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CONTROLLED RELEASE DEVICES AS ADJUVANTS IN NONSURGICAL PERIODONTAL THERAPY: A REVIEW

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Abstract:

Periodontitis is a multifactorial disease that affects the teeth's supporting tissues. Mechanical debridement and administration of antibacterial medicines have been used to treat periodontal infections. The local drug delivery (LDD) system is a potentially beneficial technique for periodontal disease management. It is not appropriate for usage as a monotherapy since it performs better clinically when used in conjunction with scaling and root planning.

KEYWORDS: Local drug delivery; periodontitis; antimicrobials

Introduction:

In 1979, Dr. Max Goodson introduced the notion of LDD.[1] The primary motivation for LDD is to insert an antibiotic or antiseptic chemical directly into the periodontal pocket, in contact with the root surface, thereby eradicating harmful germs.

Periodontitis is a multifactorial disease that primarily affects the tooth-supporting tissues. Periodontal disorders can be managed with mechanical debridement and antibacterial medication delivery.

Oral microbiota includes two variants, one being symbiotic organisms seen in healthy periodontium and the other is dysbiotic organisms seen in diseased periodontium.

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Antimicrobial supplements in recent years include probiotics, photodynamic therapy, one stage full mouth disinfection, and local drug delivery (LDD)

Local drug delivery (LDD) system is one of the possibly helpful methods for managing periodontal disease. This treatment is most effective when combined with scaling and root planing, and should not be done alone.

Antibiotics like metronidazole, chlorhexidine, minocycline, doxycycline, and tetracycline can be delivered topically to the mucosa in addition to non-surgical treatment. Applying these medications to periodontal pockets can inhibit the growth of harmful germs and reduce inflammation.

History:

Going back in time as to how the usage of local drug delivery started, a few scientists like Ellison 1970, Genco et al. 1969, Keyes 1970, Socransky 1970, used antibacterial agents and tested them and was prompted by the abundant evidence implicating microorganisms as the primary cause of periodontal diseases. According to Loesche, 1976 suggested that antibacterial agents could be effective in the control of microorganisms present in the periodontal pocket. The principal and local treatment for the antibacterial agents in the periodontal disease has been mouth rinses and to a lesser degree, topical application in adhesive carrier. They may have been effective in reducing the formation of supragingival plaque but hardly any evidence suggesting that they would reach the site of action in destructive periodontal disease. Goodson, 1979 then proposed the concept of tetracycline filled fibres which was delivered locally at the site of action in a periodontal disease. It was the controlled delivery of antibacterial agent from within the periodontal pocket. The tetracycline was impregnated in the small diameter cellulose acetate hollow fibres. After placing the fibres in the pocket, sustained levels of the antibacterial agent were seen and also there were decrease in the signs of the disease.

It was Dr. Max Goodson in 1979 who championed and developed controlled release local drug delivery of therapeutic agents into a viable concept.

Dr. Max Goodson et al. made the first proposal in 1979. Later, D. Steinberg et al. (1990) investigated chlorhexidine as a local medication delivery system. Hardy et al in 1982 delivered chlorhexidine (CHX) solution within the

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periodontalpocket of 3 mm from the apical plaque border to the bottom of the deep pockets. Stoller et al. (1998) investigated doxycycline hyclate.[2]

CLASSIFICATION:

Local drug delivery can be classified as follows,

Based on their mechanism of action.

1. Langer & Peppas (1981)

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.

Films / slabs e.g. Chlorhexidine chip.

i. non-degradable films

ii. Degradable films

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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[3]

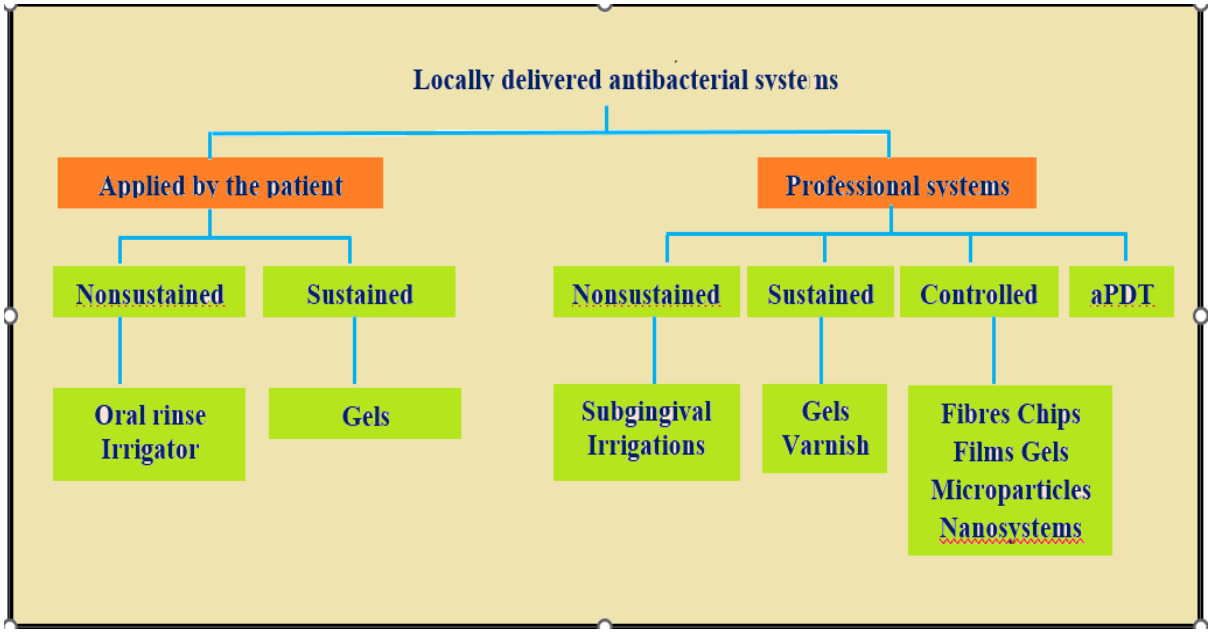

Figure 1: Classification of locally delivered antibacterial systems.[4]

Uses:

1. It can be used in conjunction with scaling, root planing, and maintenance therapy.[4]
2. Devices can be either sustained release (drug delivery for less than 24 hours) or controlled release (drug delivery for more than 24 hours).
3. No gastrointestinal tolerance is observed.
4. No side effects linked to systemic antimicrobials are observed.

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5. LDD achieves 100-fold higher concentrations in the subgingival site compared to systemic drug regimen.
6. It uses antimicrobial agents that are not appropriate for systemic administration, such as various broad-spectrum antiseptic solutions[5].
7. It is less invasive than surgery.

TABLE 1:Most important local drug delivery agents along with their commercial names have been listed below.[6]

DRUG	DELIVERY	PRODUCT AVAILABLE	DOSAGE FORM AND CONCENTRATION
Metronidazole dental gel	Sustained	Elyzol (25%)	Biodegradable gel
Minocycline	Sustained	Dentomycine gel (2%) Arestin (2%)	Biodegradable gel Biodegradable mix in syringe
Tetracycline fibre	Controlled	Acticite (25%) Periodontal plus AB	Non resorbable fibre Resorbable fibre
Chlorhexidine chip	Controlled	Periochip(2.5mg) Periocol(2.5mg) Chlosite (1.5%)	Biodegradable device Biodegradable gel
Doxycycline polymer	Controlled	Antridox (10%)	Biodegradable

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Table 3: Local drug delivery agents[6]

LIMITATION:

1. Patients who have a history of known hypersensitivity to the antibacterial used as a local medication should not take it.

2. People with asthma and infectious diseases like AIDS and tuberculosis should not get antimicrobials using ultrasonic devices.[7].

3. Placement difficulty (furcation areas/deeper periodontal pockets).

4. Labor-intensive and time-consuming.

5. Costly in comparison.[8].

RATIONALE

The majority of systemic antimicrobials are associated with microbial resistance due to inappropriate usage, failure to reach the site of infection and achieve enough concentration, and inadequate tissue penetration.[9]

The therapeutic goal of LDDS is achieved by placing antimicrobial agents directly in the subgingival sites/periodontal pocket, which releases the active drug in an immediate or controlled/sustained fashion to combat the microbial attack while minimizing its adverse effects on non-oral systemic/body sites.[10]

An ideal LDDS must be simple to give, biodegradable, biocompatible, and non-irritating to tissues.[11]

Ideal Requirement of Locally Delivered Drug:

1. The drug delivery system should deliver the drug to the base of the pocket.

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2. It should be effective against periodontal pathogens only and not on commensal microflora.
3. The target dose should be sufficient enough to kill the targeted organisms also should not have any adverse effects.
4. Substantivity.
5. Prolonged shelf life.
6. It should be both biodegradable and biocompatible.
7. Ease of placement.
8. Should be economical[12,13,14]

ADVANTAGES:

1. Maintains an antibacterial agent concentration in subgingival locations that is 100 times greater.

2. The method works well for substances like chlorhexidine that cannot be administered systemically.

3.It is possible to administer little amounts.

4. Drug resistance and superinfection are uncommon.

5. A decrease in the frequency of medication administration.[15]

DISADVANTAGES:

1. Difficulty accessing deeper pockets in furcation lesions.
2. Does not affect nearby structures, including tonsils and buccal mucosa, potentially leading to reinfection.
3. Time-consuming.
4. In presence of generalized pockets , other periodontal therapies should be used.

VARIOUS DRUGS/AGENTS USED IN THE LOCAL DRUG DELIVERY SYSTEM

1. Tetracycline

2. Doxycycline
3. Minocycline
4. Metronidazole
5. Chlorhexidine

TETRACYCLINE:

Tetracycline has been widely used to treat periodontal disorders. Tetracycline is a bacteriostatic antibiotic that prevents bacterial protein synthesis and inhibits tissue collagenase activity.

FIBERS(ACTISITE):

These are non-resorbable, biologically inert plastic copolymers (ethylene and vinyl-acetate) loaded with 25%w/w tetracycline HCL powder and packaged as a 0.5mm diameter, 23cm long thread. Recently, bio-resorbable tetracycline fibre based on collagen films have been produced and are commercially marketed as PERIODONTAL PLUS AB (Fig 2).

Figure 2: Periodontal plus ab[18]

GELS:

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Tetracycline serrati peptidasefig. (3) containing periodontal gel, the purpose was to reduce the polymer concentration and to obtain reasonable viscosity at a lower concentration of pluronic acid.

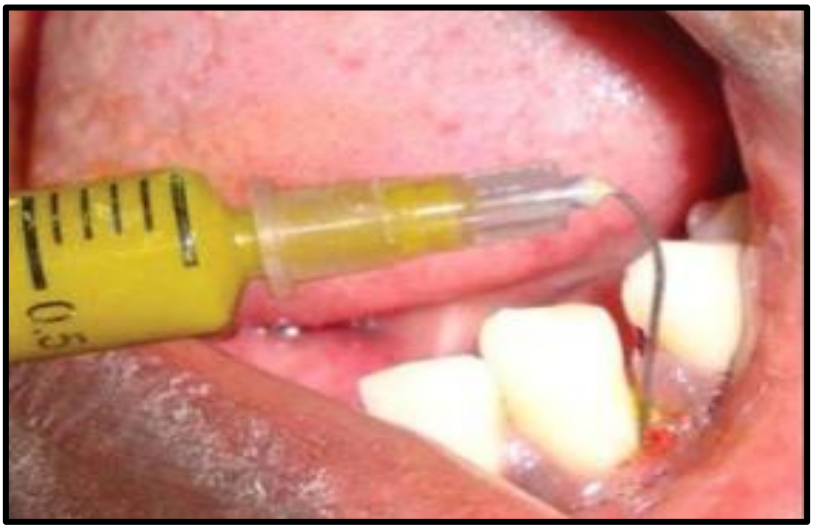

Figure 3: Application of Tetracycline Gel [18]

Doxycycline:

Doxycycline is a bacteriostatic medication**.**

The efficacy of 10% doxycycline hyclate as a local antibacterial agent in reducing probing depth and obtaining clinical attachment. It is a liquid biodegradable solution that hardens after applied in the periodontal pocket.18.17

Minocycline:

Minocycline HCL, a semi synthetic tetracycline is one of the most active antibiotics for micro-organisms associated with periodontitis. The modes of local application are

1. Film
2. Microspheres
3. Ointment.

FILM;

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Ethyl cellulose films containing 30% of minocycline which completely eradicates pathogenic flora from the periodontal pocket after 14 days.

Microspheres:

A new, locally delivered, sustained release form of minocycline microspheres (ARESTIN) Fig (4) for subgingival placement is available. The gingival crevicular fluid hydrolyses the polymer and releases minocycline for a period of 14days or longer before resorbing completely.[17]

Figure 4: Arestin (Microspheres)[17]

OINTMENTS:

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

Metronidazole:

Elyzol is a topical drug that is applied viscously to the periodontal pocket and contains an oil-based metronidazole 25% dental gel (Fig. 5). According to one study, using combination therapy for probing depth reduction produced better results throughout a 9-month monitoring period.[16,17]

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Figure 5: Elyzol (Metronidazole)[16]

CHLORHEXIDINE:

Chlorhexidine is an antifungal and antibacterial agent that is a member of the biguanide family. The pocket flora is only temporarily affected by chlorhexidine, which is used in mouthwashes.[16]

PERIOCHIP:

A tiny chip made of a biodegradable hydrolyzed gelatin matrix mixed with glycerine, water, and 34% chlorhexidine cross-linked with glutaraldehyde Figure 6: The chip releases chlorhexidine in vitro in two phases: for the first 24 hours, about 40% of the chlorhexidine is released, and for the next 7–10 days, the remaining chlorhexidine is released in a nearly linear pattern.[17]

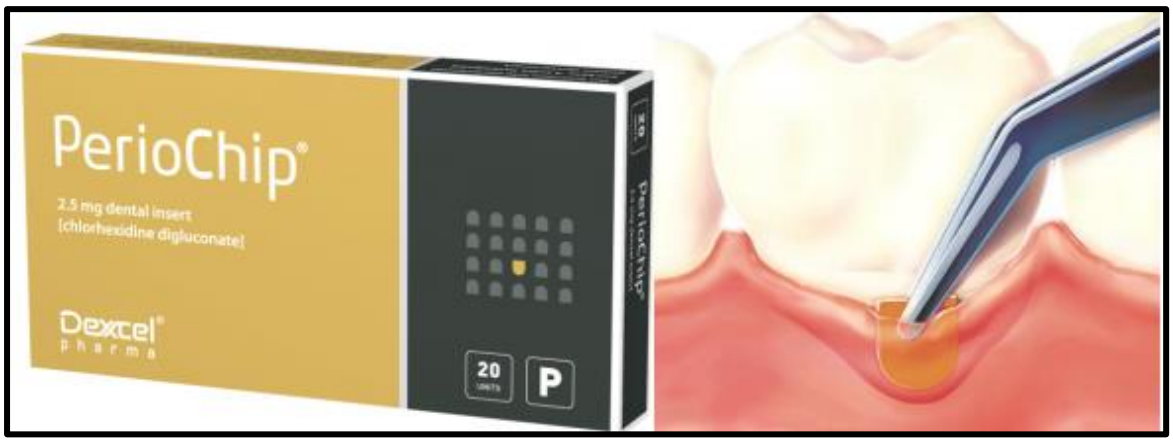

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Figure 6: Application of Periochip (Chlorhexidine).[17]

PERIOCOL-CG:

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

It has been shown that it resorbs after 30 days and their coronal edge degrades within 10 days.[17]

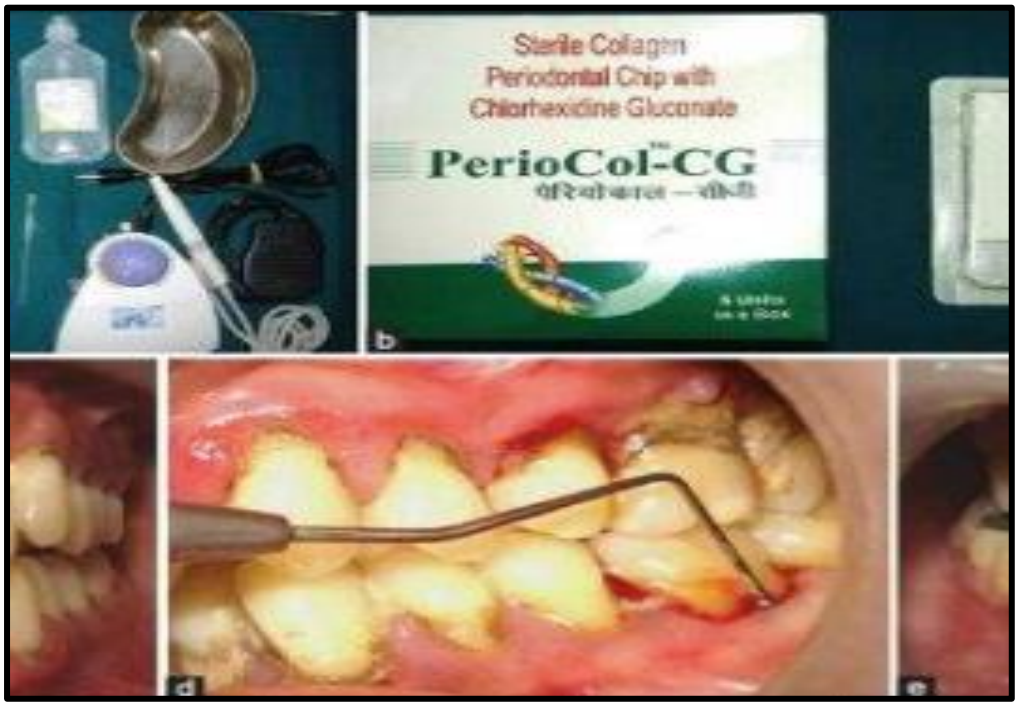

Figure 7: Application of Periocol-CG.[17]

CHLOSITE:

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

Figure 8: Chlo-Site[16]

HERBAL AGENTS USED IN LOCAL DURG DELIVERY

Recently, usage of the herbal product has increased because of the relatively safe nature of herbal extracts.

Neem: Neem leaf extract can help reduce bacterial load in dental plaque levels that cause the initiation and progression of periodontitis.

Cranberry and garcinia fruit: Berries(fruits) have been recognized as a rich source of bio actives with a broad spectrum of activities such as anti-inflammatory, anti-bacterial, anti-oxidant, anti-viral, and anti-cancer among others. Americancranberry (*Vaccinium macrocarpon*), has demonstrated excellent efficacy in the treatment of various ailments. Another berry, *Garcinia cambogia***,** commonly known as brindle berry is used as a weight-loss supplement, especially in people suffering from Type-2 diabetes mellitus.

Aloe vera: Aloe vera is the commonly used medicinal cactus plant that belongs to the Liliaceae family. It is effective in reducing gingival bleeding, inflammation, and swelling.

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Lemon Grass: At a concentration of 2% lemongrass, essential oil appears to be an effective local drug delivery agent as an adjunct to mechanical nonsurgical periodontal therapy.

Green Tea: Green tea is an effective local drug delivery agent as it contains a number of bioactive chemicals such as flavonoids, including catechins and their derivatives. Mageed MJ et al .[22]investigated the antimicrobial effects of green tea extracts on Porphyromonas gingivalis, and he found that alcoholic green tea extract was able to inhibit Porphyromonas gingivalis.

Tea Tree Oil: Elgendy Et al [23]suggested that TTO is effective as an adjunctive treatment of scaling and root planing on the clinical parameters. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2, lipoxygenase, and inducible nitric oxide synthase enzymes and inhibits the production of the inflammatory cytokines.

Oak: Oak has been evaluated as a local drug delivery agent in periodontal diseases.

Babul: Its bark contains tannins (24-42%) which have analgesic, anti-inflammatory properties.

Bakul: One of the major pharmacologically active ingredients lupeol is present in bakul has anti-inflammatory and anti-microbial properties.

CONCLUSION

When local drug administration is used in conjunction with scaling and root planing, it may enhance outcomes in areas that don't react well to traditional treatment. The best chance of success with this therapeutic approach may be seen in a small number of localized persistent lesions in patients who are otherwise under good care. Drug-resistant bacterial strains can be prevented and the misuse of chemotherapeutic medicines can be minimized by the prudent administration of antimicrobial medications in accordance with prudent pharmacologic principles. It is possible that the local medication delivery used as an adjuvant could provide a specific but constrained positive effect. Consequently, the doctor will have to base their decisions on the intended results of the therapy.

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