Role of Metronidazole as a Local Drug Delivery in the Treatment of Periodontitis:A Review

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ABSTRACT

Periodontitis is an inflammatory disease affecting the tissues surrounding the teeth, leading to its progressive destruction. The diagnosis of periodontitis is based on clinical findings including the presence and extent of periodontal pockets, loss of clinical attachment, pattern and extent of the alveolar bone loss, or a combination of those findings. The pathogenesis of periodontal disease is mainly by gram-negative bacteria in microbial dental plaque that propagates a localized inflammatory host reaction leading to the release of inflammatory mediators, destruction of connective tissue, periodontal pocket formation and alveolar bone resorption and if left untreated causing tooth loss. Bacteria play a significant role in the pathogenesis of periodontal diseases. Various approaches to treating periodontitis have been focusing on the reduction or eradication of specific periodontal pathogens. These approaches are based on the systemic or local administration of antimicrobial agents. The systemic use of antibiotics raises a number of issues. A prolonged administration increases the risk of problems such as antibiotic resistance and adverse drug reactions. Thus studies focusing on the development of localized drug delivery systems for the release of antibiotics in the periodontal pockets are becoming more frequent. This approach leads to higher concentrations of the drug at the target sites, minimizing or reducing the potential systemic side effects. Various locally delivered chemotherapeutic agents are available such as tetracycline fibers, chlorhexidine chip, doxycycline hyclate, metronidazole gel, minocycline ointment and minocycline microspheres, etc.As anaerobic bacteria are believed to be the predominant causative factor leading to periodontitis and metronidazole, a member of nitroimidazole class of antibiotics specifically targets anaerobic microorganisms which are used in the treatment of chronic periodontitis. This article reviews the effect of metronidazole gel as a local drug delivery on periodontitis.

KEYWORDS: Antibiotics, Local drug delivery, metronidazole, metronidazole gel, Periodontitis

INTRODUCTION

The concept of bacterial specificity in periodontitis is of greatest importance in planning periodontal prevention and treatment. Periodontal therapy focuses on thorough removal of plaque, calculus and plaque products and the restoration of a normal bacterial flora.[1]Various subgingival microbial species have been associated with destructive periodontal disease activity. The probably causing periodontal pathogens are Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Peptostreptococcus micros,Campylobacter rectus, Eikenella corrodens, Fusobacterium nucleatum, Eubacterium spp.,Treponema denticola, Selenomonas spp., beta-hemolytic streptococci, a variety of enteric rods and pseudomonads,enterococci, staphylococci and possibly yeasts. It is essential to eradicate or adequately suppress the periodontopathic microorganisms in the subgingival microbiota for periodontal healing. [2]

Periodontal disease can be either treated by surgical and nonsurgical therapy. Nonsurgical mechanical treatment, which includes mechanical plaque control, scaling and root planing, are the first recommended steps and an essential phase of periodontal therapy.[3] Conventional mechanical debridement cannot eliminate all the bacteria that causes periodontal diseases from the subgingival environment, especially those inhabiting inaccessible areas such as furcations, grooves, concavities and deep pockets.[4] Thus antimicrobial agents may help to further suppress periodontal pathogens and may be required in conjunction with scaling and root planing. These agents made a breakthrough in the nonsurgical treatment of periodontal pocket, and they target the microbes causing periodontitis. Various studies have shown better results with the adjunct use of various local drug delivery systems such as tetracycline fibers, metronidazole gel, minocycline ointment and minocycline microspheres, chlorhexidine chip, and doxycycline hyclate, without exposing the individual to systemic complications.[5]

Metronidazole is one of the most common broad-spectrum antibiotics and is active against most of the

How to cite this article:
Mohamed Haris PM, Panickal DM. Role of Metronidazole as a Local Drug Delivery in the Treatment of Periodontitis:A Review. Int J Oral Health Med Res 2017;3(6):141-145.

periodontal pathogens.[5] As anaerobic bacteria are believed to be the predominant causative factor in periodontitis and metronidazole, specifically targets anaerobic microorganisms that are used in the treatment of chronic periodontitis.[3]

Metronidazole is a 5-nitroimidazole antimicrobial compound developed in France, and it is having a wide spectrum of activity against protozoal infections and anaerobic bacterial infections. Metronidazole was initially introduced in the treatment of trichomoniasis in the late 1950s. Then its therapeutic use has subsequently been expanded to include anaerobic bacterial infections.[6]

In the beginning, metronidazole was thought to interact with biochemical pathways present only in obligate anaerobes. Now it has been known that cytotoxic metabolites of metronidazole directly interact with bacterial DNA, and possibly other macromolecules, resulting in cell death. Upon entry into an anaerobic organism, metronidazole is reduced at the 5-nitro position by electron transport proteins that are part of anaerobic metabolic energy-yielding pathways. Variation of the metronidazole molecule creates a continuous concentration gradient favoring the diffusion of additional metronidazole into the cell. Reduction of the parent compound produces many short-lived cytotoxic free radicals. These type of free radicals react with macromolecules, particularly DNA, resulting in cell death. However, resistance to metronidazole occurs in some anaerobic bacteria, e.g. Fusobacterium species, it is comparatively rare and appears due to a decrease in the ability of the bacterium to actively reduce the 5-nitro position.[7]

At present metronidazole is one of the most widely used antibacterial compounds in the treatment periodontal diseases such as aggressive periodontitis and chronic progressive periodontitis that does not react positively to conventional treatment. It is effective against widely accepted periodontal pathogens and regularly used alone or combined with amoxicillin as an empirical treatment of periodontitis. The dosage of metronidazole follows the same as it is used in soft tissue infections. Oral bioavailability of metronidazole is generally reported >90%. It penetrates well into the different tissues, including the uterus, pancreatic tissue, central nervous system. When compared, concentrations in adipose tissue and colonic mucosa were significantly lower than respective plasma or serum concentrations. In the treatment of periodontitis, the presence of antimicrobial in periodontal tissues is of more importance. It penetrates to the gingival crevice fluid in concentrations comparable with those found in plasma.[8]

Metronidazole has been clinically used for the treatment of gingivitis, acute necrotizing ulcerative gingivitis (NUG), chronic periodontics and aggressive periodontitis. It is used as a monotherapy and also in combination with both root planing and surgery or with antibiotics.It has been used successfully to treat NUG. Metronidazole has been used as an adjunct in the treatment of aggressive periodontitis, especially localized juvenile periodontitis, the adjunctive use of metronidazole in conjunction with thorough mechanical debridement results in the reduction of spirochetes and gram-negative anaerobic rods, including P. intermedia, P. gingivalis, and T. forsythia.

Metronidazole is bacteriocidal to anaerobic organisms. It is effective against organisms like Porphyromonas gingivalis and Prevotella intermedia. It is not a drug of choice for A.actinomycetemcomitans infections but may be effective at therapeutic levels because of its hydroxyl metabolite. However, it is effective when used in combination with other antibiotics.[9]Systemic metronidazole therapy seems to be more effective when treating adult periodontitis patients revealing deeper pockets that contain a susceptible gram-negative anaerobic microbiota.

Most common adverse reactions associated with metronidazole involve the gastrointestinal tract. Some of the patients experience nausea which may be accompanied by a headache, anorexia, and vomiting. Drowsiness, depression, skin rashes and vaginal and urethral burning have been observed. Metronidazole affects the activity of hepatic enzymes involved in with the metabolism of ethanol and producing unpleasant symptoms because of the accumulation of acetaldehyde in the blood. Alcohol ingestion to be strictly contraindicated in patients receiving metronidazole.It has an Antabuse effect. Metronidazole crosses the placenta barrier and enters the fetal circulation system. It is as well secreted in breast milk. Because of the involvement of metronidazole with tumorigenicity in some animals, the drug is contraindicated in pregnant women or nursing mothers.[7]

METRONIDAZOLE GEL (ELYZOL*)

A topical medication containing an oil –based metronidazole 25% dental gel (glycerol mono-oleate and sesame oil). Metronidazole gel is an antibiotic available in readily flowable, resorbable, bioresorbable drug delivery system consisting of 25% metronidazole-benzoate. Basically, it is a fluid, available with the help of a syringe and blunt cannula. The gel is applied to the pocket in viscous consistency, where it is liquidized by the body heat and then hardens again, forming crystals in contact with water. As a precursor, the preparation contains metronidazole-benzoate, which is readily converted into active substances by esterases in GCF. It reaches peak concentrations in GCF 4 hours after administration and maintains levels above 100mg/ml for the first 8 hours. This product maintains concentration exceeding the minimum inhibitory concentration for anaerobic pathogens susceptible to metronidazole (1mcg/ml) for approximately 36 hours.[9,10] Decay of the drug concentration in crevicular fluid follows an exponential pattern which has a sustained drug delivery.

Microbiological observations have indicated that this

local delivery device has marginal effects with respect to decreasing total anaerobic bacteria colony forming units in subgingival plaque. This may be due to the low number of bacteria and shows a slow rate of multiplication.[11]

Two 25% gel applications can be used at a 1-week interval. Studies has shown that metronidazole gel is equivalent to scaling and root planing but not have shown adjunctive benefits with scaling and root planing.[9]

The following were some of the Studies done on Local drug delivery of metronidazole :

Yosuf W.Z et al. (1984)[12] compared subgingival metronidazole in dialysis tubing and subgingival chlorhexidine irrigation in the control of chronic inflammatory periodontal disease and the results showed that subgingival 0.5% metronidazole in dialysis tubing and 0.2% chlorhexidine irrigation was found to be equally effective in chronic periodontitis patients.

Stolze K et al. (1992)[13]had conducted a study on the systemic absorption of metronidazole after one application of a metronidazole 25% dental gel into inflamed periodontal pockets on patients with periodontal disease and they concluded that the systemic load after one application of metronidazole 25% dental gel will be less than after swallowing one metronidazole 250 mg of tablet.

Ainamo et al. (1992)[14] compared the effect of metronidazole 25% gel with subgingival scaling in adult periodontitis and found that both periodontal pocket depth and bleeding on probing were significantly reduced in both groups.

Klinge B et al. (1992)[15] compared the clinical efficacy of scaling with the application of three different preparations/dose frequencies of topical metronidazole in the treatment of adult periodontitis. The four treatments were: (A) metronidazole 25% dental gel administered once a week for two weeks; (B) metronidazole 15% dental gel applied once a week for two weeks; (C) metronidazole 15% dental gel applied twice a week for two weeks; (D) subgingival scaling, performed once only. The results showed that all the three antibiotic treatments (A, B, C) reduced the symptoms of periodontal pathology and are comparable to those seen after subgingival scaling (D). When using a topical drug therapy, it seems important to use a preparation that requires as few applications as possible. They found that the best candidate for drug therapy would be the treatment done with (A) metronidazole 25% applied once a week for two weeks.

Hitzig C et al. (1994)[16] evaluated the clinical effects of a single application of a 5% metronidazole collagen device in periodontal pockets deeper than 5 mm, in association with debridement and without the reinforcement of home care and hygiene as practiced by the patient at anytime.The results indicated that topical metronidazole provides an effective adjunctive treatment of advanced periodontitis.

Hitzig C et al. (1997)[17] evaluated the effect on the subgingival microflora of a single topical administration of a 95% collagen and 5% metronidazole device in combination with debridement was investigated in adult periodontitis patients in comparison with mechanical treatment alone. These results show that a single application of topical metronidazole seems to be effective as adjunctive antimicrobial treatment in adult periodontitis.

Noyan U et al. (1997)[18] conducted a study on selected clinical and microbiological parameters obtained by treatment with local (Elyzol®) and systemic {Flagyl ®) use of metronidazole alone and /or mechanical subgingival debridement in adult periodontitis. The results showed that both of the combined treatment groups responded to therapy with better resolution of infection than the purely mechanical and purely metronidazole treatments and the local metronidazole in the combination with scaling and root planing seems to be more effective in terms of producing both clinical and microbial improvements.

Griffiths G.S et al. (2000)[19] compared the clinical effects of subgingival scaling (SRP) with SRP plus subgingival application of 25% metronidazole gel, Elyzol (SRP gel), in patients with chronic adult periodontitis.They concluded that adjunctive therapy of SRP gel was superior to the conventional treatment of SRP alone, and these differences were maintained for 9 months.

Pavio M et al. (2004)[20] had done a meta-analysis to assess the effectiveness of local delivery of metronidazole alone or as an adjunct to mechanical therapy in patients with chronic periodontitis.

The results demonstrated more effect on metronidazole as an adjunct to SRP in the treatment of chronic adult periodontitis.

Sato S et al. (2008)[21] conducted a study to monitor metronidazole concentrations in the gingival crevicular fluid (GCF) collected from periodontal pockets of dogs after treatment with an experimental 15% metronidazole gel.They concluded that single administration of the 15% metronidazole gel released the drug in the GCF of dogs in levels several-fold higher than the minimum inhibitory concentration for some periodontopathogens grown in subgingival biofilms for up to one hour and the drug could be detected in the GCF at least 48 hours after the gel application.

Yellanki SK et al. (2010)[22] had conducted a study on six batches of metronidazole gels and were prepared using natural, biodegradable polymers chitosan, guar gum and locust bean gum in variable concentrations.They concluded that metronidazole gels could be successfully prepared using natural polymers which can be targeted in the treatment of the periodontal disease and also reduce dosing frequency, increase the bioavailability of metronidazole that will result in better patient compliance with minimal side effects.

Pandit N et al. (2013)[23] had evaluated and compared the efficacy of subgingivally delivered minocycline microspheres and 25% metronidazole gel when used as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis. The study concluded that treatment with minocycline microspheres and metronidazole gel improve, probing pocket depth (PPD), and clinical attachment level (CAL) in patients with periodontitis compared to SRP alone.

C. C. Bergamaschi1 et al. (2016)[24] had compared the effect of Metronidazole (delivered locally as a gel or systemically as a tablet) as an adjunctive therapy with full mouth periodontal debridement (1 h of ultrasonic calculus/plaque removal) in smokers with chronic periodontitis.They concluded that adjunctive use of Metronidazole (gel or tablet) to periodontal debridement had similar clinical and microbiological improvement compared to treatment with placebo + periodontal debridement in smokers with chronic periodontitis up to 6 months post-treatment.

Singh HP et al. (2016)[25]conducted a study to compare and evaluate the efficacy of local delivery of Aloe vera and metronidazole, as an adjunct to scaling and root planing (SRP) in chronic periodontitis patients.The results found that both test groups are comparable and the local application of Aloe vera can be an effective and affordable herbal substitute for metronidazole.

CONCLUSION

Local drug delivery does not provide a superior result when compared to scaling and root planing and for the therapy of aggressive periodontitis that may require systemic antibiotics to eradicate the disease. Thus the benefits of using these systems as a monotherapy are questionable. In conjunction with scaling and root planing, the adjunctive use of local drug delivery may enhance the results in sites that don't respond to conventional therapy alone.The advantage of Local delivery over systemic therapy attains higher concentrations of drug at the intended site of action using a lower dosage with an associated reduction in adverse effects.

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Source of Support: Nil
Conflict of Interest: Nil