SYSTEMIC VS LOCAL DRUG DELIVERY SYSTEMS IN THE TREATMENT OF PERIODONTAL DISEASES-A REVIEW.

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ABSTRACT

Periodontitis is an inflammatory response to bacteriological infections that destroys the attachment of teeth resulting in periodontal pocket formation. Treatment of periodontitis varies widely from non-surgical to surgical options depending on how far the disease has progressed. Nonsurgical methods are systemic delivery of antimicrobials, scaling and root planing and local delivery of drug. Each drug delivery system has its merits and demerits. The success of any drug delivery system designed to target periodontal infections depends upon its ability to deliver the antimicrobial agents to the base of the pocket at a bacteriostatic or bactericidal concentration. This article highlights the impact of Systemic Vs Local drug delivery in the treatment of Periodontal diseases.

KEYWORDS

Periodontitis, Systemic drug delivery, Local drug delivery, Periodontal Pockets.
INTRODUCTION

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both."\(^1\) The inflammation in the periodontal tissue is initiated by microbial plaque and bacterial infection. The nature of the periodontal disease depends on the interaction among the bacterial agent, environment, and host’s defense mechanisms to the bacterial challenges mainly in form of gram negative anaerobic bacteria.\(^2\)

It is considered to be an infection because there is a bacterial etiology and an immune response. Once destruction of tissue occurs, the condition is referred to as a disease. Usually, the host response can contain subgingival bacterial challenges and subclinical infections, which are resolved without any clinical manifestation or pathosis.\(^3\) However, if the host-parasite equilibrium is lost, an exuberant host response can result in destruction of the periodontium too. It is a well-established fact that periodontal disease is the result of local bacterial infection with pathogenic microflora such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroids forsythus, Peptostreptococcus micros, Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Eubacterium spp, Treponema denticola, Selemonas spp., beta hemolytic streptococci, a variety of enteric rods and pseudomonas, enterococci, staphylococci and possibly also yeasts within the periodontal pocket.\(^2,4\)

Aim of the periodontal treatment is to eradicate gingival inflammation, bleeding, periodontal pocket depth and to arrest destruction of bone, by removal of the bacterial deposits, thus shifting the pathogenic microbiota to one compatible with periodontal health. Mechanical scaling and root planing (SRP) is the therapeutic approach for periodontitis.\(^5\) However, the effectiveness of the conventional treatment is limited by the lack of accessibility to bacteria in deeper periodontal area leading to reinfection of these sites.\(^6\) It was concluded that such cases could be related to persistence of pathogens in the pocket or production of specific virulence factors interfering with the host cell (eg. leukotoxin) or recolonization of treated sites from reservoirs of bacteria in dentinal tubules and soft tissues.\(^7\) Inspite of the excellent results achieved, mechanical debridement alone, has shown to leave behind a significant number of pathogenic microorganisms in relatively inaccessible areas.\(^8\)

A microbiological approach to periodontal therapy aims primarily at suppressing specific pathogenic bacteria and permitting subsequent recolonisation of microbiota compatible with health.\(^8\) Studies conducted, revealed antimicrobial agents to be helpful as adjuncts in treating periodontal disease, hence investigators sought different methods to deliver these antimicrobials to periodontal pockets. The various methods employed, have included rinsing, irrigation, systemic administration and local application using sustained and controlled delivery devices.\(^8\)

For an antibiotic to be effective in periodontal treatment, it must penetrate well into the gingival sulcus and produce gingival fluid concentrations higher than the minimum inhibitory concentrations (MIC) of the suspected pathogens.\(^9\) Understanding of etiology and pathogenesis of periodontitis have led to increasingly
effective pharmacological interventions. In this regard, safe and intrinsically efficacious medications can be delivered into periodontal pockets to suppress or eradicate the pathogenic microbiota or modulate the inflammatory response, thereby limiting tissue destruction.

Each drug delivery system has its merits and demerits. The success of any drug delivery system designed to target periodontal infections depends upon its ability to deliver the antimicrobial agents to the base of the pocket at a bacteriostatic or bactericidal concentration. It must also facilitate retention of the medicament long enough to ensure an efficacious result.[11]

**SYSTEMIC DRUG DELIVERY**

In the last 25 years, reports stating that systemically administered antibiotics are excreted via saliva and gingival fluid, have triggered great interest in antibiotic therapy.[10] It has been shown that systemic administration of antibiotics results in changes in plaque flora, reduction in gingivitis and decrease in the rate of bone resorption. In systemic administration, however, the drug must be given in high doses in order to maintain effective concentration of the drug in the gingival crevicular fluid.[11]

Systemic periodontal antimicrobial therapy is based on the premise that specific microorganisms cause destructive periodontal disease and that the antimicrobial agent in the periodontal pocket can exceed the concentration necessary to kill the pathogens.[11] The systemic antimicrobial agents enter periodontal pockets following their intestinal absorption and passage from the blood stream into oral tissues, gingival crevicular fluid and saliva.[12]

**Various systemic delivery antimicrobials available** –

Single drug therapies with penicillins, tetracyclines, metronidazole or clindamycin have been used frequently in periodontal practice.[8] However, since periodontitis lesions often harbor a mixture of pathogenic bacteria, drug combination therapies have gained increased importance.[8,13] Valuable combination therapies include metronidazole–amoxicillin for A. actinomycetemcomitans and various anaerobic periodontal infections[14,15] and metronidazole–ciprofloxacin for mixed anaerobic and enteric rod/ Pseudomonas periodontal infections.[16]

**Advantages**[11]

1. Systemic antibiotics can reach microorganisms at the base of deep periodontal pockets and furcation areas, via the serum.
2. Affects tissue invasive organisms – residing within the connective tissues.
3. Eradication of periodontal pathogens colonizing the oral mucosa and other extra dental sites – the potential reservoirs of bacterial reinfection.
4. Multiple sites are treated simultaneously.
5. Less time consuming (when compared to local drug delivery).
6. A variety of drugs are available.

**Disadvantages**

1. Development of resistant bacterial strains.
2. Superimposed infections.
3. Uncertain patient compliance.
4. Possible allergic sensitization of patients.
5. The drug must be given in high doses in order to maintain an effective drug concentration in the gingival crevicular fluid. This may result in various side effects like nausea, vomiting and gastrointestinal disturbances.

**IMPACT OF SYSTEMIC DRUG DELIVERY IN PERIODONTAL THERAPY**

Systemic antibiotic therapy does not significantly affect supragingival plaque accumulation. Reduction in dental plaque depends mostly on patients’ oral hygiene efforts. However, Ng & Bissada (1998) reported that systemic doxycycline administration for 6 weeks was associated with significantly reduced plaque accumulation and gingival inflammation at week 12 post treatment compared with placebo.

Systemic antibiotics might not have a significant effect on gingival inflammation, with the possible exception of metronidazole, doxycycline and metronidazole–amoxicillin combinations. It might be that systemic antibiotic therapy is ineffective against gingival inflammation related to supragingival plaque but may help decrease gingivitis caused by susceptible subgingival microorganisms.

Several systemic antibiotic therapies have no significant impact on periodontal pocket depth compared with controls. However, Noyan et al. (1997) and Elter et al. (1997) reported that 7 days of metronidazole therapy reduced pocket depth significantly compared with controls. Winkel et al. (2001) showed that 7 days of metronidazole–amoxicillin combination therapy produced greater probing depth reduction and significantly increased the proportion of periodontal sites gaining clinical attachment than did control medication, especially in pockets having initial depths greater than or equal to 7 mm. Various studies showing the impact of systemic drug delivery in periodontal therapy shown in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects(age) and Periodontal Condition</th>
<th>Systemic antibiotic regimen</th>
<th>Periodontal treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng &amp; Bissada (1998)</td>
<td>32 patients (32–72 years) Generalised moderate adult periodontitis</td>
<td>Doxycycline 200 mg for the first day and then 100 mg, once daily for 6 weeks</td>
<td>Each group was divided into Split-mouth design: half of the mouth received one session of root planing; the other half received no local Therapy.</td>
<td>Significant reduction in the proportion of plaque accumulation and gingival inflammation at week 12 post treatment compared with placebo.</td>
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<tr>
<td>Watts et al. (1986)</td>
<td>Test: 13 patients Control: 7 patients Adult periodontitis</td>
<td>Metronidazole 200 mg, three times daily 7 days Placebo, three times daily, 7 days</td>
<td>Scaling and root planing followed by random assignment to either antibiotic or placebo group.</td>
<td>Significant reduction in the proportion of gingival bleeding sites compared with controls</td>
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<td>Lopez &amp; co-workers (1998)</td>
<td>Test: 23 patients (mean age: 44 years) Placebo: 21 patients (mean age: 44 years) Moderate to advanced adult periodontitis</td>
<td>Metronidazole200 mg, three times daily +amoxicillin 375mg, three times daily, 8 days</td>
<td>Subjects were randomly assigned to receive antibiotics or placebo. No effort was made to change the oral hygiene habits of the patients.</td>
<td>Less gingival bleeding for up to 12 months compared with placebo.</td>
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<tr>
<td>Noyan et al. (1997)</td>
<td>10 patients (35–51 years) Test: 5</td>
<td>Metronidazole 250 mg, three times daily 7 days</td>
<td>Patients divided into 2 groups (5 patients each) consisting of 1</td>
<td>Reduced pocket depth significantly as compared with</td>
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</table>
Control: 5 Adult periodontitis

Scaling and root planing 2) Systemic metronidazole treatment. Only data for systemic antibiotic group (test), and scaling and root planing group (control) were presented.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Patients</th>
<th>Antibiotic Therapy</th>
<th>Probing Depth</th>
<th>Clinical Attachment Gain</th>
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<tbody>
<tr>
<td>Winkel et al. (2001)</td>
<td>22 patients (29–54 years) A. actinomycetemcomitans positive periodontitis combined with either P. gingivalis, B. forsythus, P. intermedia co-infection</td>
<td>Metronidazole 250 mg, three times daily + amoxicillin 375 mg, 3 times daily, for 7 days</td>
<td>Scaling and Root planing with oral hygiene instructions were given. 6 weeks later, Repeated the same with antibiotic therapy and placebo was given.</td>
<td>Probing depth reduced, significantly increase in proportion of clinical attachment levels.</td>
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<tr>
<td>Collins et al. (1993)</td>
<td>30 patients (23–70 years) Refractory periodontitis</td>
<td>Amoxicillin 250 mg with Clavulanic acid (125 mg), four times daily, 14 days in conjunction with subgingival delivery of povidone–iodine, and chlorhexidine mouthwash rinses twice daily.</td>
<td>Refractory treatment protocol consisted of systemic antibiotic therapy, topical povidone–iodine, 3% hydrogen peroxide rinse to remove coronal staining, and twice-daily with chlorhexidine (0.12%) rinse</td>
<td>Reduced probing depth with 56% decrease in the number of pockets &gt; 6 mm at 6 weeks post treatment. Clinical attachment gain of at least 1 mm in 41% of deep sites at 3 years post treatment.</td>
</tr>
</tbody>
</table>
The value of systemic antibiotics in patients with chronic periodontitis is not clear. With the adverse effects such as development of microbial resistance, host hypersensitivity and superimposed infections, management of severe types of periodontitis should not rely solely on systemic antibiotics but upon a combination of mechanical debridement possibly in conjunction with surgery, subgingival administration of antiseptics by dental professionals, patient’s oral hygiene efforts and effective and safe systemic antibiotics.[24]

**LOCAL DRUG DELIVERY**

Ever since the introduction of systemic antibiotics, various drugs have been used in the treatment of periodontitis. The various disadvantages of systemic antibiotics had led to the introduction of local drug delivery as the treatment option. It was in the year 1979, Dr. Max Goodson et al first proposed the concept of controlled delivery in the treatment of periodontitis. Since then, a number of studies have been carried out over the years with different antimicrobial agents and in different clinical situations.[25]

Local antibiotic therapy involves the direct placement of an antimicrobial agent into subgingival sites, minimizing the impact of the agent on non oral body sites.[5] The primary goal in using an intra-pocket device for the delivery of an antibacterial agent is the achievement and maintenance of therapeutic levels of the drug for the required period of time. This inhibits or kills the pathogens, without any harm to the tissues. Studies suggest that the critical period of exposure of the pocket to an antibacterial agent is in the range of 7-10 days.[25]

Local delivery of drug proves to be more superior than systemic drug administration in periodontitis patients as Local drug delivery provides, High drug concentration, Minimal side effects and less reliance on patient compliance for taking the medication.[25]

Noyan et al (1997)[21] reported local metronidazole in combination with scaling and root planing to be more effective than systemic metronidazole in terms of producing both clinical and microbial improvements in adult periodontitis patients.

Akalin et al (2004)[26] compared the clinical efficacies of systemic Doxycycline (SD) and local Doxycycline (LD) in the treatment of chronic periodontitis in 45 patients and the results showed that the Local Doxycycline treatment provided significantly higher Probing Depth reduction than the Systemic Doxycycline treatment.

**Indications for LDD**[27,28]

1) Isolated periodontal pockets (>5mm), with successful phase 1 therapy (scaling and root planing),
2) Medically compromised patients where surgical therapy is contraindicated.
3) As an adjunct to mechanical debridement,
4) In patients suffering from recurrent or refractory periodontitis.
5) Periodontal Maintenance Therapy

**Contraindication of LDD** [27,28]

1) Periodontal patients with known hypersensitivity reaction to any of the antimicrobials for periodontal therapy.
2) Patients susceptible to infective endocarditis are contraindicated for irrigation devices to avoid the risk of bacteremias.
3) Delivery of antimicrobial agents using ultrasonic scalers are contraindicated in asthmatics, infective conditions (AIDS, TB etc) and those with cardiac pacemakers.
4) In pregnant and lactating mothers where use of the particular antimicrobial is contraindicated.

**Various local delivery antimicrobials available are** [29,30]

1. Tetracycline – non resorbable fibres
2. Metronidazole gel
3. Minocycline ointment
4. Chlorhexidine chips
5. Doxycycline hyclate in a resorbable polymer
6. Resorbable tetracycline in fibrillar collagen
7. Minocycline microspheres
8. Azithromycin gel

Vehicles that have been employed for sustained delivery in periodontics include pastes, ointments, gels, fibers, strips, spheres, discs and chips.

**Advantages of LDD** [31]

1. Improved patient compliance
2. Improved pharmacokinetics
3. Improved drug access to the site of disease
4. Lowers the total drug dosage
5. No risk of emergence of resistant microorganism
6. Drug can reach the site of action in adequate concentration
7. Maintain the drug level for a sufficient period of time
Disadvantage of LDD \[^{[32]}\]

1. Time consuming and laborious
2. Difficulty in placing therapeutic concentration of antimicrobial agent into deeper periodontal pockets and furcation lesions
3. Personal application of antimicrobial agents by patients as a part of their home self-care procedure is compromised.

**IMPACT OF LOCAL DRUG DELIVERY IN PERIODONTAL THERAPY**

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis.\[^{[25]}\] It has been observed that the local route of drug delivery can attain 100-fold higher concentrations of an antimicrobial agent at subgingival sites compared with a systemic drug regimen. This reduces the total patient dose by over 400 fold thereby reducing the potential problems with the use of systemic antibiotic drug regimens and development of drug-resistant microbial populations at non oral body sites. These can be safely used in medically compromised patients for whom surgery is not an option and contraindicated in patients with known hypersensitivity to the antimicrobial used, asthmatics and infective conditions such as AIDS, Tuberculosis.\[^{[31]}\]

Feasibility of treating periodontal disease by controlled drug delivery of antimicrobials from within the pocket with tetracycline filled hollow fibers placed in the gingival sulcus to have a dramatic effect both on the periodontal microflora and the clinical manifestations of the disease. The fibers released the entire drug in the first 2 hours.

Various studies showing the impact of local drug delivery in periodontal therapy are shown in Table 2.

Table:-2

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects(age) and Periodontal condition</th>
<th>Local drug therapy used</th>
<th>Periodontal Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindhe et al (1979)[^{33}]</td>
<td>5 patients with Adult periodontitis</td>
<td>Local tetracycline delivery using hollow fibre devices for 2 days</td>
<td>Each patient had four pairs of contralateral sites that were treated either by scaling or tetracycline application and one pair was used as an untreated control.</td>
<td>Improvement seen in both microbial and clinical parameters similar to scaling and root planing during the short term evaluation.</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Patients</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>Minabe et al (1991)</td>
<td>16 patients with Periodontal disease</td>
<td>Tetracycline cross linked collagen film for 9 weeks</td>
<td>Selected patients were randomly allocated to: 1) 4 consecutive administration of tetracycline immobilized cross linked collagen film (TC film) at intervals of 1 week (TC group); 2) Root planing treatment (RP group); 3) Combination (TC + RP group); 4) No treatment (control group). By the end of 9 weeks all the groups showed a reduction in the clinical parameters. TC+RP group showed significant reduction in bleeding on probing and gain in clinical attachment levels.</td>
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<tr>
<td>Jones et al (1992)</td>
<td>Adult periodontitis</td>
<td>2% minocycline</td>
<td>All patients were given a single sitting of scaling and root planing then divided into experimental and control groups. The experimental group received 2% minocycline while the control group received only SRP. Sub gingival minocycline as an adjunct to SRP produced significant clinical benefits over SRP alone in patients with adult periodontitis.</td>
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<tr>
<td>Polson et al (1997)</td>
<td>180 patients Moderate to Severe Periodontitis</td>
<td>Subgingivally delivered biodegradable drug delivery system containing either 10% doxycycline hyclate, 5% sanguinariuin for 9 months</td>
<td>10% doxycycline hyclate delivered in a biodegradable delivery system was found to be an effective means of reducing the clinical signs of adult periodontitis.</td>
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</table>
| Jeffcoat et al (2000) | 45 subjects Adult periodontitis | Chlorhexidine-gelatin chip for 9 months | Control groups received either placebo + Scaling or Root planing or SRP alone. SRP treated subjects experienced loss of bone in 1 or more sites, no
Test groups received active CHX chip or SRP alone. Subject treated with active chip+SRP lost bone. CHX chip when used as an adjunct to scaling and root planing significantly reduce alveolar bone loss.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Disease</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eickholz et al (2002)(^38)</td>
<td>111</td>
<td>Moderate to Severe periodontitis</td>
<td>Application of Doxycycline adjunctive to non surgical periodontal therapy over a period of 6 months.</td>
<td>In each patient, 3 different treatment modalities assigned-SRP alone, SRP with subgingival vehicle control and SRP with subgingival application of 15% Doxycycline gel. Adjunctive use of subgingival doxycycline was found to be safe and provide more favourable relative attachment level gain and probing depth reduction.</td>
</tr>
<tr>
<td>Gopinath et al (2009)(^39)</td>
<td>15</td>
<td>Chronic periodontitis</td>
<td>Minocycline microspheres for over 180 days</td>
<td>Scaling and Root planing given to all patients.</td>
</tr>
</tbody>
</table>

Sustained or controlled release local delivery antimicrobial agents are available for use as adjuncts to scaling and root planing in the treatment of periodontitis. These products are placed into periodontal pockets in order to reduce subgingival bacterial flora and clinical signs of periodontitis. A high level of the active agent is deposited in the periodontal pocket and the delivery vehicle facilitates prolonged drug delivery.

Studies assessing the efficacy of local delivery antimicrobial agents generally show statistically significant improvement in clinical and microbial parameters. However, whether they can reduce the need for surgery, improve long-term tooth retention or are cost effective would need to be ascertained in further studies.

Clinicians can thus consider the use of local delivery antimicrobial agents in treatment of chronic periodontitis as an adjunct to scaling and root planing when localized recurrent and/or residual probing depth \(\geq 5\) mm with inflammation is still present following conventional therapies.
CONCLUSION

The requirements for treating periodontal disease include means for targeting an anti-infective agent to infection sites and sustaining its localized concentration at effective levels for a sufficient time while concurrently evoking minimal or no side effects. At present, there is no single universal drug or delivery device that would be effective in all situations. Currently, a lot of research is being undertaken, incorporating a variety of drugs and the different modes or vehicles to dispense them. The clinician’s decision to use drug deliveries should be based upon a consideration of clinical findings, the patient’s dental and medical history, scientific evidence, patient preferences, and advantages and disadvantages of alternative therapies.

REFERENCES


