periodontal anatomy, and poor compliance and performance with recommended procedures.

The task of professionally applying local antimicrobial agents in periodontitis patients with numerous advanced lesions distributed throughout their mouth is time-consuming and labor-intensive. Nonsustained subgingival drug delivery is limited by a only brief exposure of the target microorganisms to the applied antimicrobial agent. Antimicrobial agents locally applied into periodontal pockets do not markedly affect periodontal pathogens residing within adjacent gingival connective tissues and on extra-pocket oral surfaces

(tongue, tonsils and buccal mucosa), which increases the risk of later reinfection and disease recurrence in treated areas. Local agents used for irrigation includes chlorhexidine, povidine iodine, stannous fluoride ,hydrogen peroxide.

V. INHIBITION OF PERIODONTAL DISEASE PROGRESSION

There are conflicting data with respect to the efficacy of minocycline gel (applied two times) in deep pockets (≥ 7 mm). Timmerman et al (1996) [19] reported that there was no benefit of employing 2% minocycline gel as an adjunct to SRP to reduce probing depths at deep sites, whereas van Steenberghe et al (1999) [20] noted that combined therapy provided a better result than SRP alone at sites ≥ 7 mm deep. When Michalowicz et al (1995) [21] monitored the number of sites manifesting a loss of clinical attachment (a 1-mm threshold) after placement of tetracycline fibers plus SRP versus SRP alone, they reported less disease progression after combined therapy (4% versus 9% of all the treated sites; $N > 200$ sites per group; 9-month monitoring period). In another study that compared doxycycline gel versus SRP, there was no statistically significant benefit regarding inhibition of disease progression associated with drug therapy (Garrett et al 1999) [22]. After employing chlorhexidine chips plus SRP, Jeffcoat et al [23] noted that these sites achieved a mean 0.1 mm gain of bone, whereas 15% of the sites administered SRP alone lost bone (0.04mm) during a 9-month clinical trial . Overall, it is difficult to project outcomes regarding the ability of local drug delivery to inhibit disease progression because a limited number of studies, diverse study protocols, and different thresholds for disease progression were used.

VI. COMPARISON: SYSTEMIC VERSUS LOCAL DRUG DELIVERY OF ANTIBIOTICS

Local and systemic drug therapies provide different benefits. For example, local drug delivery provides a high drug concentration, it is efficacious, there are limited side effects, and it does not need to be administered daily for a defined time period. On the other hand, systemic administration of antibiotics facilitates treatment of bacterial reservoirs of reinfection such as the tonsil, saliva, and tissue invasive bacteria (Greenstein G 1998) [24]. It also is more time efficient for the clinician, costs less, and multiple drugs can be used simultaneously. However, the issue is unresolved with respect to the number of sites that should be treated with local drug delivery before it is deemed more practical to treat with systemic antibiotics. Clinicians need to make this determination for each patient requiring adjunctive anti-infective therapy.

When the efficacy of local and systemic drug delivery was directly compared among individuals with chronic periodontitis, the results were not statistically significantly different [25]. However, there are limited data directly comparing the efficacy of local and systemic drug delivery systems. Therefore, when contemplating administering localized adjunctive drug delivery, clinicians should consider data pertaining to the efficacy of systemic drug delivery at deep probing sites [26] and successful treatment among patients non – responsive to conventional therapy.

In addition, patients infected with *Actinobacillus actinomycetemcomitans* (Aa), a tissue invasive organism, present a distinct problem, because these individuals often do not respond to conventional therapy (Slots 1999, Van Winkelhoff, 1996) [27,28]. With regard to the efficacy of local drug delivery among patients infected with *Actinobacillus actinomycetemcomitans*, Mandell et. al. 1986 indicated that tetracycline fibers failed to reduce *Actinobacillus actinomycetemcomitans* levels, Reip et al 1999 [29] noted that *Actinobacillus actinomycetemcomitans* was suppressed but not eliminated after metronidazole gel was administered. Similarly, Mombelli et al. 2002 [30] reported that local delivery with tetracycline fibers was not effective in the treatment of Aa infections. Furthermore, it also should be noted that it may be prudent to culture and perform antibiotic sensitivity testing to ensure selection of the most effective drug therapy among individuals who do not respond to conventional therapy.

VII. CONCLUSION

A substantial amount of information has become available and at present the following trends may be identified with regards to various local delivery systems. As a monotherapy, local drug delivery systems incorporating a variety of drugs can improve periodontal health. There is no single universal drug that would be effective in all situations. Therefore, at non-responsive sites, bacterial and antibiotic sensitivity testing may be necessary to determine putative pathogens and their susceptibility to specific antimicrobial agents.

Local drug delivery often appears to be as effective as scaling and root planing with regards to reducing signs of periodontal inflammatory disease : redness, bleeding upon probing, probing depth, and loss of clinical attachment .Local drug delivery systems usually do not provide a benefit beyond what is achievable with conventional scaling and root planing in the treatment of adult periodontitis. Therefore, their routine utilization is unnecessary.

Local delivery may be an adjunct to the conventional therapy. The sites most likely to be responsive to this adjunctive treatment method may have refractory or recurrent periodontitis, or specific locations where it is difficult to instrument root surfaces. However, the data are limited to support this concept. At present, there are

insufficient data to indicate that one local drug delivery device is clearly superior to all the other systems. However, desired characteristics include ease of placement, controlled release of drugs and resorbability. In conjunction with conventional treatment, systemically administered drugs appear to be as effective as local drug delivery.

To date, results from studies assessing local drug delivery systems have not justified extending the time interval between supportive periodontal maintenance visits. There are preliminary, but very limited data, regarding the ability of local delivery to help suppress future disease progression. There are insufficient data to indicate that local drug delivery induces bacterial resistance to antimicrobial agents. Long term studies are needed to address this important issue.

Prudent administration of antimicrobial agents following judicious pharmacologic principles will preclude the abuse of chemotherapeutic agents and reduce the potential of developing or selecting drug resistant bacterial strains. Local drug delivery systems with controlled release properties have the potential to be used as a therapeutic component in the management of periodontal diseases. However, additional randomized, controlled studies are needed to help delineate the types of lesions, periodontal diseases, or specific situations where local delivery systems would be most beneficial.

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