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Local Drug Delivery In Periodontics - A Review

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ABSTRACT :
Periodontitis is an inflammatory disease of the supportive tissues surrounding the teeth which is seen world wide in all groups of people. Various methods of treatments were used in the management of periodontal infection[(1)].Various effective methods including mechanical debridement of plaque , topical and systemic administration of antibacterial agents in the treatment of such conditions. There are various options of antimicrobials which can be locally delivered such as metronidazole, chlorhexidine, doxycycline and tetracycline[(2)].

KEY WORD: Tetracycline, Doxycycline, Chlorhexidine

INTRODUCTION:
Periodontal disease occurs due to several pathological conditions affecting the tooth supporting structures . Such as chronic periodontitis, systemic disease-associated periodontitis and necrotizing periodontitis. It is well known that periodontal disease caused due to local bacterial infection with pathogenic microflora in the periodontal pocket. The inflammation is initiated by microbial plaque and bacterial infection. The bacteria form a highly structured and complex biofilm in the periodontal pocket later , the biofilm reaches sub-gingivally and it becomes hard to remove it during regular oral hygiene practices. The microflora involved in periodontitis mainly of gram negative anaerobic bacteria[(1)(2)].
Traditional therapies such as mechanical debridement to remove the subgingival flora and providing clean , smooth and biocompatible root surface but in several conditions due to the complex anatomy of the root and the site of lesion may hinder the treatment and prevent the sufficient removal of the bacterial load. The control of supragingival plaque is very essential to prevent recolonization. In several clinical studies it is mentioned clearly shows that scaling and root planning with optimal oral hygiene produce an alteration of the subgingival plaque , it is enough to stop periodontal destruction in most cases. Patient who couldnt achieve acceptable plaque control during or after the treatment mostly suffer from reccurent periodontitis, so oral hygiene is very important for successful outcome after the treatment[(3)].
Antibacterial agents used along with mechanical debridement in the treatment of periodontal infection. Due to lack of accessibility the result is limited. The periodontal pocket provides an ideal environment for the growth of anaerobic pathogenic bacteria's, thus for the effective treatment the antibiotics has to reach the depth of the periodontal pocket. The etiopathogenesis of periodontal disease has provided the practitioners and researchers with a number of diagnostic tools and technique that has provided various treatment options[(2)].

History :

It was first proposed by Dr. Max Goodson et al in 1979.
He used tetracycline in the hollow fibers. Later,
D. Steinberg et al (1990) researched chlorhexidine as a local drug delivery.
Nakagawa T et al (1991) used minocycline.
Ainamo et al (1992) studied 25% metronidazole gel.
Stoller et al (1998) studied doxycycline hyclate[(1)].

Ideal Requirement Of Locally Delivered Drug :

1. The drug delivery system should deliver the drug to the base of the pocket.
2. It should be effective against periodontal pathogens only and not on commensal microflora.
3. Drug must show in-vitro activity against the organisms.
4.The target dose should be sufficient enough to kill the targeted organisms also should not have any adverse effects.
5. Substainity.
6. Prolonged shelf life.
7. It should be both biodegradable and biocompatible.
8. Ease of placement.
9. Ready to use chairside.
10. Should be economical[(4)(5)(7)].

CONTRAINDICATION :

Local drug delivery should not be used in the following conditions,
1. Periodontal patients with known hypersensitivity reaction to any components of the LDD systems to be used.
2. As a replacement to scaling and root planning during initial periodontal therapy and maintenance.
3. In pregnant or lactating patients.
4. Patients susceptible to infective endocarditis to avoid the risk of bacteremia.
5. As a replacement for surgical periodontal therapy in cases indicated for periodontal surgery.
6. As a replacement for systemic antibiotic therapy , where their systemic administration is indicated[(6)].

ADVANTAGES :

1. Attains a 100 fold higher concentration of antimicrobial agents in sub-gingival sites.
2. The concentration of the drug in periodontal pocket is not affected by the fluctuation in plasma levels.
3. The technique is suitable for agents which cannot be given systemically, such as chlorhexidine.
4. Small doses can be administered.
5. Superinfection and drug resistance are rare.
6. Reduction in frequency of drug administration[(4)(6)].

DISADVANTAGES :

1. Difficulty in placing into the deeper parts of the pockets of the furcation lesions.
2. Does not have any effect on adjacent or near by structures such as tonsils , buccal mucosa ect so may cause chances of reinfection.
3. Time consuming.
4. In presence of generalized pockets , other periodontal therapies should be used[(4)(6)].

CLASSIFICATION :

1. **Langer & Peppas (1981**)- Based on their mechanism of action.
a. Diffusion controlled systems.
b. Chemically controlled systems.
c. Solvent activated systems.
d. Release induced by external forces.

2. **Kornman(1993)**
a. Reservoirs without a rate controlling system.
b. Reservoirs with a rate controlling system.

3. **Rams Ans Slots (1996) -** Based on application of therapy.
a. Personally applied.
i. Non-sustained subgingival drug delivery.
ii. Sustained subgingival drug delivery.
b. Professionally applied.
i. Non-sustained subgingival drug delivery.
ii. Sustained subgingival drug delivery.

4. **Soskolne Wa (1997) -** Based on dosage form.
a. Fibers e.g. Tetracycline.
b. Films / slabs e.g. Chlorhexidine chip.
i. Non-degradable films
ii. Degradable films
c. Injectable systems e.g. Minocycline

5. **Greenstein & Tonetti(2000)-** Based on duration of action
a. Sustained release devices
b. Controlled release devices
6. SOSKOLONE WA FRIEDMAN M. - Depending on degradability:
a. Non-degradable devices
b. Biodegradable devices[(1)(10)].

Various Drugs/Agents Used In The Local Drug Delivery System :
1. Tetracycline
2. Doxycycline
3. Minocycline
4. Metronidazole
5. Chlorhexidine
Other drugs like clarithromycin, Alendronates, ofloxacin, clindamycin.etc,

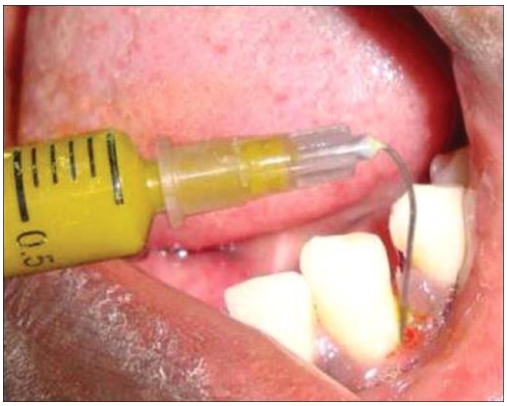
TETRACYCLINE :
Tetracycline have been widely used for the treatment of periodontal diseases. Which is frequently used to treat refractory periodontitis , like localized aggressive periodontitis. The Tetracycline containing fibers are the first available local drug. Tetracycline is a bacteriostatic antibiotic that interferes with bacterial protein synthesis and inhibits tissue collagenase activity[(1)(2)(9)].

FIBERS(ACTISITE):
These are non-resorbable biological inert , generally considered as safe, plastic copolymer (ethylene and vinyl-acetate) loaded with 25%w/w tetracycline HCL powder packaged as a thread of 0.5mm in diameter and 23cm in length. When packed into the periodontal pocket, it is well tolerated by oral tissues, and for 10days it sustains tetracycline concentrations. Recently bio-resorbable tetracycline fibers has been developed with base of collagen films, which is commercially available as PERIODONTAL PLUS AB(Fig1.1). It offers the advantage of no further appointment for removal as it biodegrades within 7days[(1)(9)].

Fig(1.1) PERIODONTAL PLUS AB

GELS:

Tetracycline serratiopeptidase fig (1.2) containing periodontal gel, the purpose was to reduce the polymer concentration and to obtain reasonable viscosity at a lower concentration of pluronic acid. Bio-erodible injectable poly for tetracycline controlled delivery formulations loaded with tetracycline by 10% or 20% showed complete in vitro degeneration concomitant with drug release[(2)(9)].



Fig(1.3) TETRACYCLINE GEL.

Doxycycline:

Doxycycline is a bacteriostatic agent. A biodegradable formulation containing;
10% by weight doxycycline,
33% by weight poly (DL-Lactide) and
57% by weight N- methyl 2-pyrrolidone.
Approximately 95% of the polymer is bio-absorbed or expelled from the periodontal pocket naturally within 28 days. The efficiency of 10% doxycycline hyclate as a local delivery antimicrobial agent for achieving probing depth reduction and gaining clinical attachment. It is a liquid biodegradable system that hardens when placed in the periodontal pocket[(9)(2)].

Minocycline:

Minocycline HCL, a semi synthetic tetracycline is one of the most active antibiotics for micro organisms associated with periodontitis. It has a significant antimicrobial activity against a wife range of organisms as well as an anti-collagenase effect[(1)].
There are three modes of local application are available;
1. Film
2. Microspheres
3. Ointment.

FILM;
Ethyl cellulose films containing 30% of minocycline which completely eradicates pathogenic flora from the periodontal pocket after 14 days[(2)].

Microspheres:
A new, locally delivered, sustained release form of minocycline microspheres (ARESTIN)Fig(1.3) for subgingival placement is available. The 2%minocycline is encapsulated into bio-resorbable microspheres in a gel carrier and has resorption time of 21days. The gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14days or longer before resorbing completely[(2)].

Fig(1.3) ARESTIN(Microspheres).

OINTMENTS:
2% minocycline hydrochloride in a matrix of hydroxyethyl-cellulose, amino alkyl-methacrylate, triacetat & glycerine.

1**. DENTOMYCIN** - European union, fig(1.4).
2. **PERIOCLINE -** Japan, fig(1.5).
The concentration of minocycline in the pocket is about 1300□g/ml, 1hr after single topical application of 0.05ml ointment(1mg of minocycline) and is reduced to 90□g/ml after 7hrs[(2)].
Fig(1.5)PERIOCLINE. Fig(1.4)DENTOMYCIN.

<u>Metronidazole:</u>
Elyzol, Fig(1.6)is a topical medication containing an oil-based metronidazole25% dental gel, applied in viscous consistency to the periodontal pocket. consists of 25% of metronidazole benzoate in a matrix consists of glyceryl mono-oleate and sesame oil. The gel is placed subgingivally with a syringe and a blunt cannula. The drug concentration is crevicular fluid follows an exponential pattern which is compatible with sustained drug delivery. Among the other antibiotics that have been considered for periodontal treatment, metronidazole has often been chosen because of its selective efficacy against obligate anaerobes. When metronidazole gel plus scaling and root planning were compared to root planning alone, the results have not been consistent. One investigation suggested that there was a better result over a 9 month observation period when combined therapy was employed for probing depth reduction[(1)(2)].

Fig(1.6)ELYZOL(Metronidazole).

CHLORHEXIDINE:

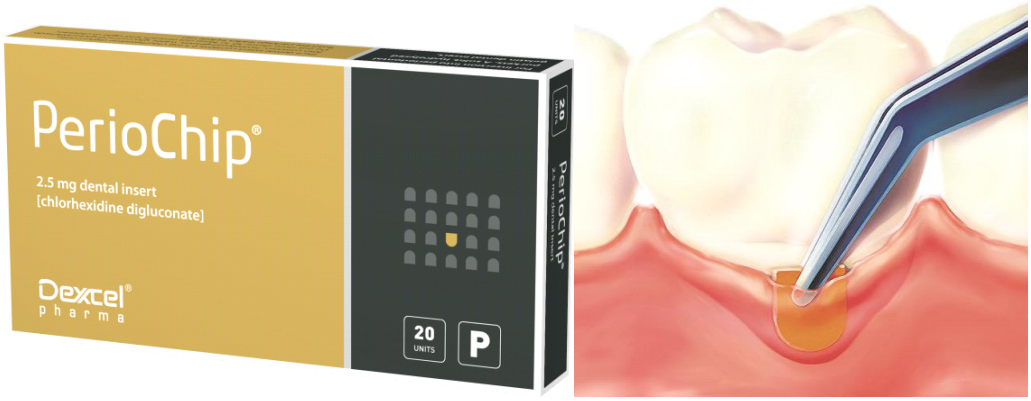
Chlorhexidine belong to the family of biguanide, it is used as an antifungal and antibacterial agent. It is mainly active against gram positive group of organisms. It is bacteriostatic at low and bactericidal at high concentrations. Chlorhexidine is being used in mouth rinses, chlorhexidine has only a short lived effect on the pocket flora[(1)].

It is available in the forms of;

1. Mouth rinses
2. Gels
3. Varnishes
4. Chips.

PERIOCHIP:

A small chip composed of biodegradable hydrolysed gelatin matrix, comprised of 34% chlorhexidine cross-linked with glutaraldehyde and also containing glycerine and water, Fig(1.7). The chip is 5mm long, 4mm wide with 2.5mg of chlorhexidine gluconate. The chip releases chlorhexidine in vitro in a biphasic manner, initially releasing approximately 40% of the chlorhexidine within the first 24 hrs, and later releasing the remaining chlorhexidine in an almost linear fashion for 7-10 days[(2)].



Fig(1.7)PERIOCHIP(Chlorhexidine).

PERIOCOL-CG:

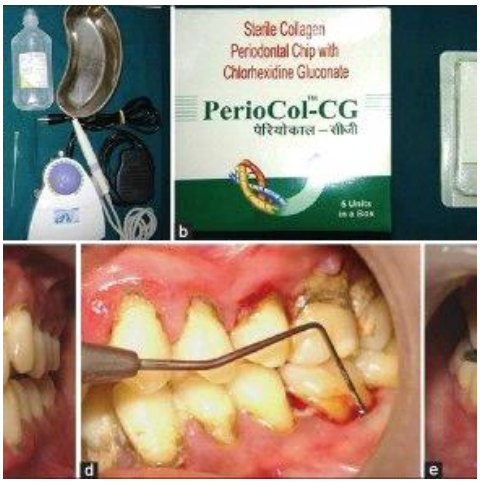
It is prepared by incorporating 2.5mg chlorhexidine from a 20% chlorhexidine solution in collagen membrane.

Size of the chip : 4 x 5 mm

Thickness of the chip: 0.25-0.32mm

Weight of the chips: 10mg wt, Fig(1.8).

It has been shown that it resorbs after 30 days and their coronal edge degrades within 10 days[(2)].



Fig(1.8)PERIOCOL-CG.

CHLO-SITE :

It is an agent containing 1.5% chlorhexidine of xanthan type
(Xanthan gel - saccharide polymer).Fig(1.9).

The chlosite gel gets vanished from the pocket within 10 - 30 days of injection and effective concentration of chlorhexidine against microorganisms is established for at least 15days in the region.

It stick inside the pockets and are not easily washed out by gingival fluid or saliva. It is very efficient in treatment of periodontal pocket and peri-implantitis[(1)(2)].

Fig(1.9)CHLO-SITE.

CONCLUSION:

Local drug delivery into the periodontal pocket is an effective treatment associated with mechanical debridement. How ever the drug fails to completely replace the conventional scaling and root planning. Thus the benefit of these drug as a monotherapy is questionable.

It can be concluded that local drug delivery though not a substitute for conventional therapy, but can be of added benefit if used as an adjunct with the conventional scaling and root planning.

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