Lec 9 Locally delivered, controlled-release antimicrobials

Objectives

Periodontitis is a bacterial infection. The focus of most nonsurgical periodontal therapy, including scaling and root planing is to combat infection. Chemical antibacterial strategies include systemic drug delivery, oral rinses or toothpaste, and irrigating devices, but none of these therapies has provided significant clinical benefit in reducing the signs of periodontitis.

In the past few decades, a new strategy has emerged. **Several controlled-release delivery systems have been developed to deposit antimicrobials directly into the periodontal pocket and maintain effective concentrations of the drug for an extended period**.

In some cases, they are used as monotherapy, and in other cases, they are administered adjunctively with scaling and root planinig, which is generally considered by the professional community to be the **best** approach. Locally delivered, controlled-release antimicrobials have been designed to maintain **high and clinically relevant concentrations** of drug within the GCF for extended periods of time

Types

A. Chlorhexidine-based products:

1. Chlorhexidine chip

2. PerioCol-CG

3. Chlo-Site

B. Doxycycline-based products:

1. Ligosan slow release 2. Doxycycline gel (Atridox)

C. Periodontal Plus AB

D. Minocycline Microspheres (Arestin)

Chlorhexidine-based products:

Chlorhexidine chip:

DESCRIPTION

Chlorhexidine chip is a small, orange-brown, rectangular chip (rounded at one end) for insertion into periodontal pockets.

- Each chip weighs approximately 6.9 mg and contains 2.5 mg of chlorhexidine gluconate in a biodegradable matrix of hydrolyzed gelatin
- It also contains glycerin and purified water.
- Each chip is individually packed in a separate compartment of an aluminum blister pack.
- Store at 20° - 25°C with excursions permitted to 15° - 30° C (59° - 86°F).

DOSAGE AND ADMINISTRATION

- One chip is inserted into a periodontal pocket with probing pocket depth (PPD) 5mm or greater.
- Treatment is recommended to be administered **once every three months** in pockets with PPD remaining 5mm or greater.
- The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion.
- The chip should be grasped using forceps (such that the rounded end points away from the forceps) and inserted into the periodontal pocket to its maximum depth.
- The chip **does not need** to be removed since it biodegrades completely.

In the unlikely event of chip dislodgement, several actions are recommended, depending on the day of chip loss.

• If dislodgement occurs **7 days or more after placement**, the dentist should consider the subject to have received a full course of treatment.

• If dislodgement occurs within **48 hours after placement**, a **new chip** should be inserted.

• If dislodgement occurs **more than 48 hours** after placement, the **dentist should not replace the Chip, but reevaluate the patient at 3 months** and insert a new chip if the pocket depth has not reduced to < 5mm.

MECHANISM OF ACTION

• 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**.

Chlorhexidine is active against a broad range of microbes. It disrupts the cell membrane and causes precipitation of the cytoplasm, resulting in cell death.

• No adverse alterations in the oral microbial flora or overgrowth of opportunistic microorganisms have been observed.

INDICATIONS AND USAGE

• Chip is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with periodontitis.

• Chip may be used as a part of a periodontal maintenance program, which includes good oral hygiene and scaling and root planing.

CONTRAINDICATIONS

• Chip should not be used in any patient who has a known sensitivity to chlorhexidine.

INFORMATION FOR PATIENTS

Patients should avoid brushing for minimum **3 days** & dental floss at the site of chip insertion for **10 days** after placement, because flossing might dislodge the chip. Afterwards, all other oral hygiene measures may be continued as usual.

• No restrictions regarding dietary habits are needed. They have to be cautious and gentle when eating from treated side.

• Dislodging of the chip is uncommon; however, patients should be instructed to notify the dentist promptly if the chip dislodges.

• Patients should also be advised that, although some mild to moderate sensitivity is normal during the first week after placement of chip, they should notify the dentist promptly if pain, swelling or other problems occur.

PerioCol-CG:

• It is a small, 10-mg chip.
• Designed as a collagen matrix into which chlorhexidine gluconate (2.5 mg) is incorporated from a 20% chlorhexidine solution that is its active ingredient.
• The chip is designed for insertion into the periodontal pocket and resorbs after 30 days, but its coronal edge degrades within 10 days.
• It releases chlorhexidine in vitro at a rate of approximately 40% to 45% in the first 24 hours, followed by a linear release for 7 to 8 days, and it has a shelf life of 2 years.

Chlo-Site:

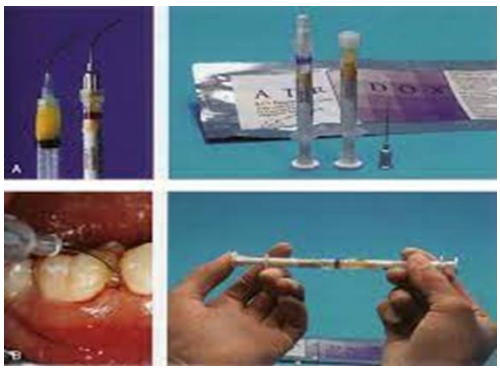
• Chlo-Site is a xanthan gel, containing 1.5% chlorhexidine in 0.5 mL of gel, which is injected into the periodontal pocket.
• The gel contains two types of chlorhexidine: a slow-release chlorhexidine digluconate (0.5%) and a rapid-release chlorhexidine dihydrochloride (1.0%).
• The gel is retained within the pocket and is not easily dislodged by the GCF or saliva.
• The gel disappears from the pocket in 10 to 30 days and is reported to achieve a chlorhexidine concentration in GCF of more than 100 µg/mL for an average of 6 to 9 days and to maintain an effective concentration for at least 15 days

Doxycycline-Based Products

Ligosan Slow Release:

• Is a resorbable doxycycline gel for periodontal application provided in a laminate pouch and stored under refrigeration.
• It contains 1, 2, 4, 8, 10, or 16 single-application cylinder cartridges, each containing 260 mg
of ligosan slow release.
• The product is used by inserting the cartridge into the caulking gun, opening the spray nozzle, and then discharging the gel to the bottom of the pocket.
• The maximal value in the GCF will be within the first 5 hours. Concentrations in the GCF remained above 16 µg/mL for at least 12 days.
• Mechanical hygiene in the area should be avoided for 7 days.

Doxycycline gel (ATRIDOX):



DESCRIPTION:

• ATRIDOX product is a subgingival controlled-release product composed of a two-syringe mixing system. Syringe A contains 450 mg of the ATRIGEL Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly (D-L-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains 50 mg of doxycycline hyclate which is equivalent to 42.5 mg doxycycline.

• The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% of doxycycline hyclate.

• Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of the drug pfor a period of 7 days.

MECHANISM OF ACTION:

• Doxycycline is bacteriostatic, inhibiting bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites.

• No overgrowth of opportunistic organisms was observed after the use of the doxycycline gel.

INDICATIONS AND USAGE:

It is indicated for use in the treatment of periodontitis for a gain in clinical attachment, reduction in probing depth, and reduction in bleeding on probing. The doxycycline gel is biodegradable and does not require removal. The doxycycline gel is used by injecting the mixed contents of the two syringes directly into the pocket. The pocket contents are then covered with a periodontal dressing or a cyanoacrylate dental adhesive.

Periodontal Plus AB:

• Periodontal Plus AB is a bioresorbable tetracycline fiber.

• It is 25 mg of pure fibrillar collagen evenly impregnated with approximately 2 mg of tetracycline hydrochloride.

• The fibers are packaged as a strip containing four individually packed and separable sterile product packs.
• The fiber biodegrades in the periodontal pocket within 7 days.
• The fiber should be retained with a periodontal dressing or covered with a dental adhesive for 10 days.

Minocycline Microspheres: (Arestin)

DESCRIPTION:

• ARESTIN®

(minocycline hydrochloride) Microspheres is a subgingival controlled-release product containing the antibiotic minocycline hydrochloride incorporated into a bioresorbable polymer for professional subgingival administration into periodontal pockets.
Each unit-dose cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base.

MECHANISM OF ACTION:

• Minocycline belongs to the tetracycline class of antibiotics and has a broad spectrum of activity. Its bacteriostatic, antimicrobial activity results from the inhibition of protein biosynthesis.

INDICATIONS AND USE:

• ARESTIN is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with periodontitis.
• ARESTIN® may be used as part of a periodontal maintenance program which includes good oral hygiene, and scaling and root planing.

DOSAGE AND ADMINISTRATION:

• ARESTIN® is provided as a dry powder, packaged in a unit-dose cartridge with a deformable tip, which is inserted into a spring-loaded cartridge handle mechanism to administer the product.

• The administration of ARESTIN® does not require local anesthesia.
• Professional subgingival administration is accomplished by inserting the unit-dose cartridge to the base of the periodontal pocket and then pressing the thumb ring in

the handle mechanism to expel the powder while gradually withdrawing the tip from the base of the pocket.

• ARESTIN® does not have to be removed, as it is bioresorbable, nor is an adhesive or dressing required.

PATIENT INSTRUCTIONS:

• Avoid chewing hard, crunchy, or sticky foods with the treated teeth for 1 week, as well as avoid touching treated areas.
• Patients should also postpone the use of interproximal cleaning devices around the treated sites for 10 days after administration of ARESTIN.

Rationale for local delivery and controlled release

Periodontal diseases are bacterial infections; the requirement for bacteria to initiate the periodontal lesion is well recognized. The antibacterial effect of SRP or other mechanical therapy generally results from a **reduction of the bacterial load or an alteration of the composition of the bacterial flora** at the periodontal site, but the antibacterial effect of mechanical treatment alone **is insufficient**, providing the rationale for chemically augmenting the mechanical therapy.

Many strategies have been used to deliver antimicrobial agents to the periodontal pocket at effective doses to reduce the bacterial microflora, including:

✓ Systemic administration
✓ Local administration by local irrigation of fluid formulations or placement of various gels or ointments.
None of these strategies has proved as effective as controlled-release antimicrobials. A drawback of antimicrobials delivered to the pocket but not in controlled-release formulations results from the dynamics of the GCF.

The GCF fills the periodontal pocket space, but the copious flow out of the pocket continuously moves GCF contents to the oral cavity. The flow rate can be markedly enhanced in the setting of inflammation. Antimicrobials delivered to the pocket are quickly washed out of the pocket by the GCF, rapidly reducing the concentration of drug locally to sub-antimicrobial levels.

GCF drug concentrations may need to be elevated above usual levels because microorganisms in the pocket can exist within a protective biofilm structure in the periodontal pocket. Bacterial biofilms can be highly resistant to penetration by fluids, emphasizing the critical need for high GCF concentrations of active antimicrobials, which are achievable only with locally delivered, controlled-release agents (but not possible with locally delivered antimicrobials not in controlled-release formulations or by systemic routes.

Other benefits of locally delivered, controlled release antimicrobials include decreased systemic, off-target effects and a decreased risk for promoting microbial resistance.

Clinical significance:

• Controlled-release agents maintain clinically effective intra-pocket concentrations of antimicrobial for an extended period of time.

• Significantly more patients showed pocket depth reductions 2 mm or more following SRP plus adjunctive therapy versus SRP alone.

Clinical Indications

1. Adjunctive Therapy:

Locally delivered, controlled-release antimicrobials enhance the clinical efficacy of SRP. Studies showed that SRP plus adjunctive therapy could be considered a new standard for nonsurgical periodontal therapy.

2. Surgical Therapy:

Pocket sites that do not seem to respond adequately to nonsurgical therapy and evidence residual probing depth with inflammation are often treated with follow-up surgical therapy. Adjunctive use of locally delivered, controlled-release antimicrobials can improve clinical outcomes after periodontal surgery in regenerative and non-regenerative settings.

3. Peri-implantitis:

Similar to periodontitis, peri-implantitis is an inflammatory disease process that is initiated by local microorganisms and that affects the tissues surrounding an

implant. An opportunity exists to treat diseased implant sites chemically by targeting the local microflora. There is a potential rationale for the use of locally delivered, controlledrelease antimicrobials for the treatment of peri-implantitis.

4. Tobacco Smoking:

Smoking is a well-known risk factor for the development or progression of periodontitis, and it can limit the effectiveness of periodontal therapy. The adjunctive use of locally delivered, controlled-release antimicrobials can enhance the efficacy of SRP in smokers.

Adverse Effects:

- Potential for hypersensitivity reactions (i.e., not to be used in patients with a known sensitivity to any ingredient).
- Potential for the overgrowth of non-susceptible microorganisms, including fungi.
- Headache
- Infection (including upper respiratory tract infection)
- Pain, tooth disorder and toothache
- Autoimmune Syndromes
- Swelling/ inflammation