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Local Drug Delivery System – A Comprehensive Review

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ABSTRACT *Periodontitis and gingivitis are diseases of the oral cavity which one tends to encounter very often in daily practice. The ideal treatment for this disease has been scaling and root planning along with administration of systemic antibiotics if and when needed. The most common problem encountered with this line of treatment is the inability to maintain contact with the diseased site for a sufficient amount of time and to reach the depth of the pocket. Local drug delivery system is a new approach by which drugs can be administered into the depth pocket by various methods for a prolonged period of time leading to a greater elimination of bacteria from the pocket and resolution of the disease. This comprehensive review article tries to cover the indications, contraindications,types of local drug delivery systems at length and the latest advances in them.*

INTRODUCTION

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with increased probing depth formation, recession or both."[1]Most often than not, Gingivitis and Periodontitis are associated with dental plaque. Plaque is a highly organized matrix consisting of bacterial populations that include Aggregtibacteractinomycetemcomitans, Porphyromonasgingivalis, Prevotellaintermedia, Campylobacter rectus and a variety of other rods and yeasts. The primary line of treatment is to debride the pocket and the subgingival component in order to eliminate bacteria.

Scaling and root planing (SRP) has always been the ideal choice in cases of gingivitis or periodontitis butrecolonization can occur as early as 60 days post SRP[2]. Systemic antibiotic administration is usually employed as an adjunct to scaling and root planing in order to prevent recolonization, for a period of 7-14 days, but it requires a high concentration to be administered every few hours in order to maintain the effective dose level. This can lead to several adverse effects including GI tract disturbances, allergies, and resistance.[3]

Local drug delivery systems are available as adjuncts to scaling and root planing and as aids in the control of growth of bacteria on barrier membranes. When placed into periodontal pockets, they reduce probing depth, sub gingivalmicro flora, and clinical signs of inflammation.[1] It involves using the same drug that you would administer systemically but via local devices consisting of biocompatible polymers that can be inserted into the pocket or sub gingival diseased area in order to release the drug at regular intervals in a controlled manner and in smaller doses.

Scaling and root planing is usually performed along with one of the following therapies in order to gain optimum results:

1. Systemic administration of antibiotics:

- Tetracycline 25-500 mg q.i.d, Doxycycline 100 mg o.d and minocycline 100 mg b.d for 7 days effective against gram negative and gram positive cocci and bacillus.

- Metronidazole – effective against anaerobic gram negative bacilli 250 mg t.d.s for 10-14 days.

- Amoxicillin/ Augmentin 250-500 mg t.d.s used for broad spectrum action.

- Clindamycin 150 mg t.d.s or q.i.d for 7-10 days.

2.Topical Mouth Rinse

- Chlorhexidine 0.2% 10 ml mouth rinse prescribed twice a day

- Listerine

3.Oral Sub Gingival Debriding Agents

- 1. 7%, 3% Hydrogen Peroxide pocket irrigation via PerioTrays

- 0.12% , 0.1 %Chlorhexidine

- Normal saline

The main disadvantage with all of the above methods is the inability to maintain or sustain a constant dose of the drug at the site of infection for a long period of time. Mouth rinses donot reach beyond 5mm into the periodontal pocket[5], systemic antibiotics cannot be administered repeatedly as it may cause resistance aswell as several side effcects[6] whereas oral debriding agents donot maintain contact with the infected area for a prolonged period of time.

In order to overcome these drawbacks, Local Drug Delivery system is an efficuous, easy method at providing therapeutic concentration of the drug, at the site of infection by small regulated dosages and high patient acceptibility.

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LOCAL DRUG DELIVERY SYSTEM

Local drug Delivery also known as Site-Specific delivery is an advanced approach introduced by Goodson et al in 1979. Periodontal pocket provides a natural reservoir bathed by GCF, which is easily accessible for the insertion of delivery devices. The gingival fluid provides a leaching medium for the release of a drug from the solid dosage form and for its distribution throughout the pocket. Thus this makes the periodontal pocket a natural site for treatment with local release delivery system. (Aubrey,1997)[7]

According to Greenstein and Tonetti[7], local application of pharmocological agents must fulfill the following criteria:

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

Local Drug Delivery abides with all the above steps.It is a method by which a drug is placed in the pocket, and the therapeutic dose is released in a controlled manner over a period of time.The advantage of this mechanism is that it reaches the base of the periodontal pocket which is ususally inaccessible to oral mouth rinses , and causes sustained release of a short dose of drug over a long period of time without having to load the dose repeatedly unlike systemic antibiotics and sub gingival irrigation.This helps to reduce or eliminate the pathogenic bacterial count, decreases probing depth, stabilizes attachment and controls or minimizes bleeding which eventually leads to controlling of the disease.[8,9]

Local Drug delivery can be used as an adjunct to surgical scaling to ensure that any remnants of pathogens still residing in the pocket are completely eliminated. It can also be used in the maintenance phase post scaling and root planing, to ensure that the disease doesnot recur. It can aslo be used as an add on to systemic drug administration in order to increase the availibility of the drug the site of infection/inflammation, in small increments for a prolonged period of time.[10]

Indications:

1. In cases where surgical treatment is not an option.
2. As an adjunct to scaling and root planing.
3. Periondontal Maintenance therapy.
4. In patients suffering from recurrent periodontitis.
5. In Periodontal regnerative therapy.
6. Hypersensitivity to conventional intra canal irrigants like sodium hypochlorite.
7. Patients who have undergone endodontic therapy but still complain of recurrent infections[11,12]

Contra-Indications:

1. Patients with hypersensitivity to the drug.
2. Patients susceptible to infective endocarditis inorder to reduce risk of bacteremia.
3. Use of ultrasonic device based drug delivery system is contraindicated in asthmatics, patients with cardiac pacemakers, AIDS and tuberculosis.[11]

Advantages:

1. Attains a 100- fold higher concentration of anti microbial agent in subgingival sites.
2. Reduces patient dose by over 400 fold thereby reducing chances of drug resistance and side effects caused by systemic antibiotics
3. Small doses can be administered.
4. Maintain contact with the pathogens in the infected area for a prolonged period of time.
5. Maintains effective concentration.[13]

Disadvantages:

1. Patient may not comply to placement of the drug subgingivally.
2. Difficulty in placing the device at the base of the pocket.
3. Lack of manual dexterity.[10]
4. Does not have any effect on adjacent or nearby structures such as tonsils, buccal mucosa etc so may cause chances of re-infection.
5. Time consuming
6. Costly

Greenstein & Tonetti in 2000, classified Local Drug Delivery system based on the duration of action into[8]:

A. Sustained release Devices

- Drug delivery for less than 24 hours.
- Require multiple applications.
- Follow first order kinetics.

B. Controlled Delivery Devices

- Duration of drug exceeds 24 hours.
- Administered once.
- Follow zero order kinetics.

Intra Pocket devices can be of two types depending on their degradibility viz.

➔ Non-degradable devices (first generation):

- These devices are to be removed by the dentist thereby controlling the time of exposure to the device depending on the status of pocket healing. Major disadvantage is an extra visit to the dental office.

➔ Degradable Devices (second generation):

- These devices get degraded on its own in the Sulcus, but the time of exposure and contact cannot be controlled by the dentist.[14]

According to Liechty et al the drug can follow one of the following mechanism for controlled release[15]:

1. Desorption of surface bound/ adsorbed drugs
2. Diffussion through the carrier matrix
3. Diffusion(in the case of nano capsules) through the carrier wall
4. Carrier matrix erosion
5. Combined erosion/diffusion process

The efficacy of a drug delivery system is mainly affected by the biological environment and the properties of the polymer and the drug.[16] The mode of delivery primarily controls the drugs success and failure.

DRUGS USED IN LOCAL DRUG DELIVERY:

The drugs most commonly used are[4]:

1. Tetracyclines

- This group of antibiotics are broad spectrum bacteriostatic antibiotics that are more effective against gram positive bacteria than gram negative. They have been frequently used in treating refractory periodontitis including localized aggressive periodontitis (LAP).

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- They have the ability to concentrate in the periodontal tissues and inhibit the growth of Aggregatibacter actinomycetemcomitans.

- Their concentration in gingival crevice is 2 to 10 times than that in serum therefore a high drug concentration is delivered into the periodontal pockets.

- Even at a low GCF concentration (2 to 4 µg/ml) they are very effective against many periodontal pathogens.

- Tetracycline HCL – It is administered in a dose of 12.7mg over a period of 7-10 days. It is able to maintain concentrations of tetracycline in gingival fluid in excess of 1,300 µg/ml for 7 day period.

2. Minocycline-

- It is a tetracycline effective against a broad spectrum of microorganisms. In patients with adult periodontitis, it supresses spirochetes, Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum, Eikenella corrodens and Actinobacillus actinomycetemcomitans.

- A single Minocycline microsphere isloaded with 1mg of antibiotic and an average dose of 46.2mg is adminstered. Minocycline gel is dispensed in a 2.5g tube and 0.5g is administered in a single application.

3. Doxycycline-

- It is a semisynthetic tetracycline that has a bacteriostatic action against Porphyromonas gingivalis, Prevotella intermedia and Campylobacter rectus. 42.5 mg of doxycycline hyclate is dispensed in a syringe and is administered for 7 days.

4. Metronidazole-

- It is a nitroimidazole compound that is bactericidal to anaerobic organisms and disrupts bacterial DNA synthesis. It is not the drug of choice for infections caused by A.actinomycetemcomitans infections however is effective against it when used in combination with other antimicrobials. It is also effective against anaerobes such as Porphyromonas gingivalis and Prevotella intermedia.

- It has been used clinically to treat gingivitis, ANUG, chronic periodontitis and aggressive periodontitis. It has been used as monotherapy and also in comibation with SRP and with other antibiotics.

- It is administered as Metronidazole benzoate in gel form and 0.3g of gel is sufficient for treatment of pocket for 6-8 teeth whereas 1g of gel is sufficient for pockets of approx. 20 teeth.

5. Chlorhexidine[27]

- It is one of the most effective topical agents, long been used as an effective antimicrobial agent. It has been shown to be an effective agent in plaque inhibition (Loe et al 1976) because it is well retained in the oral cavity, reacting reversibly with receptors in the mouth due to its affinity for hydroxyapatite and acidic salivary protein.

- It has a bactericidal effect due to the cationic molcecule binding to extra microbial complex and negatively charged microbial cell walls, thereby altering the cells osmotic equilibrium thereby inhibiting pellicle formation.

- It is effective against gram positive, gram negative and yeast organism. It is also effective against Candida albicans.

- It is administered in a dose of 2.5mg per chip over a period of 7-14 days and shows a biphasic release profile.

LOCAL DRUG DELIVERY DEVICES:

The mode of administration of local drug delivery system can vary according to the dentist and the preferred drug of action. At present, 5 products have become commercially available viz.Tetracycline fibers, Metronidazole gel, Minocycline Ointment, Chlorhexidine Chip and Doxycycline Hyclate in a resorbable polymer.[8] The various devices and methods used to administer these drugs are discussed in detail below.

1. Fibers:

- These are thread like devices which act as reservoirs for the drug and are inserted in the pocket and held in place by a periodontal dressing or secured in place with cyanoacrylate adhesive for sustained release.

- Tetracycline is most commonly released by this device.

- There are two types of fibers that are commercially available viz. Hollow fibers and Monolithic fibers.

- Tetracycline release through hollow fibers was first introduced by Goodson and Offenbacher. Hollow fibers are fibers made of cellulose acetate or Cupraphane cellulose filled with tetracycline but without rate control delivery.

- They release the drug by diffusion through the reservoir wall. The major drawback with this system was that the drug was released at a very high rate on the first day and was not released in a controlled manner leading to early exhaustionof the drug.[17]

- Monolithic fibers were made in order to retard the drug release from the fibers. These fibers were made by impregnating drug into molten polymer , spinning it on high temperature followed by a quick cooling.[18]

- The current FDA approved Tetracycline fibers being used is ACSTITE which is a non resorbable cylindrical drug delivery device made of a biologically inert Ethylene Vinyl Acetate (EVC) Copolymer that is 23cm long, 0.5 mm in diameter and contains 12.7mg tetracycline loaded with 25% tetracycline HCl powder.[19] It is placed in the pocket for 7-10 days. This delivery system is able to maintain concentrations of tetracycline in gingival fluid in excess of 1,300µg/ml for a 7 day period with mean concentrations of 43 µg/ml in the superficial portions of the pcoket wall. [20,21]

- According to Tonnetii et al, a study conducted on a sample of 20 patients over a period of 3 months, a single application of fiber therapy along with scaling and root planing when compared to only scaling and root planing , a vehicle control and an untreated control, the tetracycline fibers resulted in a decrease in probing depth by 1.6mm , increase in attachment level by 0.9mm and decrease in bleeding on probing by 70%.[22]

- A recent advancement to tetracycline fibers has been developed which is a bio-resorbable teracycline fiber with a base of collagen film , available as PERIODONTAL PLUS AB. Its main advantage is that it does not require an additional appointment for removal as it biodegrades within 7 days. The fibril itself releases anti collagenase enzyme as it degrades. This system is dispensed in vials containing

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25 mg of fibrillar collagen which contains 2mg tetracycline HCl. It has said to generate a concentration of 1500 µg/ml of GCF. It has an added advantage of having a hemostatic ability.[10]

2. Films:

- These are devices in which the drug is encapsulated and distributed throughout the polymer. The mechanism of release depends on the polymer being used.

- Water insoluble non degradable polymer composed films release drugs by diffusion alone whereas those that are released by diffusion and matrix erosion/dissolution use soluble or biodegradable polymers.[23]

- The ideal film thickeness should not be more than 400 micrometres and should have sufficient adhesiveness.

- Films of various polymers have been made for controlled release of drugs such as natural biodegradable devices composed of cross linked fish gelatin (bycoprotein) containing chlorhexidine diacetate or chlorhexidine hydrochloride, have been developed by Steinberg. Biodegradable polymer based films such as poly (lactide co glycolide) (PLGA) containing tetracycline have been developed as well. Advantage of this being no additional appointment needed as the film erodes in the gingival crevice.[17]

- Non biodegradable ethyl cellulose based films delivering chlorhexidine diacetate, metronidazole, tetracycline and minocycline have also been developed and clincally tested.

- The film being most commonly used is PerioChip which is a bioabsorbable device composed of cross linked hydrolysed gelatin and glycerine for local delivery of chlorhexidine digluconate. This system shows an initial burst effect by which 40% of chlorhexidine as released in the first 24 hours followed by a constant slower release over about 7 days.[24]

- Each chip is 5mm long, 5mm wide, 1mm thick pliable strip loaded with 2.5mg of chlorhexidine gluconate. The advantage of this chip is that it does not require any additional aids for retention because of its adhesive nature.[25]

- The GCF concentration is about 1000 µg/ml over a period of 7 days. The number of chips to be placed depends on the number of lesions. The chip biodegrades in about 8-10 days.

- According to a study conducted by Jeffcoat et al on 447 subjects observed over a period of 9 months where chlorhexidine chips were placed in pockets 5-8mm deep , the chip applications were repeated at 3 or 6 months treated with scaling root planing and chip placement led to a decrease in probing depth by 0.95mm and gain in clinical attachment level by 0.75mm.[24]

- The only adverse effect noticed by this delivery system is the yellow staining of teeth due to iron sulphides being formed.

- Perguini et al further developed a new delivery system utilising ipriflavone in a new chitosan/PLGA film delivery system. He compared monolayer films made of ipriflavone loaded PLGA micromatrices in chitosan film with multilayer films composed of chitosan/PLGA/chitosan and showed that multilayered films represent a suitable dosage form to prolong ipriflavone release for 20 days.[26]

- Periocol CG is another preparation formulated by incorporating 2.5mg of chlorhexidine from a 20% chlorhexidine solution in collagen membrane. Size of the chip is 4x5mm and thickness is 0.25-0.32mm and 10mg wt. The collagen in this system attracts cytokines , fibroblasts and clotting fctors and accelerates clot attachment , eventually resorbing after 30 days.[27]

- Ethyl cellulose film containing 30% minocycline can also be used and results in eradication of pathogenic flora from pocket after 14 days. (Pragati et al)[17]

3. Gels:

- These comprise of injectable system of local drug delivery where semi solid preparations distributed with adequate concentration of drug is injected or placed in the required site with help of a blunt cannula.

- The major advantage with gels is their biocompatibility and bioadhesivity and they are eliminated through normal metabolic pathways.[28]

- The disadvantage with this system is that the thickness of the syringe needle prevents the needle from reaching the depth of the pocket and the amount of pressure required to force the gel out of the needle makes the placement unstable.

- A multi mode syringe is most commonly used for delivery of the gel.

- The commonly used hydrogels and oleo gels are tetracycline (2.5%), Metronidazole (25%), metronidazole benzoate (40%), Minocycline gel (2%).[17]

- 10% doxycycline hyclate gel (ATRIDOX) contains 42.5mg doxycycline that shows levels in GCF peaking to about 1,500-2000 µg/mL in 2 hours. And the levels remained above 1000 µg/mL through 18 hours. The gel solidifies into a wax like consistency within minutes of placement.[29]

- In a study conducted by Polson et al on a sample of 179 patients over a period of 9 months, application of Doxycycline gel showed a reduction of probing depth by 1.80mm and a gain in attachment level by 1.00mm.[29]

- Chlo-Site is also a gel that contains 1.5% chlorhexidine of xanthan type gel that gets resorbed from the pocket within 15-30 days. It has excellent bioadhesive properties.[27]

- Another common gel used is Elyzol 25% dental gel, which contains metronidazole concentrations above 1000 µg/mL in the pocket for about 8 hours.[30]

- In a study conducted by Kianne and Radvar on 46 patients suffering from adult periodontitis, a single application of metronidazole gel over 6 months showed a decrease in probing depth by 0.93mm, increase in attachment level by 0.54mm and decrease in bleeding in probing by 33.2%.[31]

4. Strips:

- Acrylic strips fabricated by either solvent casting or pressure melt method coated with 25% tetracycline hydrochloride, metronidazole or chlorhexidine have also seen to be effective in reducing the number of motile rods.

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- The most effect has been observed with amoxicillin-clavulanic acid loaded strips where the effect persisted even after 3 weeks of removal.[17]

- Kimura et al used the first controlled released strip containing ofloxacin using poly methacrylic acid and hydroxypropyl cellulose as polymer which showed good long term clinical improvement.[17]

- The only disadvantage with this system is that the drug delivery is not prolonged.

5. Micro particle system:

- This system consists of a biodegradable polymer, which dissolves and releases the drug containing micro particles between 10-500 microns.

- The polymer is usually a poly alpha hydroxyl acid such as poly lactide (PLA) or poly lactide-co-glycolide(PLGA)

- PLGA microspheres containing minocycline is usually used in order to get rid of Porphyromonas gingivalis from the periodontal pocket.[17]

- Baker et al fabricated a biodegradable micro particle system containing tetracycline consisting poly micro particle in a thermo reversible gel base that is injected in liquid form and sets into gel at body temperature.[17]

- The new FDA approved microsphere is ARESTIN, which is a 2% minocycline microsphere encapsulated into bioresorbable microspheres (20-60 μm) in diameter and has a resorption time of 21 days. GCF hydrolyses the polymer and releases the minocycline for a period of 14 days before completely resorbing.[17]

6. Nano Particles:

- Due to their small size, these have high dispersibility in aqueous medium, controlled release rate, increased stability and also have access to regions that are inaccessible to other drugs like deep periodontal pockets. [18]

- These systems reduce the frequency of administration and provide a uniform distribution of active agent over an extended period of time.[17]

- They have a particle size ranging from 50-180 nm.

- Biocompatible nanoparticles composed of 2-hydroxyehtyl methacrylate (HEMA) and polyethylene glycoldimethacrylate (PEGDMA) could be used as a drug delivery system.[17]

- Dung et al used Antisense oligonucleotide loaded chitosan tripolyphosphate (TPP) nano particle and showed sustained release of oligonucleotides.[17]

- Pinon et al conducted a preliminary in vivo study in dogs with periodontal defects using Triclosan loaded polymeric nanoparticles and concluded that triclosan loaded nano particles can penetrate junctional epithelium.[17]

CONCLUSION

From the preceding review of various drug delivery systems it can be concluded that biodegradable nanoparticles containing antibiotics in a biocompatible polymer can serve to be very beneficial to eradicate bacteria. This system produces good results when used solely, however, when used in conjunction with scaling and root planning, the results maybe enhanced. Local drug delivery system with sustained release has the potential to be included as one of the primary therapies in management of periodontal diseases. These devices are proving to be more reliable, convenient, easy to use, less risk prone and is more patient compliant.

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