

Research Article

Local Drug Delivery: A Comparative Study Between Two Agents of Same Group

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ABSTRACT

Background: Periodontitis, a disease involving supportive structures of the teeth prevails in all groups, ethnicities, races and both genders. The relationship between bacterial plaque and the development of periodontal disease is well established. Antibacterial agents have been used effectively in 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. Systemic administration of drugs leads to therapeutic concentrations at the site of infection, but for short periods of time, forcing repeated dosing for longer periods. Local delivery of antimicrobials has been investigated for the possibility of overcoming the limitations of conventional therapy. The use of sustained release formulations to deliver antibacterials to the site of infection (periodontal pocket) has recently gained interest. These products provide a long-term, effective treatment at the site of infection at much smaller doses.

Methods: A case-control study was carried out on 60 patients suffering from chronic periodontitis. In Group A only scaling and root planing was carried out

whereas in Group B tetracycline fibers were used along with scaling and root planning and Group C Doxycycline gel was used with scaling and root planning

Result: Tetracycline fibers & Doxycycline gel as an adjunct to scaling and root planing was found to be more effective in reducing inflammation than scaling & root planing alone. The number of sites with bleeding on probing were 4 in Group C as compared to 7 in Group B after 30 days. The mean decrease in probing depth was more in Group C than Group B & A after 30 days. General linear model showed that decrease in probing depth was only slightly statistically significant with both mechanical therapy as well as adjunctive use of tetracycline fibers.

Conclusion: Local drug delivery with doxycycline gel & tetracycline fibres is an effective and simple non surgical method to improve periodontal health which can be practiced even by a general dental practitioner.

INTRODUCTION

Periodontal diseases are considered as infections of periodontium with a bacterial etiology, an immune response and subsequent tissue destruction.¹ Putative pathogens associated with periodontal disease are susceptible to a variety of antiseptics and antibiotics.^{2,3}

Methods employed to convey antimicrobial agents into periodontal pockets include rinsing, irrigation, systemic administration and local application using sustained and controlled delivery devices.

Several studies for controlling the subgingival plaque by local drug delivery have been published by other investigators. These methods, using hollow-fiber devices (Lindhe et al, 1979), acrylic resin strips (Addy et al, 1982), and monolithic fibers (Goodson et al, 1983), seem to be effective in changing the microflora in periodontal pockets and in reducing periodontal inflammation.

Tetracycline hydrochloride is a semi-synthetic antibiotic effective against all gram positive & many gram negative bacteria and exerts antibacterial activity by inhibiting bacterial protein synthesis⁴. It is the first antibiotic whose efficacy was evaluated in periodontal studies. Apart from its antimicrobial activity it exhibits additional pharmacological activities such as collagenase inhibition. The drug is acidic & demineralises dentin & cementum which may enhance attachment of fibroblast to the root surface. These properties are of significance in the management of periodontal diseases. Tetracyclines are bacteriostatic for many pathogens at concentrations found in the gingival crevicular fluid after systemic administration (3-6 microgram/ml). However, local delivery of these agents provides high concentrations that are bacteriocidal. Local application of tetracyclines has been associated with minimal side effects.

Doxycycline is potentially valuable antibiotic with broad spectrum of activity against numerous periodontal pathogens. It has the ability to concentrate in the gingival crevicular fluid at a levels substantially greater than in the serum.^{5,6} It demonstrate anticollagenolytic & antiproteolytic activity that aid in osseous regeneration & also help in periodontal disease progression. In the present study the role of tetracycline fiber & Doxycycline polymer gel in periodontal therapy is assessed as both are broad spectrum antibiotics capable of achieving high concentration in the sulcular fluid.

MATERIALS AND METHOD

The study was carried at Dr Z.A Dental College, Department of Periodontics, AMU, Aligarh on 60 patients suffering from chronic periodontitis with probing depth of 5mm. In each patient two quadrants were selected which were divided in three groups:

Control Group(Group A). - Only scaling and root planing (SRP) was carried out
Experimental Group (Group B). - SRP + tetracycline fiber
Experimental Group(Group C). - SRP + Doxycycline polymer

The teeth selected in three groups were molars and premolars only. The clinical parameters obtained at each test site were:

- (i) Probing depth using Williams probe
- (ii) Bleeding on probing (BOP)

The tetracycline fiber marketed as periodontal plus AB is available as vials with tetracycline impregnated collagen fibers. These fibers are brownish in color and resorbable. These fibers are soaked

in saline and packed into the periodontal pockets with a cotton forcep or curette until the pocket is filled upto or slightly below the gingival margin. To avoid dislodging of the fiber patients were instructed not to brush or floss the treated areas and were placed on twice a day 0.2% chlorhexidine rinses.

The ATRIDOX is a subgingival controlled-release product composed of a two syringe mixing system. Syringe A contains 450 mg of bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains 50 mg of doxycycline hyclate which is equivalent to 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% of doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days.

The clinical parameters including pocket depth were recorded on Day 0 and 30 days. The data was subjected to statistical analysis.

RESULTS

TABLE 1: Mean \pm SD of Pocket Depth in various groups

| Groups | Baseline | 30 days |
|---------|-------------------|-------------------|
| Group A | 7.6 \pm 0.5164 | 4.9 \pm 0.73786 |
| Group B | 7.8 \pm 0.63246 | 4.6 \pm 0.84327 |
| Group C | 8.1 \pm 0.73786 | 4.5 \pm 0.52705 |

TABLE 2: Comparison of pocket depth between Group A & Group B after 30 days

| | Mean \pm SD | t value | p value |
|---------|-------------------|---------|---------|
| Group A | 4.9 \pm 0.73786 | 1.1973 | 0.2386 |
| Group B | 4.6 \pm 0.84327 | | |

TABLE 3: Comparison of pocket depth between Group B & Group C after 30 days

| | Mean \pm SD | t value | p value |
|---------|-------------------|---------|---------|
| Group B | 4.6 \pm 0.84327 | 1.9728 | 0.0558 |
| Group C | 4.5 \pm 0.52705 | | |

TABLE 4: Comparison of pocket depth between Group A & Group C after 30 days

| | Mean \pm SD | t value | p value |
|---------|-------------------|---------|---------|
| Group A | 4.9 \pm 0.73786 | 0.4497 | 0.6555 |
| Group C | 4.5 \pm 0.52705 | | |

TABLE 5: Comparison of bleeding on probing

| | Group A | Group B | Group C |
|-------------------|---------|---------|---------|
| SITES WITH BOP | 6 | 7 | 4 |
| SITES WITHOUT BOP | 14 | 13 | 16 |

RESULTS

The analysis of the data indicates the following:

- a) SRP, use of tetracycline fiber & Doxycycline gel as an adjunct to SRP are all effective in reducing bleeding on probing and probing depth.
- b) Use of doxycycline gel as an adjunct to SRP is more effective in reducing inflammation than SRP alone & tetracycline fibres and SRP (Table 5).
- c) Use of doxycycline gel as an adjunct to SRP shows better results than SRP alone & tetracycline fibres when decrease in probing depth is compared in the various groups (Table-2,3,4).
- d) Decrease in probing depth after 30 days following scaling and root planing was statistically significant in all the groups when compared to baseline.
- e) The probing depth after 0 & 30 days were compared in various groups. The results showed that decrease in probing depth after 30 following use of tetracycline as an adjunct to SRP was slightly statistically significant (Table-3).

The results indicated that local drug delivery with tetracycline fibers & Doxycycline gel as an adjunct to conventional therapy is effective in reducing the probing depth but the statistically significant results are obtained using Tetracycline fibers.

DISCUSSION

Dental plaque which is a primary etiological factor for periodontal disease is composed of bacterial aggregates that are adherent to one another and to surfaces and interfaces. These bacteria form a highly resistant biofilm with an exopolysaccharide matrix protection which prevents drug penetration.

Mechanical therapy which disrupts plaque biofilm is effective for the majority of patients with mild to moderate periodontitis. But mechanotherapy has its own limitations as it is a blind procedure performed in a closed environment and instruments may not reach the base of deeper pockets due to tooth or pocket morphology. Hence antimicrobial agents can be used as an adjunct to conventional therapy. Tetracycline group of antibiotic contains Tetracycline HCL, Doxycycline hyclate & Minocycline.

The tetracyclines comprise a group of broad spectrum antimicrobial agents that were introduced into clinical practice in the late 1940's. These are primarily bacteriostatic agents that are effective against many Gram negative species such as *Actinobacillus actinomycetemcomitans*. The proven efficacy of this group of drugs in the management of periodontal diseases may be related not only to their antimicrobial actions but to a number of additional properties that have been recently identified. These include collagenase inhibition, anti inflammatory actions, inhibition of bone resorption and their ability to promote the attachment of fibroblasts to root surfaces.

Consequently tetracyclines have also been used as an adjunct to bone grafting in periodontal defects and as agents for conditioning root surfaces to enhance the regeneration of periodontal tissues. When tetracyclines are taken orally considerations must be given both to the potential unwanted effects and to interactions with other drugs that are taken concurrently. Such problems are minimized however when the drugs are incorporated into controlled slow release

formulations which are currently being researched and marketed for intraoral use. Another injectable biodegradable gel based on poly(DL-lactide) dissolved in a biocompatible solvent N-methyl-2-pyrrolidone (NMP) was widely studied. This injectable gel commercially available as 'Atridox' is loaded with 10% doxycycline hyclate showed high levels of doxycycline (250 mg/ml) in the GCF for a period of seven days. Interestingly, levels of 10–20 mg/ml were still present for three to five days after the polymer had been removed. It is possibly because of minute particles of polymer remaining within the pockets or because of the substantive effects of tetracyclines within the periodontal pocket-adjacent-tooth-surface environment. In another study, Atrigell (10% doxycycline gel) containing 5% sanguinarine was found to be superior to the control in the treatment of adult periodontitis. So Biodegradable gels are other useful prospects for the delivery of therapeutic agents into periodontal pockets.

Goodson et al⁷, observed that tetracycline filled hollow fibers placed in the gingival sulcus have dramatic effect both on the periodontal flora and clinical manifestation of disease. Of theoretical importance was the observation that virtual elimination of spirochetes from the gingival sulcus is possible by a single placement of tetracycline filled hollow fibers and spirochetes once eliminated from a site do not recolonize despite the persistence of viable organisms elsewhere in the mouth. Lindhe et al⁸ in his experiments demonstrated that use of tetracycline filled hollow fiber devices markedly changes the composition of the subgingival flora of initially diseased

periodontal sites. Pavia et al⁹ showed that tetracycline and its derivatives minocycline, oxytetracycline and chlortetracycline strongly adsorb to tooth surfaces retaining their antibacterial activity and are quite effective in treating chronic periodontitis. Thomas et al¹⁰ compared the effects of tetracycline fibers plus scaling and root planing versus scaling and root planing alone. It was observed that the use of fibers provided no significant advantage with regards to probing depth reduction or clinical attachment gain. In 2004 Rodrigues et al¹¹ compared antibiotic resistance profile with local and systemic tetracycline and observed that there are less chances of bacterial resistance with locally delivered tetracyclines. Local drug delivery with tetracycline fibers has also a role to play in the treatment of peri-implantitis sites as observed in microbiological studies¹². To conclude scaling and root planing is an extremely effective treatment modality for controlling early to moderate periodontitis. Although all sites treated do not respond totally, the majority do. This would then leave a minority of sites requiring more aggressive treatment which would include locally delivered antimicrobials because of the infective nature of the disease. It would seem that the tetracyclines afford a unique set of pharmacological properties that are ideally suited for the management of periodontal disease. Review of literature and the result of present study suggest that tetracyclines are a useful adjunct to conventional surgical or non surgical treatment but are no substitute for these measures.^{13,14} The use of local delivery systems with antimicrobials will not replace the necessity for thorough scaling and root planing. Whether done

before, during or after the placement of the drug delivery system scaling and root planing remains the most important treatment modality in periodontics.

CONCLUSION

Local drug delivery with doxycycline gel & tetracycline fibres is an effective and simple non surgical method to improve periodontal health which can be practiced even by a general dental practitioner.

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