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RESEARCH ARTICLE

TETRACYCLINE AS A ROOT BIOMODIFYING AGENT

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ABSTRACT

Periodontal regeneration is the ultimate goal of periodontal therapy. For this purpose, numerous modalities have been advocated including, the modification of the root surface that is biomodification procedures in order to detoxify, decontaminate, and demineralise the root surface. Tetracycline has been well known as a broad spectrum antibiotic, although its effect as a root conditioning agent is yet to be explored. Hence, to explore the same, EBSCO HOST was searched for entries since 1966 – 2014, which included:- Journal of Periodontology, Annals of Periodontology, Periodontology 2000, Journal of Clinical Periodontology, International Journal of Periodontics and Restorative dentistry, Journal of Indian Society of Periodontology and Journal of Periodontal Research. A total of 11 studies were reviewed, out of these 11 studies, only, 4 reported evidence of regeneration for tetracycline. It was found that the role of tetracycline as a root biomodifying agent in regeneration is still controversial and questionable.

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INTRODUCTION

The nature of the periodontally exposed roots has been identified as one of the major factor influencing periodontal regeneration. These diseased root surfaces are unfavourable for new attachment (Trombelli and Okomoto, 1995). Traditional treatment of pathologically altered root surfaces has relied on mechanical therapy alone (Blomlof *et al*., 1995). However, this procedure leads to smear layer formation that impairs and hinders the periodontal healing and regeneration. Thus, emphasis has been given to root surface modification through various agents, which promote root decontamination and exposure of the collagen matrix aiming at new attachment formation and, therefore, periodontal regeneration (Belal *et al*., 2012; Urist *et al*., 1973 and Terranova *et al*., 1986). Tetracycline is a broad spectrum antibiotic and is found to be effective against periodontal pathogens (Hopra *et al*., 2001). One of the acidic preparation, tetracycline hydrochloride is used for root biomodification, since a long period (Isik *et al*., 1997). There have been controversial evidences of new attachment following root surface modification by tetracycline. So, there is a need to evaluate it as a root biomodifying agent

History

Chlortetracycline and oxytetracycline, both discovered in the late 1940s, were the first members of the tetracycline group to be described.

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These molecules were products of *Streptomyces aureofaciens* and *S. rimosus*, respectively. Other tetracyclines were identified later, either as naturally occurring molecules, e.g., tetracycline from *S. aureofaciens, S. rimosus*, and *S. viridofaciens* and demethylchlortetracyc line from *S.aureofaciens*, or as products of semisynthetic approaches, e.g., methacycline, doxycycline, and minocycline (Janknegt *et al*., 2000). Despite the success of the early tetracyclines, analogs were sought with improved water solubility either to allow parenteral administration or to enhance oral absorption. These approaches resulted in the development of the semisynthetic compounds rolitetracycline and lymecycline.

The most recently discovered tetracyclines are the semisynthetic group referred to as glycylcyclines, e.g., 9-*(N,N*-dimethylglycylamido)-6-demethyl-6-deoxytetracycline, 9-(N-N ethylglycylamido)-minocycline, and 9-*t*-(butylglycylamido)-minocycline.[65] These compounds possess a 9-glycylamido substitutent. The antibiotics can be referred to as first-generation (1948 to 1963), second-generation (1965 to 1972), and third-generation (glycylcycline) tetracyclines (Janknegt *et al*., 2000). The 9-*t*-butylglycylamido derivative of minocycline (tigilcycline; formerly known as GAR-936) commenced phase I studies in October 1999 and is currently undergoing phase II clinical trials. Some of the earlier compounds, e.g., clomocycline, are no longer marketed, and others, e.g., rolitetracycline, lymecycline, and chlortetracycline, are not available in all countries (Finch *et al*., 1997).

MATERIALS AND METHODS (Sharma *et al.*, 2015)

EBSCO HOST was searched for entries since 1966 – 2014, which included these journals:- Journal of Periodontology, Annals of Periodontology, Periodontology 2000, Journal of Clinical Periodontology, International Journal of Periodontics and Restorative dentistry, Journal of Indian Society of Periodontology and Journal of Periodontal Research. To identify studies not found in the databases search, certain issues of the following journals were searched manually: Journal of Periodontology, Journal of Clinical Periodontology, Journal of Indian Society of Periodontology and Journal of Periodontal Research, Chronicles of Dentistry, Indian Journal of Oral Sciences, text books.

Inclusion criteria

Randomized controlled trials in systemically healthy human subjects; comparative, histologic and animal studies, narrative reviews published in English; presenting any modality of root surface biomodification.

Exclusion criteria: Studies lacking baseline–outcome comparisons; with insufficient data; with more than one variable in addition to root surface biomodification; and case reports, because of their weaker clinical evidence.

RESULTS AND DISCUSSION

Tetracycline is a broad spectrum antibiotic and is found to be effective against periodontal pathogens. They are so named for their four ("tetra") hydrocarbon rings ("cycl") derivation ("ine"). All are obtained from soil actinomycetes (Hopra *et al*., 2001). A total of 11 studies were reviewed, out of these 11 studies, only, 4 reported evidence of regeneration for tetracycline. One of the acidic preparation, tetracycline hydrochloride is used for root biomodification, as it has a low pH(1-2) in concentrated solution, acts as a calcium chelator and its application results in enamel and root surface demineralisation (Isik *et al*., 1997).

Actions of tetracycline in root biomodification:

- Removes smear layer
- Demineralization of dentin (Lowengut *et al*., 2000)
- Exposes collagen matrix
- Uncovers and widens dentinal tubules
- A matrix is provided, supporting, migration and proliferation of cells related to periodontal wound healing (Trombelli *et al*., 1995)
- Tetracycline hydrochloride increases the binding of matrix proteins to dentin and stimulates fibroblast attachment & growth (Terranova, 1986).
- Antimicrobial activity is maintained for atleast 14 days (Golub *et al*., 1984).
- Substantivity
- Inhibits neutrophil collagenase (Golub *et al*., 1985)
- Decreases epithelial cell attachment (Terranova *et al*., 1986).
- Tetracycline HCL treatment of the dentin surface increases binding of fibronectin.

The adsorbed fibronectin stimulates fibroblast attachment and growth, while suppressing epithelial cell attachment and growth. This biochemical manipulation may provide a useful approach for the treatment of periodontally involved teeth (Terranova *et al*., 1986). A lingering antimicrobial action (substantivity) and enhanced cell attachment to tetracycline treated root surfaces are often mentioned as reasons for selecting tetracycline instead of citric acid (Frantz *et al*., 1988). A study was done to compare the fibroblast adhesion and growth between tetracycline hydrochloride demineralised and non- demineralised dentinal slabs. Results showed that tetracycline hydrochloride treatment of dentin surface increases binding of fibronectin. The absorbed fibronectin stimulates fibroblast attachment and growth, while suppressing epithelial attachment and growth (Claffey *et al*., 1987).

A study evaluated the efficacy of tetracycline in regenerative periodontal surgery in beagles. The alveolar bone around mandibular premolars was surgically reduced upto 6 mm from the cementoenamel junction in two beagles. The denuded root surfaces were exposed for 3 months. Root surface conditioning with 1% tetracycline and coronally repositioned flaps was done. Results indicated that connective tissue gain occurred after topical use of tetracycline (Silverstein *et al*., 1988). Silverstein (1988) conducted a study on seven individuals in moderate adult periodontitis subjects with tetracycline or control solutions for 6 minutes at the time of surgery and monitored the sites for 6 months. There were no significant differences in clinical parameters between tetracycline-treated and control sites. U.V. fluorescence analysis of crevicuiar fluid samples failed to detect tetracycline release from root surfaces.

A 100 mg/ml solution of tetracycline has been investigated as a potential adjunctive treatment to polytetrafluoroethylene membranes (e-PTFE) in the treatment of class II furcation defects in mandibuiar molars (Machtei *et al*., 1993). The solutions were applied for 5 minutes prior to placement of the membranes, but the only positive finding was a significantly greater reduction in pocket depths in tetracycline-treated sites when compared to controls after 3 and 6 months *($p<0.02$)* (Parachis *et al*., 1993 and Minabe *et al*., 1994). Tetracycline root conditioning however, did not enhance the clinical gain of either horizontal or vertical attachment. This apparent lack of clinical efficacy may be related to the duration of applications to the root surfaces (Parachis *et al*., 1993). A 0.5 mg/ml solution of tetracycline HCl applied to root surfaces for 5 min has also been shown to be inconsistent in removing the smear layer after instrumentation as well as being ineffective in achieving patency of dentinal tubules (Parachis *et al*., 1993).

Minabe *et al*. (1994) studied the effect of root conditioning with minocycline HCI in removing endotoxin from the roots of periodontally-involved teeth to obtain the expected effect of the root treatment with minocycline solution; i.e. removal of the endotoxin, the combining of minocycline with a mechanical root preparation, such as polishing or root planing, seems to be effective. Trombelli *et al*. (1995) evaluated surface characteristics of periodontitis-exposed instrumented human cementum and dentin surfaces following topical application of tetracycline HCl. The results suggests that topical application of tetracycline produces morphologic alterations of

periodontitis-exposed cementum and dentin that appears related to application interval rather than concentration of the drug. A comparative scanning electron microscopic study was performed to evaluate and compare the surface morphology of human root dentin following various concentrations and application times of tetracycline HCl The results showed that concentration of tetracycline HCl solution between 50 mg/ml and 150 mg/ml showed a statistically significant opening of dentinal tubules (Isik *et al*., 2000). Another study compared the dentin surface changes following the applications of tetracycline and citric acid to the instrumented root surface of periodontally involved teeth under scanning electron microscope. Results suggested tetracycline to be more effective in root conditioning (Shetty *et al*., 2008). Minocha Tanuj *et al*. (2013) conducted a study to evaluate and compare the root surface changes subsequent to the application of citric acid, tetracycline, EDTA, and the combination of citric acid and tetracycline, and its influence on the adhesion of a fibrin clot. The root specimens treated with the combination of citric acid and tetracycline as well as citric acid alone, best supported the fibrin clot. Macheti *et al* (Minocha *et al*., 2012) found that the treatment of human roots with tetracycline-HCl during periodontal surgery did not result in new attachment and has no additional effect of tetracycline root preparation on guided tissue regeneration in the treatment of Class II furcation defects. Thus, the contradictory results indicate that further studies are needed to fully evaluate tetracycline root preparation in conjunction with regenerative therapy.

Conclusion

Within the limitations of this review, it is possible to conclude that the application of tetracycline as a root biomodification provide no or minimal clinical benefit with respect to gain in attachment levels or reduction in probing pocket depths. Thus, its role in regeneration is still unpredictable and controversial. Therefore, further studies are needed to ascertain the positive effect of tetracycline as a root biomodifying agent on regeneration in larger sample size.

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