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PERIOCHIP : A REMEDY FOR PERIODONTAL DISEASES

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ABSTRACT

Periodontal diseases is the dental diseases associated with the mouth infection. Basically gingivitis grow to form the periodontal disease. It infects the periodontal pocket.so overcome this type of diseases, now a days periodontal chip are used. These are polymeric chips containing active pharmaceutical ingredient with base materials which protect the pocket from infection. Various kinds of periodontitis can be cured by the means of periodontal chip. Mainly tetracyclines are used as antimicrobial agent in chip with suitable excipients. Chip can be prepared by solvent casting method. Chip is mainly advantageous for those drugs whom systemic administration is not suitable. So by this way desired release of drug can gated with good acceptance from patient.

Keywords: Gingivitis, Mouth infection, Gum diseases, *In vitro* antibacterial activity, Antiseptic chip, Periodontal flap.

INTRODUCTION

Periodontal diseases are chronic, predominantly gram negative infections of the oral cavity that are initiated in the gingiva and if untreated lead to alveolar bone destruction and eventual tooth loss. Severe periodontitis is found in 5-15% of most populations. Juvenile or early onset aggressive periodontitis that leads to premature tooth loss affects about 2% of the youth.In the last 30 years there has been a lot of research on the pathogenesis of periodontitis and we now understand that the host response to the organisms causing periodontitis varies between individuals. Certain systemic disorders and conditions alter host tissues and physiology which may impair host barrier integrity and host defense to periodontal infection resulting in more destructive disease. In the past two decades a field of periodontal research, known as Periodontal Medicine has emerged investigating the link between periodontal disease and other systemic diseases. There is enough evidence to suggest that periodontal infections can adversely affect systemic health with manifestations such as coronary heart disease(CHD) and CHD-related events such as angina and infarction, atherosclerosis, stroke, diabetes mellitus, preterm labor, low birth weight delivery and respiratory diseases. Also smoking is the factor which may cause periodontal pocket destruction.

TYPES OF PERIODONTITIS

Gingivitis represents a spectrum of diseases whose onset is commonly attributed to the presence of bacteria, but there are other forms of gingivitis that are not primarily plaque-related. Systemic diseases such as diabetes and leukemia can exacerbate plaque-associated gingivitis, as can endocrine changes (puberty, pregnancy), medications (nifedipine, cyclosporine and phenytoin) and malnutrition (vitamin C deficiency). The 1999 classification includes categories for all these forms of dental plaque-induced gingivitis. Non-plaque induced gingival lesions can result from specific bacterial pathogens such as *Neisseria gonorrhea*, from viral infections and from fungal infections.

These gingival diseases are classified differently from plaque-associated gingivitis. Mucocutaneous disorders (e.g., lichen planus, pemphigoid), allergic reactions (e.g., restorative materials, toothpastes, and gum), trauma (chemical, physical or thermal) as well as disorders of genetic origin such as hereditary gingival fibromatosis can also cause no plaque- induced gingival lesions. There are forms of periodontal disease that clearly differ from chronic periodontitis. In the 1989 classification, patients were placed into the early-onset category if they exhibited significant attachment loss in

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the presence of little local factors (plaque and calculus) and were less than 35 years of age. It is true that this disease often occurs in people under 35 years of age, but it may also affect older patients.

The workshop participants concluded that the term early-onset periodontitis was too restrictive and recommended it be replaced with "aggressive periodontitis." Diagnosis of aggressive periodontitis is made on clinical, radiographic and historical findings which show rapid attachment loss and bone destruction, and possible familial aggregation of disease. Except for periodontal disease, patients are systemically healthy. Other features that may be present are periodontal tissue destruction that is greater than would be expected given the level of local factors, elevated levels of *Actinobacillusactinomycetemcomitans*or *Porphyromonasgingivalis*, phagocyte abnormalities and increased production of prostaglandin E2 and interleukin Aggressive periodontitis was also subcategorized into localized and generalized forms to replace localized and generalized juvenile periodontitis. Classification is similar to chronic periodontitis in terms of number of teeth involved and severity of attachment loss.

The classification of periodontal diseases and conditions in this volume should provide a workable framework upon which to study and develop effective treatments for this complex group of infections. It is anticipated that as we learn more about the etiology and pathogenesis of periodontal diseases, future revisions to the classification will be needed. All classification systems have inconsistencies or inaccuracies. The present effort is no exception. Nevertheless, the current classification represents the consensus of an international group of experts and it is hoped that the serve.

DRUG CANDIDATES FOR PERIODONTAL CHIP

- ✓ Drugs with extensive first pass metabolism Eg. Tetracycline
- ✓ Drugs with poor solubility.
- ✓ Drugs with high lipophilicity or high partition coefficient.
- ✓ Drugs which are metabolized by stomach enzymes.
- ✓ Drugs which are volatile in nature Eg. Nitroglycerine
- ✓ Dugs which are unsuitable for topical route
- ✓ Drugs whose biological half-lives are very short.
- ✓ Drugs which are unstable in acidic pH of stomach.

DRUGS USED IN PERIODONTAL DISEASES

The choice of antibiotic in clinical practice may be based on microbiological analysis of the samples obtained from affected sites. More often, therefore, the choice of antibiotic is empirical and based on the clinical signs. Systemic antibiotic therapy for periodontal treatment usually involves monotherapy based on metronidazole, tetracycline, doxycycline, minocycline), clindamycin, ciprofloxacin and the β-lactams (amoxicillin with or without clavulanic acid). *Metronidazole* is a nitro imidazole compound with a broad spectrum of activity against protozoa and anaerobic bacteria. In medicine, it is used in the treatment of trichomonal genital infections, as a prophylactic agent before abdominal surgery, and in the management of severe anaerobic infections. The antibacterial activity against anaerobic cocci, anaerobic Gram - negative bacilli, and anaerobic Gram – positive bacilli had led to its use in the treatment of periodontal diseases. In periodontal treatment, metronidazole has been used both in tablet forms, and less commonly, as a topical application. The drugs is well-absorbed after oral administration and the peak plasma level is usually reached in about one hour. The half-time of metronidazole is about 8 hours and the principal site of metabolism is the liver. Metronidazole is excreted in the urine.

Tetracyclines are a group of broad-spectrum, bacteriostatic antibiotics. They are the first antimicrobial drugs which have been scientifically investigated in periodontology. This group includes tetracycline hydrochloride, minocycline and doxycycline. In their double-blind clinical studies, Rams and Keyes and McCulloch et al., showed that systemic intake of tetracycline statistically significantly reduced probing pocket depth. The risk of the occurrence of periodontal destruction after 7 months was decreased by 43%, and destruction was not stopped in more than one third of the patients. Some authors described the reappearance of the disease after systemic tetracycline therapy. Possible cause of further disease progression are microorganisms inadequately suppressed by tetracycline, such as A. actinomycetemcomitans.

Tetracycline therapy could lead to superinfection with enteric bacteria, staphylococci or with Candida albicans. It seems that the older studies showed beneficial effect against A. actinomycetemcomitans, while newer studies do not support this. This can partly be explained by the higher resistance to these antibiotics. Besides this, positive effects were observed in studies conducted in North America, where different A. actinomycetemcomitansserotypes are present with different virulence factors, than in Europe. We did not find studies in the literature by European authors showing beneficial effect of tetracyclines against A. actinomycetemcomitans. Concerning the choice of tetracyclines, the advantages of doxycycline are one daily dosage, rare gastrointestinal adverse effects, as well as normal calcium absorption. Especially interesting is the usage of low-dosage doxycycline (20-30 mg) during 6-9 months. Clinical attachment gain has been proved, without resistance occurrence or changes in normal periodontal microflora. Besides the antimicrobial effect, doxycycline inhibits collagenase and other matrix metalloproteinase, enzymes responsible for collagen degradation during periodontal infection, so its efficacy is

partly due to this mechanism. Minocycline, as an adjunct to mechanical therapy failed to eliminate A.

Actinomycetemcomitansin all patients, and the disease reoccurred in 25% of the test subjects, despite regular check-ups every 3 months. It seems that the effect of tetracyclines is optimal in patients with 'refractory' chronic periodontitis, while it is not the best choice for treatment of localized aggressive periodontitis, due to the weak effect on A. Actinomycetemcomitansthe antibiotics from this group have.

Metronidazole is a synthetic nitro imidazole. Its action is bactericidal, acting on anaerobic bacteria, including gram-negative rods and spirochetes, through DNA synthesis blocking. Penicillin's inhibit bacterial cell-wall synthesis, and the antimicrobial spectrum of natural penicillins is narrow. Ciprofloxacin is also effective in the treatment of periodontal superinfections caused by enteric bacteria, pseudomonas or staphylococci.

Azithromycin is an antibiotic from the macrolide group, it exerts bacteriostatic activity by blocking of bacterial proteins synthesis. Clindamycin is a pyranoside antibiotic similar to macrolides, with a broad antimicrobial spectrum. Efficacy of clindamycin has been tested in several clinical studies. This drug has stopped attachment loss in a high number of patients and increased the number of sites with the attachment gain, even in patients who had already undertaken unsuccessful antibiotic therapy.

Resistance to clindamycin of certain A. actinomycetemcomitansand P. gingivalisserotypes was described. Because of the possibility of dangerous side-effects, as well as the occurrence of resistance of certain sub gingival microorganisms to this medication, it is not the first-choice antibiotic used in the treatment of periodontal diseases. It can be concluded that antibiotic monotherapy, with one medication as an adjunct to the mechanical therapy, has a favorable influence on the com position of bacterial microflora and reduction in the number of active periodontal pockets. Clinical improvement is a result of the total bacterial load suppression, and the changes in the composition of the bacterial microflora. Due to the complex composition of the sub gingival bacterial microflora, such a form of antibiotic therapy is often ineffective in eliminating exogenous bacterial pathogens.

Even Sub gingival microflora in periodontal diseases includes different pathogenic bacteria possessing differential sensitivity to antimicrobials, so the use of two or more antibiotics presents a useful option in the treatment of these diseases. The advantages of combined antibiotic therapy are broadened spectrum of antimicrobial activity, occurrence of synergistic activity and prevention of bacterial resistance development. Disadvantages of such a treatment are elevated incidence of adverse effects. Metronidazole in combination with amoxicillin or ciprofloxacin has been successfully used in the treatment of advanced periodontitis, especially infections with A. actinomycetemcomitans. Metronidazole and amoxicillin in vitro act synergistically on A. actinomycetemcomitans. Combination of metronidazole with amoxicillin or amoxicillin and clavulanic acid can eliminate A. Actinomyctemcomitansand other periodontal pathogens from the periodontal pockets for at least two years.

Metronidazole and ciprofloxacin can be effective in mixed periodontal infections, such as the presence of anaerobes, A. actinomycetemcomitans, enteric bacteria and pseudomonades. As this combination is ineffective against most gram-positive, facultative anaerobic bacteria, it can facilitate streptococcal colonization of the pockets which have no periodontal pathogenic potential. Serial use of antibiotics is indicated for a combination of antibiotics, in which one has bactericidal and the other bacteriostatic activity. Combined administration would lead to antagonistic effects and therapeutically failure.

This form of systemic antimicrobial therapy should be used in especially severe cases of recurrent or refractory periodontitis, where attachment loss was not arrested despite careful initial there Sub gingival microflora in periodontal diseases includes different pathogenic bacteria possessing differential sensitivity to antimicrobials, so the use of two or more antibiotics presents a useful option in the treatment of these diseases. The advantages of combined antibiotic therapy are broadened spectrum of antimicrobial activity, occurrence of synergistic activity and prevention of bacterial resistance development. Disadvantages of such a treatment are elevated incidence of adverse effects. Metronidazole in combination with amoxicillin or ciprofloxacin has been successfully used in the treatment of advanced periodontitis, especially infections with A. actinomycetemcomitans.

Metronidazole and amoxicillin in vitro act synergistically on A. actinomycetemcomitans. Combination of metronidazole with amoxicillin or amoxicillin and clavulanic acid can eliminate A. actinomycetemcomitansand other periodontal pathogens from the periodontal pockets for at least two years. Metronidazole and ciprofloxacin can be effective in mixed periodontal infections, such as the presence of anaerobes, A. Actinomycetemcomitans, enteric bacteria and pseudomonades. As this combination is ineffective against most gram-positive, facultative anaerobic bacteria, it can facilitate streptococcal colonization of the pockets which have no periodontal pathogenic potential. Serial use of antibiotics is indicated for a combination of antibiotics, in which one has bactericidal and the other bacteriostatic activity.

Combined administration would lead to antagonistic effects and therapeutically failure. This form of systemic antimicrobial therapy should be used in especially severe cases of recurrent or refractory

periodontitis, where attachment loss was not arrested despite careful initial therapy, or in cases of disease reactivation during the supportive phase of therapy, occurring despite good oral hygiene and repeated mechanical sub gingival instrumentation. One of the combinations effective in the prevention of recurrent periodontitis in high-risk individuals is doxycycline and metronidazole.

DRUGS OTHER THAN ANTI MICROBIAL AGNETS USED IN PERIODONTAL CHIP

- Flurbiprofen
- Benzocain
- Dextromethorphan
- Clotrimazole
- Nystatins
- Butamben
- Tetracain
- Amlexanox
- Glecro-phenol mixture
- Thymoquinone
- Levofloxacin Hemihydrate
- Sparfloxacin
- Ofloxacin

EXCIEPIENTS USED IN PERIODONTAL CHIP

- Chitosan
- Methylene chloride
- Polyvinylpyrrolidone
- Lactic acid solution
- Sodium benzoate
- Glycerol
- Poly lactic-co-glycolic acid
- Acetic acid
- Water

PREPARATION OF PERIODONTAL CHIP

Selected drug was dissolved and added to chitosan that had been soaked in 1% acetic acid overnight using PEG 400 as plasticizer. Both ingredients were sonicated to form a homogenous mixture and poured into a uniquely designed rectangular glass mold lined with aluminum foil. After drying overnight at room temperature, the resultant film was cut into small rectangular chips 0.5 × 0.5 sq·cm in size. A content uniformity test was conducted on some chips in a random fashion to affirm the quantity of drug administered in every chip. The chips were then stored in sterile vials and kept at room temperature.

ADVANTAGES

1. Systemic antibiotics can reach microorganisms at the base of deep periodontal pockets and furcation areas, via the serum.
2. Affects tissue invasive organisms – residing within the connective tissues.
3. Eradication of periodontal pathogens colonizing the oral mucosa and other extra dental sites – the potential reservoirs of bacterial reinfection.
4. Multiple sites are treated simultaneously.
5. Less time consuming (when compared to local drug delivery).
6. A variety of drugs are available.

DISADVANTAGES

1. Development of resistant bacterial strains.
2. Superimposed infections.
3. Uncertain patient compliance.
4. The drug must be given in high doses in order to maintain an effective drug concentration in the gingival crevicular fluid. This may result in various side effects like nausea, vomiting and gastrointestinal disturbances.

EVALUATION PARAMETERS OF THE PERIODONTAL CHIP

Formulated films were subjected to the preliminary evaluation tests. Films with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

Thickness uniformity of the films

The thickness of each film was measured using screw gauge (thickness tester) at different positions of the film and the average was calculated.

Uniformity of weight of the films

Film (size of 1 cm2) was taken from different areas of film. The weight variation of each film was calculated.

Tensile strength of the films

Tensile strength of the films was determined with Universal strength testing machine. The sensitivity of the machine is 1 gram. It consists of two load cell grips; the lower one is fixed and the upper one is movable. The test film of specific size (4 ´ 1 cm2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the film was taken directly from the dial reading in kilograms.

Drug content uniformity of films

Film (size of 1 cm2) was taken from different areas of film and placed in a 10 ml volumetric flask; 10 ml of ethyl alcohol was added and kept aside till the film dissolve completely. From this solution, 1 ml was pipette out and diluted to 10 ml with double distilled water. The absorbance of the solution was measured at 320.4 nm. The polymer solution without drug serves as a blank. In

case of HPMC film, combination of water and alcohol is used to dissolve the film.

Folding endurance

As described by Khanna et al., the folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The film was folded number of times at the same place without breaking gave the value of the folding endurance.8 This test was done on all the films for five times.

Surface pH

Periodontal films were left to swell for 1 hour on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed double distilled water under stirring and then pouring the solution into the petridish to gelling / solidify at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film. The mean of three readings was recorded.

Viscosity

Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that of films. Brookfield viscometer (LVDV-E model) attached to the helipath spindle number 18 was used. The viscosity was measured at 20 rpm at room temperature. The recorded values were the mean of five determinations**.**

***In-vitro* drug release**

In-vitro drug release was performed by taking 1 cm2 of periodontal film in a vial containing one ml of double distilled water. One ml of double distilled water was withdrawn from 1st to 5^{th} day, every day and immediately replaced with one ml of fresh double distilled water. The drug content was estimated by measuring the absorbance after suitable dilution at 320.4 nm.

DOSAGE AND ADMINISTRATION

One PerioChip is inserted into a periodontal pocket with probing pocket depth (PD) 5 mm or greater. Up to 8 chips may be inserted in a single visit. Treatment is recommended to be administered once every three months in pockets with PD remaining 5 mm or greater.

The periodontal pocket should be isolated and the surrounding area dried prior to chip insertion. The PerioChip 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. If necessary, the PerioChip can be further maneuvered into position using the tips of the forceps or a flat instrument. The PerioChip does not need to be removed since it biodegrades completely.

In the unlikely event of PerioChip dislodgement (in the two pivotal clinical trials, only 8 chips were reported lost), several actions are recommended, depending on the day of PerioChip 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 PerioChip should be inserted. If dislodgement occurs more than 48 hours after placement, the dentist should not replace the PerioChip, but reevaluate the patient at 3 months and insert a new PerioChip if the pocket depth has not been reduced to less than 5 mm.

Table 1: Classification of Periodontal Diseases.

I. Gingival Diseases • Dental plaque-induced gingival diseases • Non-plaque-induced gingival lesions
II. Chronic Periodontitis (slight: 1-2 mm CAL; moderate: 3-4 mm CAL; severe: > 5 mm CAL) • Localized • Generalized (> 30% of sites are involved)
III. Aggressive Periodontitis (slight: 1-2 mm CAL; moderate: 3-4 mm CAL; severe: > 5 mm CAL) • Localized • Generalized (> 30% of sites are involved)
IV. Periodontitis as a Manifestation of Systemic Diseases • Associated with hematological disorders • Associated with genetic disorders • Not otherwise specified
V. Necrotizing Periodontal Diseases • Necrotizing ulcerative gingivitis • Necrotizing ulcerative periodontitis

VI. Abscesses of the Periodontium • Gingival abscess • Periodontal abscess • Pericoronal abscess
VII. Periodontitis Associated With Endodontic Lesions • Combined periodontic-endodontic lesions
VIII. Developmental or Acquired Deformities and Conditions • Localized tooth-related factors that modify or predispose • to plaque-induced gingival diseases/periodontitis • Mucogingival deformities and conditions around teeth • Mucogingival deformities and conditions on edentulous ridges • D. Occlusal trauma

Table 2: List of polymers used in preparation of Periodontal Chip

Types	Example
Natural	Carbohydrates, Starch, Cellulose, Lignin, Poly amino acid.
Synthetic	Silk, Protein, Cotton and Linen.
Non -Synthetic	PVC, Polypropylene, Rubber and Nylon.
Biodegradable	CO_2, NO_2, Water and Biomass.

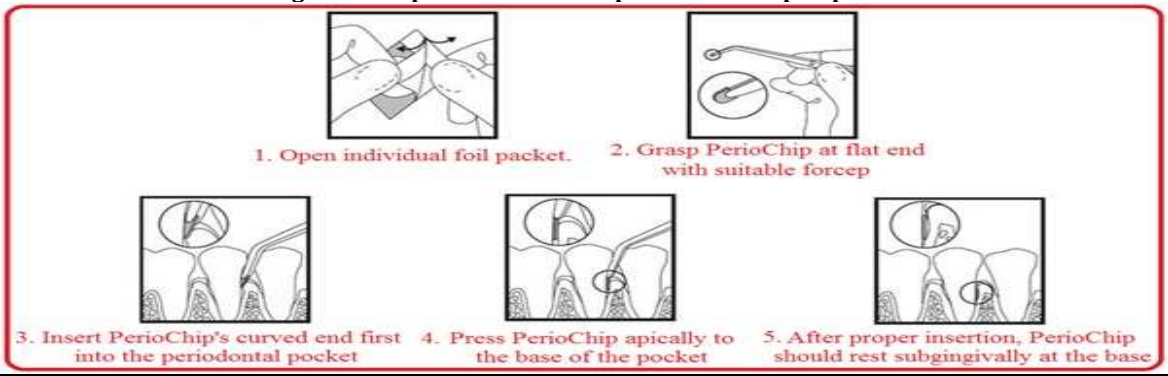
Figure 1: Periodontal chip

Figure 2: Periodontal Treatment

Figure 3: Periodontal Treatment

Figure 5: Insertion of periodontal chip in pocket

Figure 4: Steps for insertion of periodontal chip in pocket



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