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RESEARCH ARTICLE

LOCAL DRUG DELIVERY IN THE TREATMENT OF PERIODONTITIS: A REVIEW.

Dr. Shahid Sikkander (MDS student)[1], Dr. Annaji Sreedhara MDS[2], Dr. B. S Jagadish Pai MDS[3] and Dr. Razeena Salam.

1. Coorg institute of dental sciences, virajpet, Karnataka.
2. Professor,Coorg institute of dental sciences, virajpet, Karnataka
3. Professor & HOD, Coorg institute of dental sciences, virajpet, Karnataka.
4. (MDS student), Coorg institute of dental sciences, virajpet, Karnataka.

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Abstract

Periodontitis is an inflammatory disease that causes destruction of tooth supporting tissues like periodontal ligament and alveolar bone. It is characterized by multifactorial etiology with specific bacteria. Local drug delivery system includes antimicrobial dosages that produce more constant and prolonged concentration profiles within the subgingival tissue. It provides better access into the periodontal pockets. It gives the critical distress of exposing the patient to adverse effects of systemic administration. This article reviews the literature and presents novel trends in the local drug delivery system.

Introduction:-

Periodontitis is an inflammatory disease that causes the destruction of tooth supporting structures [1]. It is characterized by multifactorial etiology with pathogenic bacteria resulting in the progressive destruction of the periodontal ligament and alveolar bone with increasing probing depth, recession or both. This pathogenic bacteria occurs due to the accumulation of subgingival plaque [2]. The current concept of treating periodontal diseases is based on controlling resident mass of periodontal microbes. In fundamental sense the objective of periodontal therapy is to reduce the pathogenicity in the subgingival periodontal area. Theoretically there are two approaches in making the subgingival area less pathogenic [3]:

1. To reduce the total plaque microflora by mechanical debridement and use of antiseptic agents against non-specific microbiota
2. To reduce the level of specific pathogens in the plaque by use of antibiotic agents.

The traditional treatment of periodontitis involves oral hygiene instruction, mechanical debridement like scaling and root planing. Mechanical debridement aimed at removing the subgingival micro flora and provides a clean, smooth and compatible root surface. But in several conditions the complex anatomy of the root and the location of the lesion may disturb the treatment and prevent the adequate reduction of the microbial load. Moreover studies have shown that patient who fail to get adequate plaque control during or after subgingival treatment frequently suffer from recurrent periodontitis. Thus oral hygiene has to get more importance for the clinical outcomes of non surgical as well as surgical therapy.

Antimicrobials have been used as an adjunct with mechanical debridement in the management of periodontal infection. For the effective treatment, antimicrobial agent must reach the depth of the periodontal pocket and

Corresponding Author:-Dr. Razeena Salam.
Address:- (MDS student), Coorg institute of dental sciences, virajpet, Karnataka.

produce gingival crevicular fluid concentration more than the Minimum Inhibitory Concentration of the suspected periodontal microbes.

Antimicrobial agents have been administered both systemically and locally. Systemic administration usually indicated as an adjunct to scaling and root planing in order to prevent the recolonization of pathogenic bacteria. It is administered for a period of 7 – 14 days. But it requires a higher concentration to be administered every few hours in order to stabilize the effective dose level. It may lead to adverse effects like hypersensitivity reaction, GIT disturbances, and bacterial resistance.

These adverse effects would markedly reduce if the antibiotics applied locally. So local drug delivery used as an adjunct to scaling and root planning and as aids in the control of growth of pathogenic bacteria. According to Greenstein and Tonetti, local drug delivery must full fill the following criteria [4].

1. It must reach the intended site of action.
2. It must remain at adequate site of action.
3. It should last for a sufficient duration of time.

When placed into the periodontal pocket they reduce the probing pocket depth, subgingival bacterial flora and clinical signs of inflammation. The advantages of this method include it can reach the base of the periodontal pocket which is inaccessible to mouth washes and causes sustained release of short dose of drug over a long period of time. It has been found that local drug delivery can attain a 100 fold higher concentrations of antimicrobial agents in subgingival sites. One of the main problems placed while using local drug deliver is the difficulty in placing therapeutic concentrations of antimicrobials into deeper pockets and furcation lesion. Lack of manual dexterity, time consuming, higher cost and poor compliance limits the use of antimicrobial agents in locally. It does not have any effect on nearby structures such as tonsils, buccal mucosa etc which may cause the chance of getting reinfection.

Local drug delivery can be safely used in medically compromised patients for whom periodontal surgery is contraindicated and for periodontal maintenance therapy. It is contraindicated in patients with known hypersensitivity to antimicrobials, in asthmatics and infective conditions like AIDS and tuberculosis.

Local drug delivery are designed with concerned drugs impregnated in a medium or vehicle and available in the form of fibres, film, injectable system, gels, strips and compacts, vesicular system, microparticle system and nano particle system[5].

The antimicrobial agents that have been used as local drug delivery in the treatment of periodontal disease may be sustained release or controlled release. In sustained release, drug delivery is for less than 24 hours where as in controlled release, drug delivery is for more than 24 hours.

Various antimicrobial agents used are:-

1. Tetracycline.
2. Minocycline.
3. Doxycycline.
4. Metronidazol.
5. Chlorhexidine.

Tetracycline:-

These are broad spectrum antibiotics that are more effective against gram positive bacteria. Tetracycline is a bacteriostatic antibiotic that interferes with bacterial protein synthesis and inhibits tissue collagenase activity. Their concentration in gingival crevice is 2 to 10 times than that in serum therefore a high drug concentration is delivered into periodontal pocket. Even at low concentration, they are very effective.

Goodson et al in 1979 first proposed the concept of controlled delivery in the treatment of periodontitis. The first delivery devices involved hollow fibres of cellulose acetate filled with tetracycline. Tetracycline containing fibres are the first available local drug. It had ethylene/vinyl acetate copolymer fibre with diameter of 0.5 mm, containing tetracycline12.7mg per 9 inches.

Tetracycline fibres are commercially available as Actisite. Actisite been approved both by the United States Food and drug administration (FDA) and by the European Union's regulatory agencies. It is non resorbable, biologically inert, safe plastic copolymer (ethylene &vinyl acetate) loaded with 25% w/w tetracycline hydrochloride powder packed as thread of 0.5mm diameter &23cm length. It maintains constant concentrations of active drug in the crevicular fluid in excess of 1000 μg/mL for a period of 10 days [6]. Bioresorbable form of tetracycline is PERIODONTAL PLUS AB. It is biodegrade within 7 days, so there is no need of second appointment. In a 6-month multi-centre evaluation of adjunctive tetracycline fibre therapy by Newman et al 1994, showed that fibre therapy significantly enhanced the effectiveness of scaling and root planing in the management of localized recurrent periodontitis sites, in patients receiving regular supportive periodontal therapy [7]. A Tetracycline-Serratiopeptidase-Containing Periodontal Gel made by Maheshwari et al observed that Formulation has shown statistically significant results along with scaling and root planing [8]. Singh et al 2009 reported that there is no statically significant difference in the results achieved with local tetracycline hydrochloride or local metronidazole as adjuncts to mechanotherapy [9]. However, both antibiotic therapies resulted in better improvement in microbiological parameters when compared to mechano therapy alone. Sachdeva and Agarwal made tetracyline in the form of modified collagen matrix and used along with scaling and root planing. They concluded that there was significant pocket depth reduction and clinical attachment gain for the SRP and tetracycline fibres group compared to SRP alone [10].

Sadaf et al evaluated by using Tetracycline fibres and reported that higher reduction in plaque index, gingival index and in the clinical probing depths of the tested group than of the control group at all time intervals - 15, 30, 60 and 90 days [11]. Gupta Nidhi et al also observed that tetracycline fibre therapy enhances the benefits of SRP in the treatment of chronic periodontitis [12].

Minocycline:-
It is a broad spectrum antibiotic which is a derivative of tetracycline. It exhibits bactriostatic action. It has marked substantivity and greater lipid solubility. It is available in the form of film, microspheres, ointment and gel [13, 14].

Film:-
Ethyl cellulose film containing 30% of minocycline were tested as sustained release devices. Pragati et al proposed that the use of this device may cause complete eradication of pathogenic flora from the pocket after 14 days [15].

Microsphere:-
Recently FDA approved a new locally delivered minocycline microspheres, which is sustained release. Commercially it is named as ARESTIN. The 2% minocycline is encapsulated into bio-resorbable microspheres (20-60μm in diameter) in a gel carrier and has resorption time of 21 days. Pragati et al proposed the gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14 days or longer before resorbing completely [15].

Ointment:-
The 2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkyl-methacrylate, triacetine & glycerine. Commercially it is available as DENTOMYCIN in European Union and PERIOCLINE in JAPAN. The concentration of minocycline in the periodontal pocket is about 1300μg/ml, 1 hr after single topical application of 0.05 ml ointment and is reduced to 90μg/ml after 7 hrs [16]. Steenberghe et al showed that combined therapy provided a better result than SRP alone at sites >7 mm deep [16.] Timmerman et al reported that there was no benefit of employing 2% minocycline gel as an adjunct to SRP to reduce probing depths at deep site [17]. Jung et al reported that Reductions in PPD, BOP and gain in CAL were significantly greater at the minocycline ointment in association with flap surgery site than at the flap surgery site alone ($p < 0.05$) [18].

Doxycycline:-
Doxycycline is a bacteriostatic agent. It has the ability to down regulate MMP's [19] .The only FDA approved 10% Doxycycline in a gel system **ATRIDOX** (42.5 mg Doxycycline) is a subgingival controlled-release product composed of a two syringe mixing system .It is the only local delivery system accepted by ADA. Doxycycline levels in GCF peaked to 1,500 - 2000 μg/ml in 2 hours following treatment with ATRIDOX. Local levels of Doxycycline have been found to remain well above the MIC for periodontal pathogens (6.0μg/ml) through Day 7. 95% of the polymer is bio absorbed or expelled from the pocket naturally within 28 days [20]. Kim TS et al told that The FDA has also approved doxycycline hyclate in a bioabsorbable polymer gel as a stand-alone therapy for the reduction of probing depths, bleeding upon probing, and gain of clinical attachment [21]. Tomasi C and Jan LW observed that

locally applied controlled release doxycycline gel may partly counteract the negative effect of smoking on periodontal healing following non surgical therapy [22]. Bogren et al showed that Doxycycline had statistically significant differences in clinical parameters only at 3-month examination; after 3 month period, doxycycline and mechanical debridement were effective in reducing just a minority of microbiological pathogens [23]. Deo et al reported that doxycycline hyclate 10% as an adjunct to SRP provided significant reductions in PPD and gains in CAL compared to SRP alone [24] .

Chlorhexidine:-
It is used as anti fungal and anti bacterial agents. It is available in the form of mouth rinses, gels, varnishes, and chip to be used as a local drug delivery agent. Rolla and Melsen reported that it acts by binding to anionic acid groups on salivary glycoproteins thus reducing pellicle formation and plaque colonization and by binding to salivary bacteria and interfering with their adsorption to teeth [25]. Chlorhexidine has been shown to be an effective agent in plaque inhibition. It is well retained in the oral cavity, the reacting reversibly with receptors in the mouth due to its affinity for hydroxyapetite and acidic salivary protein. Its antibacterial action is due to an increase of the cellular membrane permeability followed by the coagulation of intracellular cytoplasm macromolecule.

Periochip:-
A small chip composed of biodegradable hydrolyzed gelatin matrix, croslinked with glutaraldehyde, also contains glycerine & water, into which 2.5mg chlorhexidine gluconate is incorporated. Perio chip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hours, and then releasing the remaining chlorhexidine in an almost linear fashion for 7–10 days. Grover et al reported that chlorhexidine chip and SRP resulted in a clinically significant improvement in PPD and CAL compared with SRP alone [26]. Jagadish Pai et al showed that Clinically significant reduction in PPD, BOP and CAL by using chlorhexidine varnish and chlorhexidine chip along with SRP but the results were not statistically significant when compared with SRP alone [27]. Medaiah et al observed by using biodegradable chlorhexidine chip that there were no statistically significant differences between SRP and SRP + CHIP group in all clinical parameters [28].

Periocol-CG:- Periocol CG is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane.Size of the chip is 4x5 mm and thickness is 0.25 - 0.32 mm and 10 mg wt [29].

Chlo-Site:- It is an agent containing 1.5% chlorhexidine of xanthan type. Xanthan gel is a saccharide polymer, which constitutes of a three-dimensional mesh mechanism, which is biocompatible with chlorhexidine [29].

Metronidazole:-
It is a nitromidazole compound. It is bacteriocidal to anaerobic organism .Mechanism of action is by disrupting bacterial DNA synthesis.

Elyzol 25%: Metronidazole concentrations of above100 μg/ml were measurable in the periodontal pocket for at least 8 hours and concentrations above 1 μ/ml were found at 36 hours [30]. It is applied in viscous consistency to the pocket, where it is liquidized by the body heat and then hardens again, and forming crystals in contact with water.

Riep et al concluded that PPD reduction and CAL gain were statistically significant after both treatments (SRP + subgingival application of metronidazole 25% dental gel and SRP alone) [31]. There were no statistically significant differences between the groups. Griffiths et al observed that Combined therapy of SRP and metronidazole 25% dental gel was superior to the conventional treatment of SRP alone [32].

Novel trends in local drug delivery:-
The most important step in treating periodontitis is eradicating pathogenic microbes from the periodontal pocket. Development of local drug delivery occurs due to reducing the limitation of mouth washes and subgingival irrigation. Many studies have been conducted for newer agents other than what we discussed earlier, in the field of local drug delivery with maximum benefit. Newer agents include simvastatin, atrovastatin, azithromycine, metformine alendronate, clarithromycin and herbal products like aloevera, neem, tulsi, tea tree oil, lemon grass, pomogranate etc [33, 34].
Kuduva et al had been observed that green tea catechin local delivery along with scaling and root planing is more effective than scaling and root planing alone [35]. Bhat et al concluded that sub gingival administration of Aloe Vera gel results in improvement of periodontal condition. Aloe Vera gel can be used as a local drug delivery system in

periodontal pockets [36]. Agarwal et al did a study to investigate the adjunctive effects of subgingivally delivered 0.5% clarithromycin (CLM) as an adjunct to scaling and root planing for treating chronic periodontitis in smokers [37]. They concluded that although both treatment strategies seemed to benefit the individuals, the adjunctive use of 0.5% clarythromycin as a controlled drug delivery system enhanced the clinical outcome. Kumari et al concluded that the atrovastatin local drug delivery as an adjunct to SRP can be used in the treatment of intrabony defect in chronic periodontitis among smokers [38].

Pradeep et al observed that local delivery of metformin into the periodontal pocket stimulated significant increase in the probing pocket depth reduction, clinical attachment level gain, and improved intrabony defect depth reduction compared to placebo in adjunct to scaling and root planning [39]. This can provide a new direction in the field of periodontal healing. Rao et al concluded that, there was greater decrease in modified sulcus bleeding index and probing pocket depth and more clinical attachment loss gain with significant intrabony defect fill at vertical defect sites treated with scaling and root planning plus locally delivered metformin, versus SRP plus placebo, in smokers with generalized chronic periodontitis [40].

Elgendy et al reported that the local delivery of tea tree oil gel in case of chronic periodontitis may have some beneficial effects to augment the results of the conventional periodontal therapy [41]. Moreover, it places a focus on the value of monitoring GCF levels of pentraxin-3 as a marker of periodontal tissue healing. Shivaraj et al proposed that locally delivered 2% lemongrass essential oil gel offers a new choice of safe and effective adjunct to scaling and root planing in periodontal therapy [42]. Hosadurga et al proposed the use of 2% curcumin gel [43] and 2% tulsi (O. Sanctum) gel [44] in the treatment of experimental periodontitis.

Conclusion:-

Current data suggests that local drug delivery of antimicrobial agents into periodontal pocket can enhance the health of periodontal tissues. It can be concluded that the adjunctive use of local drug delivery may provide a defined but limited beneficial response. The local drug delivery provides a better improvement in dealing patients with unresponsive periodontal pocket and occurs in better patient satisfaction. However, some more randomized, controlled and long term studies are needed to help the types of lesions and periodontal diseases like chronic or aggressive periodontitis where local drug delivery systems would be more useful.

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