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Photodynamic Therapy in Periodontics

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ABSTRACT

The human oral cavity is colonized by a large number of highly diverse bacteria existing in either a planktonic community or in a complex sessile community known as a biofilm (i.e. dental plaque).[1]While the majority of bacteria in these complex communities are nonpathogenic some bacteria are opportunistic pathogens and are associated with extraoral and intraoral diseases. Photodynamic therapy has been considered as a promising novel therapeutic approach for eradicating pathogenic bacteria in periodontal and peri-implant diseases. Photodynamic therapy is based on chemicals called photosensitizers that are activated by light of adequate wavelength. Its activation leads to the generation of singlet oxygen and free radicals responsible for the cytotoxic effect against specific cells. Photodynamic therapy basically involves three nontoxic ingredients: visible harmless light; a nontoxic photosensitizer; and oxygen. It is based on the principle that a photosensitizer (i.e. a photoactivatable substance) binds to the target cells and can be activated by light of a suitable wavelength. Following activation of the photosensitizer through the application of light of a certain wavelength, singlet oxygen and other very reactive agents are produced that are extremely toxic to certain cells and bacteria.

Key Words: Gingivitis, Photodynamic therapy, Periodontitis, Peri-implantitis

INTRODUCTION

Gingivitis is an inflammatory disease that is associated with proliferation of local epithelial cells and loss of gingival connective tissues but is not associated with loss of connective tissue attachment.[2] Clinical inflammation of the tissues is present and significant spontaneous or bleeding on probing is noted.[3] Gingivitis is reversible by mechanically disrupting the biofilm which in turn reduces inflammation and allows for gingival healing. The human oral cavity is colonized by a large number of highly diverse bacteria existing in either a planktonic community or in a complex sessile community known as a biofilm (i.e. dental plaque).[1]While the majority of bacteria in these complex communities are nonpathogenic some bacteria are opportunistic pathogens and are associated with extraoral and intraoral diseases. For example, *Streptococcus oralis* can be isolated from supragingival plaque, mucosal surfaces, tongue and saliva but can induce endocarditis and extraoral abscesses.[4]

Photodynamic therapy has been considered as a promising novel therapeutic approach for eradicating pathogenic bacteria in periodontal and peri-implant diseases. Photodynamic therapy is based on chemicals called photosensitizers that are activated by light of adequate wavelength. Its activation leads to the generation of singlet oxygen and free radicals responsible for the cytotoxic effect against specific cells. Photodynamic therapy basically involves three nontoxic ingredients: visible harmless light; a nontoxic photosensitizer; and oxygen. It is based on the principle that a photosensitizer (i.e. a photoactivatable substance) binds to the target cells and can be activated by light of a suitable wavelength. Following activation of the photosensitizer through the application of light of a certain wavelength, singlet oxygen and other very reactive agents are produced

that are extremely toxic to certain cells and bacteria.

The terminology used for treatment changes from photodynamic therapy (PDT) associated with treating oncological diseases to photodynamic antimicrobial chemotherapy (PACT) or antimicrobial photodynamic therapy (APT) in treating localized bacteria, fungal, viral and yeast infections.[5] Antimicrobial photodynamic therapy can be easily applied, even in sites where there is limited access for mechanical instrumentation as a result of the anatomical complexity of the root and where remaining bacteria may be present.

In addition, the antimicrobial effect of photodynamic therapy can be easily controlled by regulating the reaction; that is, by controlling the amount of light applied to activate the reaction. Using this simple procedure, bacteria can be eradicated in a very short period of time. Application of photodynamic therapy has led to significant advances in dentistry because the delivery of light is more accessible and topical application of the photosensitizer is more feasible in the oral cavity. The antimicrobial properties of photodynamic therapy make it a potential candidate for the treatment of bacterial, fungal and viral infections of the oral cavity. Therapeutic use of ultraviolet light begins in 1900 when Rabb reported that a combination of acridine orange and ultraviolet light could destroy living organisms (paramecium). In 1920 Policard noted that tumor tissues were inheritently more fluorescent than healthy tissues. In 1950 Ronchese attempted to activate endogenous fluorescent molecules in tumor tissues to delineate its border more accurately. In 1960's Winkelman used synthetic phorphyrins to detect tumour tissue. Throughout 20 century, few attempts were made to treat tumour tissues with mainly nonporphyrin photosensitizers. In the 1970's Dougherty rediscovered that fluorescein diacetate could photodynamically destroy T A-3 cells in vitro. Dougherty then began treating tumour bearing animals with fluorescein and found that it works like a photosensitizer.

Mechanism of PDT

Photodynamic therapy (PDT) involves the administration of a photoactive dye that is able to produce reactive oxygen species (ROS) upon irradiation with light. Thus, when the dye absorbs a photon, an electron is promoted from its ground state to an electronically-excited state that returns the energy through three main pathways. Upon absorption of light energy at the appropriate wavelength, a photo sensitizer undergoes a transition from a low energy singlet ground state to a higher energy triplet state. The process by which this high energy triplet state is generated is critical to the photodynamic reaction and involves the physics of electron spin configuration.[6,7] Electrons orbit the nucleus but they also have an intrinsic magnetic field which induces a spinning effect on its axis. When all electrons spinning in one direction are equal to electrons spinning in the opposite direction i.e. paired, the compound is referred to as a singlet state.[8]

Most molecules in their ground state do exist in this lower energy singlet state. When a quantum (photon) of energy from the light source is absorbed by the photo sensitizer it may induce the spin of one of the electrons to reverse. These unpaired electrons can induce high energy and result in a highly reactive molecule that is now in a triplet state (excited state).[8] Generation of a triplet state photo sensitizer plays a critical first step in the photodynamic reaction.[8]

a) **Non-radiative processes**. The excited state species release the excess of energy as heat by three different processes[9]: *Vibrational relaxation* (VR): the excited molecule decreases its vibrational energy within a single electronic state. *Internal conversion* (IC): transition between two electronic states with the same spin multiplicity, generally followed by vibrational relaxation.

b**) Radiative processes**. The excited state species return the excess of energy as

electromagnetic radiation. Divided in two kinds of processes:

Fluorescence (F): spontaneous emission of radiation upon transition between two electronic states with the same spin multiplicity. *Phosphorescence* (P): spontaneous emission of radiation upon transition between two electronic states with different spin multiplicity.

c) **Other deactivation processes**. The excited state molecules can undergo photochemical or photophysical reactions or photosensitisation. Photosensitisation is the process by which a photochemical or photophysical alteration occurs in one molecular entity (A) as a result of initial absorption of radiation by another entity called photosensitiser (photo sensitizer).[16] It can schematically be represented as follows:

$$PS + h\nu \rightarrow PS^*$$

Photochemical: $PS^* + A \rightarrow PS' + B$

Photophysical: $PS^* + A \rightarrow PS + A^*$

When molecular oxygen is involved in photosensitisation, such process is termed "photodynamic action" and two different mechanisms are possible:

Type I mechanism: the photo sensitizer in its singlet or triplet excited state reacts with a substrate via (a) electron transfer or (b) hydrogen abstraction to yield free radicals, which will readily react with oxygen to form peroxides radicals, and in turn starting a radical chain reaction.[10] Type I reactions involve hydrogen-atom abstraction or electron-transfer reactions between the excited state of the photosensitizer and an organic substrate molecule of the cells, which produces free radicals and radical ions. These free-radical species are generally highly reactive and interact with endogenous molecular oxygen to produce highly reactive oxygen species such as superoxide, hydroxyl radicals and hydrogen peroxide, which are harmful to cell membrane integrity, causing irreparable biological damage.[10]

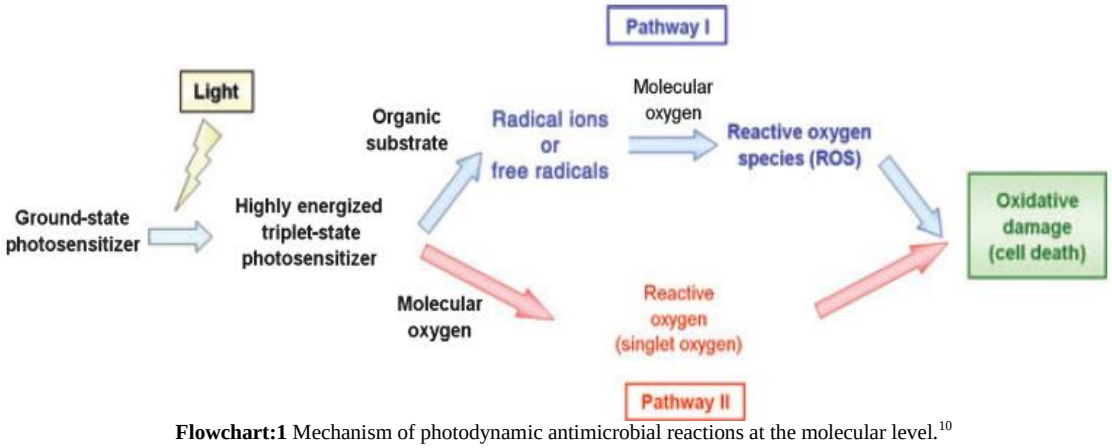
Type II mechanism: in this process, the sensitizer in its excited state (commonly in its triplet state) transfers its energy to ground-state molecular oxygen, giving rise to the PS in its ground state and singlet oxygen ($^1O_2$), a very reactive oxygen species towards electron rich substrates such as alquenes, aromatic rings, phenols, amines and thioethers.[11]

$$PS + hv \rightarrow PS^*$$

$$PS^* + {}^3O_2 \rightarrow PS + {}^1O_2$$

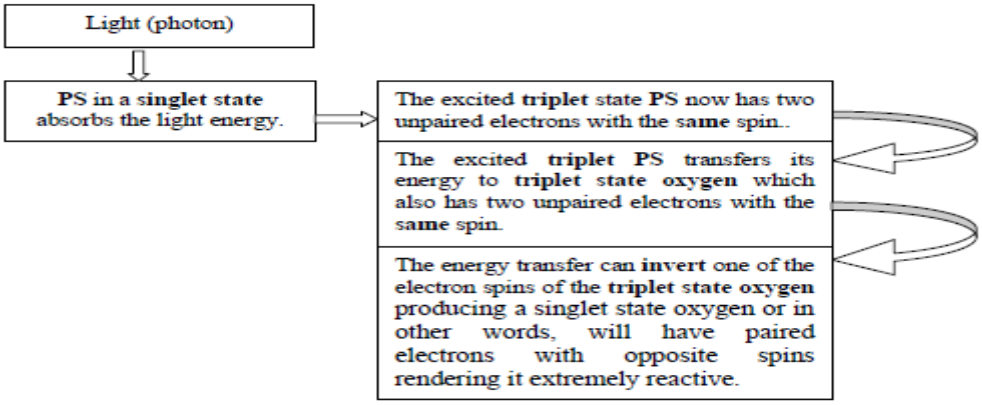
In the type II reaction, the triplet-state photosensitizer reacts with oxygen to produce an electronically excited and highly reactive state of oxygen, known as singlet oxygen ($^1O_2$), which can interact with a large number of biological substrates as a result of its high chemical reactivity, inducing oxidative damage and ultimately lethal effects upon the bacterial cell by damaging the cell membrane and cell wall. Microorganisms that are killed by singlet oxygen include viruses, bacteria, protozoa and fungi. Singlet oxygen has a short lifetime in biological systems (<0.04l seconds) and a very short radius of action (0.02l microns). Because of the limited migration of singlet oxygen from its site of formation as a result of its short lifetime, sites of initial cell damage from photodynamic therapy are closely related to the localization of the photosensitizer. Thus, the reaction takes place within a limited space, leading to a localized response and making it ideal for application at localized sites without affecting distant molecules, cells or organs[12].

Type III reaction is a unique photo sensitizer reaction because it is oxygen independent. These reactions require either high concentration of the photo sensitizer or a de-aerated system, in order to bypass the reaction with oxygen. Under anaerobic systems the radicals are generated and these can then subsequently react.[7.]



Flowchart:1 Mechanism of photodynamic antimicrobial reactions at the molecular level.[10]

The bactericidal effect of photodynamic therapy can be explained by two potential, but different, mechanisms. One is DNA damage and the other is the damage caused to the cytoplasmic membrane of the bacteria by cytotoxic species generated by antimicrobial photodynamic therapy, leading to events such as inactivation of the membrane transport system, inhibition of plasma membrane enzyme activities, lipid peroxidation and others.[10] Although it has been reported that antimicrobial photodynamic therapy can lead to DNA damage, it seems that bacterial killing by the photochemical reaction is mainly caused by damage to the bacterial cytoplasmic membrane.[11]



Flowchart:2 A Schematic Representation of Singlet Oxygen generation by a photo sensitizer.

Photodynamic action on tissues

The transfer of an electron between a photosensitizer and the substrate (the Type I reaction) results in the creation of products that have an uneven number of electrons. Such radical species are often highly reactive. Radicals can further react with additional biological substrates producing changes in structure and/or function. Superoxide and hydroxyl radicals are important radical species that are often produced by Type I reactions in biological environments. For example, Malachite Green is marketed as a photosensitizer that produces biological effects via hydroxyl radicals. Because Type I reactions require a direct interaction of the photosensitizer and the substrate, they are favored by high substrate concentrations. They are also favored by low oxygen concentrations, since oxygen competes with the substrate for interaction with the photosensitizer.[12]

In the Type II reaction, the transfer of energy from the photosensitizer to oxygen produces an excited singlet state of oxygen, appropriately called singlet oxygen. Typically, photosensitizers, like most other molecules, are in a singlet state in their normal ground state.

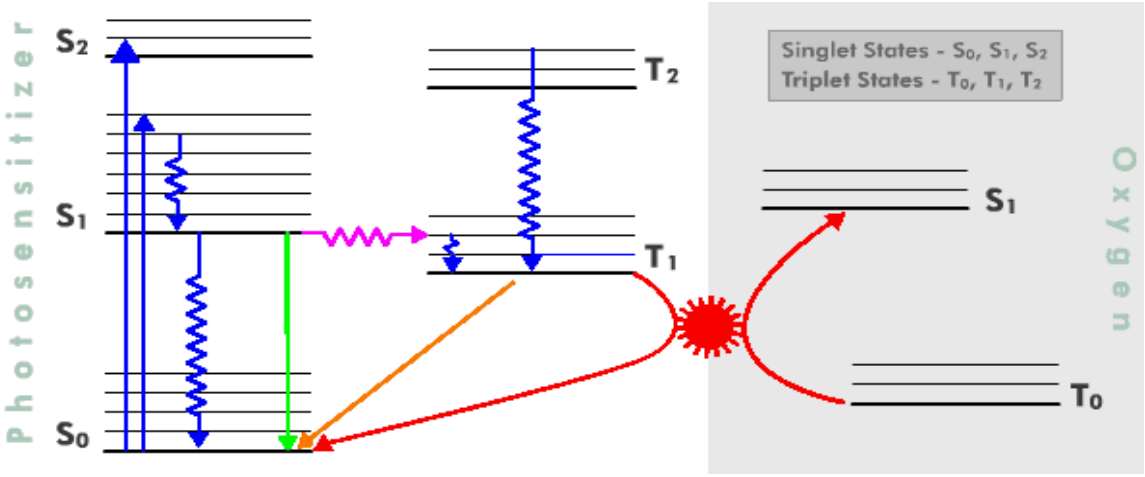


Fig:1 Jablonski Diagram depicting electronic transitions following the absorption of light by a photosensitizer, and energy transfer to an oxygen molecule, producing singlet oxygen. There is an implied vertical energy scale in this diagram such that higher electronic energy levels are above lower energy levels. Also, triplet states are drawn to the right of singlet states, and states involving oxygen are to the right of those involving the photosensitizer.[12]

Antibacterial Photodynamic Therapy

The first recorded observations of photodynamic processes in medicine refer to the inactivation of microorganisms. However, the potential of PDT against diseases of microbial origin was not exploited for several decades, largely for two reasons

The discovery of antibiotics;

Early discouraging results that some well known pathogens, especially gram-negative bacteria, were poorly responsive to PDT with the most traditional photosensitizing agents.

Gram positive and negative bacteria

The domain Bacteria is divided in two groups based on the cell's reaction to a staining method called Gram stain. The differences between gram-positive and gram negative bacteria relate to differences in their cell wall structure and chemical composition. Thin sections of gram-positive bacteria reveal thick walls, almost uniformly dense layers. In contrast, the cell walls of gram-negative bacteria are much more complex, because in addition to a peptidoglycan layer they have another layer, called an outer membrane. The structural differences between the cell walls of both kinds of bacteria reflect differences in biochemical composition.

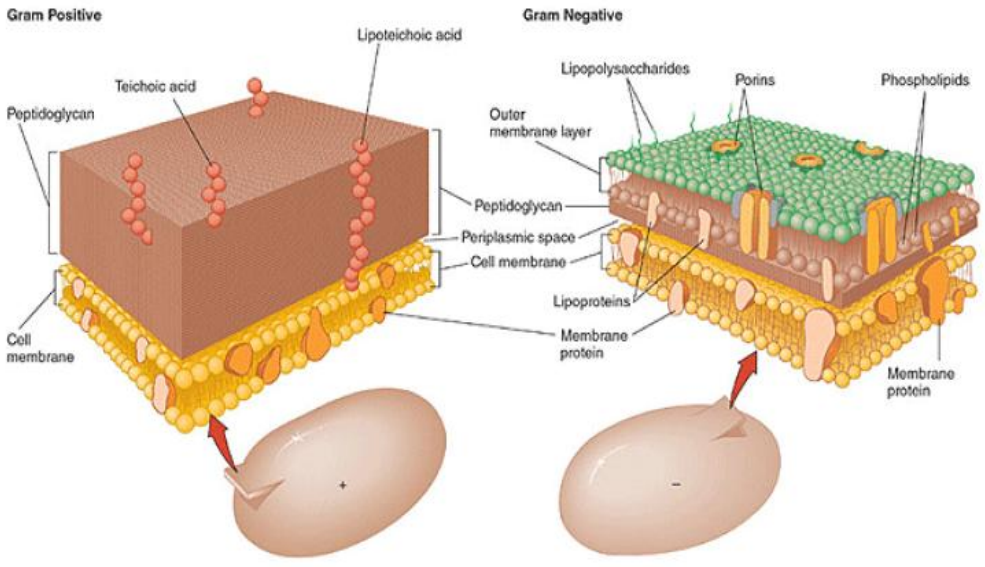
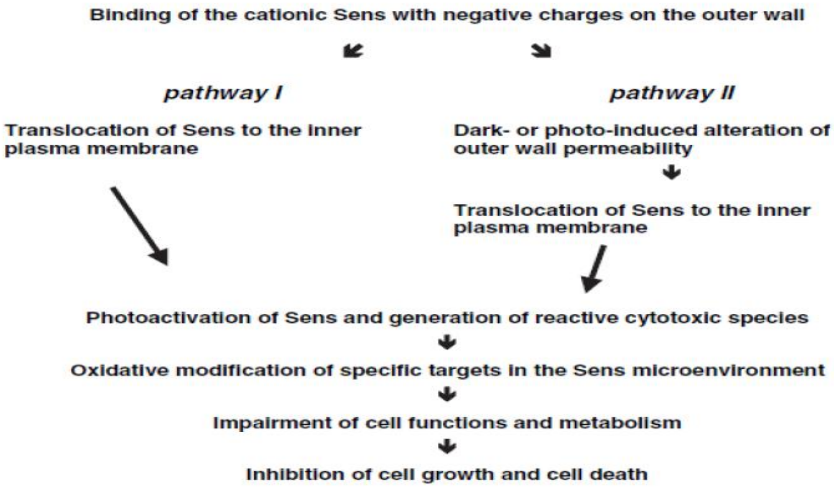


Fig:2 Schematic representation of gram positive and gram negative bacteria[13]

Mechanisms of bacterial inactivation

Notwithstanding the vast progress made over the last few years, the mechanistic details of how APDT affects microbial cells are not fully understood. As regards the uptake pathways of anionic and cationic photo sensitizer, George et al in 2009 reported that the uptake of anionic photo sensitizers by bacterial cells may be mediated through a combination of electrostatic charge interaction and by protein transporters, while the uptake of cationic photo sensitizers is mediated by electrostatic interactions and "self promoted" uptake pathways. In relation to the mechanism of photodynamic inactivation[14], Jori et al. in 2006 proposed two alternative pathways of cationic photo sensitizer for gram-positive and gram-negative bacteria[15].



Flowchart:3 Mechanism of bacterial elimination in PDT[15]

An important goal in the investigation of photosensitisation processes in antimicrobial PDT is elucidation of the mechanism of action of a selected photo sensitizer to determine whether a specific reaction proceeds via a type I or a type II pathway. On one hand, some mechanistic studies involved type I mechanisms (via electron transfer and radicals) in APDT of bacteria.

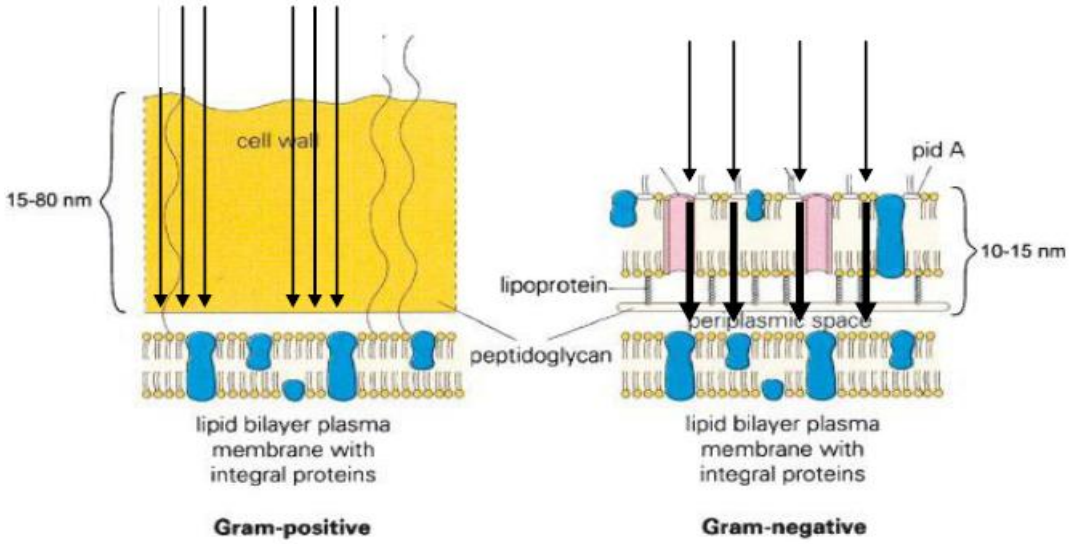


Fig:3 Schematic View of Singlet Oxygen Effects on Bacterial Membrane. The arrows represent the singlet oxygen penetrating through the cell wall to reach the plasma membrane. The gram positive cell wall is easily penetrated and the singlet oxygen interacts directly with the plasma membrane. Gram negative toxicity from singlet oxygen is the net effect of primary (thin arrows) and secondary reaction (thick arrows) products.[16]

Photodynamic Therapy in Periodontics

Based on the advantages and characteristics of antimicrobial photodynamic therapy, it has been proposed that periodontal and peri-implant diseases are potential targets of this novel antimicrobial photochemotherapy. Antimicrobial photodynamic therapy is expected to resolve the difficulties and problems of conventional antimicrobial therapy and can work as an adjunctive to conventional mechanical treatments.[9]

The photosensitizer is placed directly in the periodontal and peri-implant pocket and the liquid agent can easily access the whole root or implant surface before activation by the laser light through placement of the optical fiber directly in the pocket. As a result of the technical simplicity of the method and the high effectiveness of bacterial killing, the application of antimicrobial photodynamic therapy in the treatment of periodontal and peri-implant diseases has recently been studied extensively. Antimicrobial photosensitizing agents and the wavelengths used in periodontal and peri-implant therapy For the elimination of bacteria in supragingival and subgingival plaque, antimicrobial photodynamic therapy has been applied with various combinations of lasers and photosensitizing agents.

In antimicrobial photodynamic therapy, the particular photosensitizers employed are

1. toluidine blue O [toloniumchloride: (7-amino-8-methyl-phenothiazin-3-ylidene) dimethyl-ammonium ($C_{15}H_{16}N_3S+$)]

2. methylene blue [3,7-bis(dimethyl-amino) phenazathionium chloride tetramethylthionine chloride ($C_{16}H_{18}N_3ClS$) or phenothiazine 5-ium, 3,7-bis(dimethylamino)-chloride]
3. erythrosine

4. chlorine E-6

5. hematoporphyrin, which have been shown to be safe when employed in the medical field.

The phenothiazine dyes (toluidine blue O and methylene blue) are the major photosensitizers applied clinically in the medical field. Both have similar chemical and physicochemical characteristics.[9]

Toluidine blue O is a solution that is blue–violet in color. It can stain granules within mast cells, and proteoglycans and glycosaminoglycans within connective tissues. In the field of oral surgery, toluidine blue O has been used to detect mucosal tumors or atypical epithelia as normal mucosal epithelium cannot be stained by toluidine blue O[17]. Methylene blue is a redox indicator that is blue in an oxidizing environment and becomes colorless upon reduction. In medical practice, methylene blue is applied for identification of dysplasias or precancerous lesions of the mucosa. In vitro studies of the antimicrobial effects of photodynamic therapy in periodontal therapy. The bactericidal effect of antimicrobial photodynamic therapy on periodontal pathogens has been demonstrated in several basic studies.

In addition, it seems that antimicrobial photodynamic therapy not only kills the bacteria but may also lead to the detoxification of endotoxins because it has been demonstrated in vitro that lipopolysaccharide treated by photodynamic therapy did not stimulate the production of pro-inflammatory cytokines by mononuclear cells; thus, photodynamic therapy may inactivate endotoxins such as lipopolysaccharide by decreasing their biological activity.[9]

Analysis of a number of in vitro studies supports the contention that antimicrobial photodynamic therapy with specific photosensitizers and light sources is effectively bactericidal for periodontal pathogens. However, the most effective combination of wavelengths and photosensitizers, as well as the optimal parameters required (such as agent concentration and agent exposure time, laser power energy and irradiation time), have not yet been elucidated and therefore more basic

studies are still necessary to optimize clinical application[9]

In vivo studies of the antimicrobial effects of photodynamic therapy in periodontal therapy recently, animal studies have been performed to help clarify the clinical response to antimicrobial photodynamic therapy application in periodontal therapy. Some animal studies have reported a reduction in the microbial load in ligature-induced periodontitis following the application of photodynamic therapy.[9] Generally, antimicrobial photodynamic therapy appears to suppress periodontal pathogens and to reduce signs of inflammation effectively and safely in periodontitis in vivo. However, there is a lack of evidence to prove that antimicrobial photodynamic therapy is capable of suppressing periodontopathogens in a single dose or course.

Further in vivo studies investigating the antimicrobial effects on different periodontal pathogens need to be performed.

The use of antimicrobial photodynamic therapy may reduce signs of periodontal inflammation and alveolar bone loss in experimentally induced periodontitis. However, two studies have shown a tendency for regression within 30 days after treatment in the effects on bone levels. Consequently, the long-term therapeutic outcomes should be further evaluated in animal models. The limited number of in vivo studies available indicates that antimicrobial photodynamic therapy could be an alternative and or as an adjunctive treatment to scaling.[9]

Clinical studies of application of antimicrobial photodynamic therapy in the treatment of periodontal disease

Methods of application

Antimicrobial PDT is applied after routine Phase one periodontal therapy including mechanical debridement to remove the subgingival deposits (A,B). Following which the photosensitizer is applied into the diseased site using a syringe(C). The excess chemical is then rinsed off with water spray. Photosensitization is performed using an intensive light by a special tip applied in the pocket (D). Singlet oxygen and other very reactive agents that are toxic to bacteria are produced, resulting in photochemical disinfection of the periodontal pocket which leads to an improved wound healing in the treated site (E).

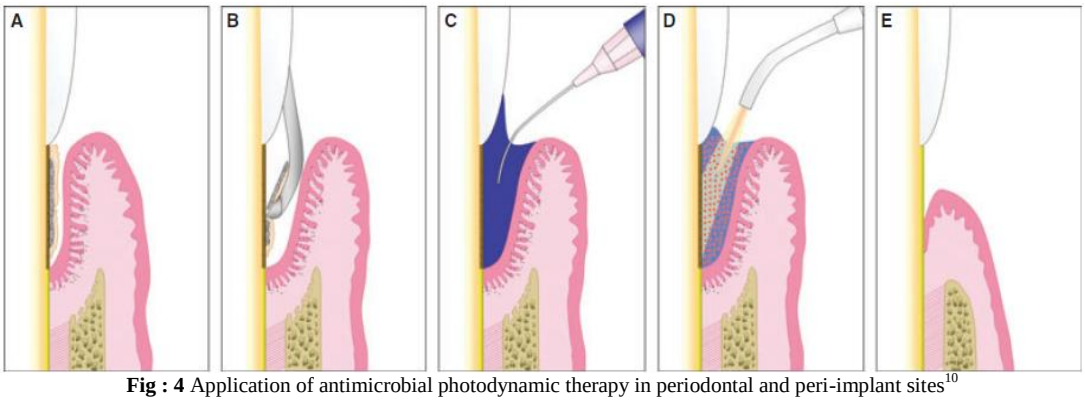


Fig : 4 Application of antimicrobial photodynamic therapy in periodontal and peri-implant sites[10]

(A) Clinical situation of a 51-year-old woman before nonsurgical periodontal therapy and antimicrobial photodynamic therapy. Full-mouth bleeding scores were 67%. The clinical parameters of the mesio-buccal site of the upper right lateral incisor were a probing pocket depth of 7 mm, clinical attachment level of 9 mm and gingival recession of 2 mm. The disto-palatal site of the upper left canine had a probing pocket depth of 9 mm and clinical attachment level of 9 mm without gingival recession.

(B) Application of the photosensitizer following supragingival and subgingival mechanical debridement using curettes and the ultrasonic scaler. The photosensitizer applied was a

Phenothiazine Chloride (HELBO_ Blue Photosensitizer, HELBO_ Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). The photosensitizer was kept in the periodontal pockets for 3 mins.

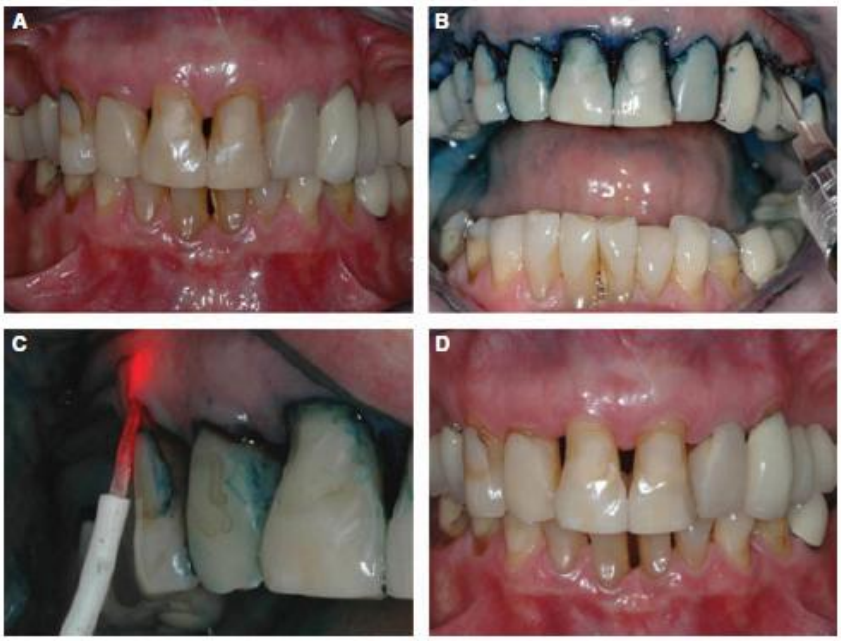


Fig: 5 **Application of antimicrobial photodynamic therapy in periodontal disease site** [10]

Irradiation with the diode laser.

Laser irradiation was performed using a diode laser of 670 nm wavelength at 75 mW of power output (HELBO TheraLite Laser, HELBO Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). Laser irradiation was performed for 1 min.

(A) The clinical situation 6 months after therapy. The full-mouth bleeding scores were reduced to 15%. The mesio-buccal site of the upper right lateral incisor showed a pocket reduction of 3 mm, with 3 mm of attachment gain without gingival recession. The disto palatal site of the upper left canine presented 4 mm of pocket reduction and 4 mm of attachment gain without causing any gingival recession. Significant clinical improvements of periodontal pockets were obtained with antimicrobial photodynamic therapy adjunctive to mechanical root debridement.

Currently, five studies are available reporting on the use of antimicrobial photodynamic therapy as an adjunct to nonsurgical treatment for initial (Andersen 2007, Braun A 2008) and maintenance (Chondros 2009) therapy of chronic periodontitis. In addition, one study has reported on the use of nonsurgical therapy in aggressive periodontal disease (de Oliveira RR 2007)[9] The reduced effectiveness of photodynamic therapy in this study may be a result of the indirect application of photodynamic therapy from the external surface of the gingiva.

Andersen et al in 2007[17] using a parallel three-arm design, compared the effectiveness of antimicrobial photodynamic therapy with that of scaling and root planing for nonsurgical treatment of moderate to advanced periodontal disease. A total of 33 patients were assigned to photodynamic therapy alone (methylene blue + 50 mW diode laser), scaling and root planing alone or scaling and root planing + photodynamic therapy. Clinical assessments of bleeding on probing, probing pocket depth and clinical attachment level were made. After three months of healing it was observed that a combination of scaling and root planing + photodynamic therapy resulted in significant improvements in the investigated

parameters over the use of scaling and root planing alone at all evaluation time points.

De Oliveira et al. in 2007[18], reported on the outcome of antimicrobial photodynamic therapy monotherapy for the treatment of aggressive periodontitis. A total of 10 patients were randomly assigned, according to a split-mouth design, to either photodynamic therapy (methylene blue + 60 mW diode laser) or scaling and root planing. Laser application was performed for 10 s per site after 3 mins of residence time of the photosensitizer. Three months later, both treatment procedures gave comparable clinical outcomes, as evidenced by probing pocket depth reductions and clinical attachment level gains, suggesting a potential clinical effect of photodynamic therapy as an alternative to scaling and root planing. In both groups, the beneficial effects were more pronounced at initially moderate and shallow pockets. Brink and Romanos et al in 2007[19] compared the clinical and microbiological effects of scaling and root planing + Nd:YAG laser (2W), scaling and root planing + 980 nm diode laser (2W), and scaling and root planing + antimicrobial photodynamic therapy [methylene blue + 670 nm diode laser (75 mW)] and scaling and root planing alone in patients with chronic periodontitis. The authors reported that in the group treated with antimicrobial photodynamic therapy + scaling and root planing, bleeding on probing was reduced significantly more, one to three months following treatment, than in the other groups.

Yilmaz et al. in 2008[20] randomly assigned a total of ten patients to receive repeated application of scaling and root planing + photodynamic therapy (methylene blue + 30 mW diode laser), scaling and root planing alone, photodynamic therapy alone or supragingival oral hygiene instructions. Methylene blue served as the photosensitizer and was used as a mouth rinse. Scaling and root planing was performed on days 1 and 7, while the laser was repeatedly applied over each papillary region (not into periodontal pockets) on days 1, 2, 4, 7, 9 and 11. After 32 days of healing, significant clinical and microbiological improvements were only observed in the scaling and root planing + photodynamic therapy and scaling and root planing alone groups. By contrast, improvements following photodynamic therapy treatment alone, as well in those receiving oral hygiene instructions, did not reach statistical significance. Regarding laser treatment, there were no complaints (such as discomfort, sensitivity or pain) from subjects immediately after therapy or at 3 weeks post-therapy.

Braun et al. in 2008[21] evaluated the effect of adjunctive antimicrobial photodynamic therapy (methylene blue + 100 mW diode laser) in chronic periodontitis using a split-mouth design. A totnal of twenty patients received a scaling and root planing procedure and the quadrants were randomly assigned to an additional treatment with photodynamic therapy. Accordingly, it was concluded that the clinical outcomes of conventional scaling and root planing may be improved by adjunctive antimicrobial photodynamic therapy in patients with chronic periodontitis.

Christodoulides et al. in 2008 evaluated the clinical and microbiological effects of the adjunctive use of antimicrobial photodynamic therapy (methylene blue + 75 mW diode laser) to nonsurgical periodontal treatment. Based on these findings, it was concluded that a single episode of photodynamic therapy, as an adjunct to scaling and root planing, failed to result in an additional improvement in terms of probing pocket depth reduction and clinical attachment level gain. However, it resulted in a significantly higher reduction in bleeding scores, which should be taken into consideration under clinical conditions.

Similar results were also observed when the same device was used as an adjunct to nonsurgical periodontal treatment in patients on periodontal maintenance in a study reported by Chondros et al (2009).

Mongardini et al 2012 investigated the effect of PDT on the clinical and microbiological short term findings on periodontitis patients in maintenance and reported an enhanced short term clinical and microbiological outcome in supportive periodontal therapy. Sgolastra et al 2013 reported that the use of adjuvant PDT compared to conventional SRP alone provides short term benefits in form of reduced bleeding on probing and probing depth.

Macedo GD 2013 compared the effect of PDT on clinical and metabolic effects in patients with type 2 diabetes mellitus in conjunction with NSPT and doxycycline and did not observe any additional benefits on clinical parameters including bleeding on probing or probing depth but a slight decrease in HbA1c was observed.

When interpreting the available data, it should be kept in mind that the evidence from randomized controlled clinical studies, evaluating the potential clinical benefit of photodynamic therapy in the treatment of periodontitis, is still limited. The main drawbacks may be related to the rather limited number of patients, the short-term duration of studies (i.e. 3 or 6 months) and the fact that the most effective protocol of antimicrobial photodynamic therapy has not been established. The available data seem to indicate that the adjunctive use of antimicrobial photodynamic therapy in nonsurgical periodontal therapy may improve the clinical outcome, but further studies are warranted before definitive conclusions can be drawn on the clinical relevance of antimicrobial photodynamic therapy in periodontal therapy.

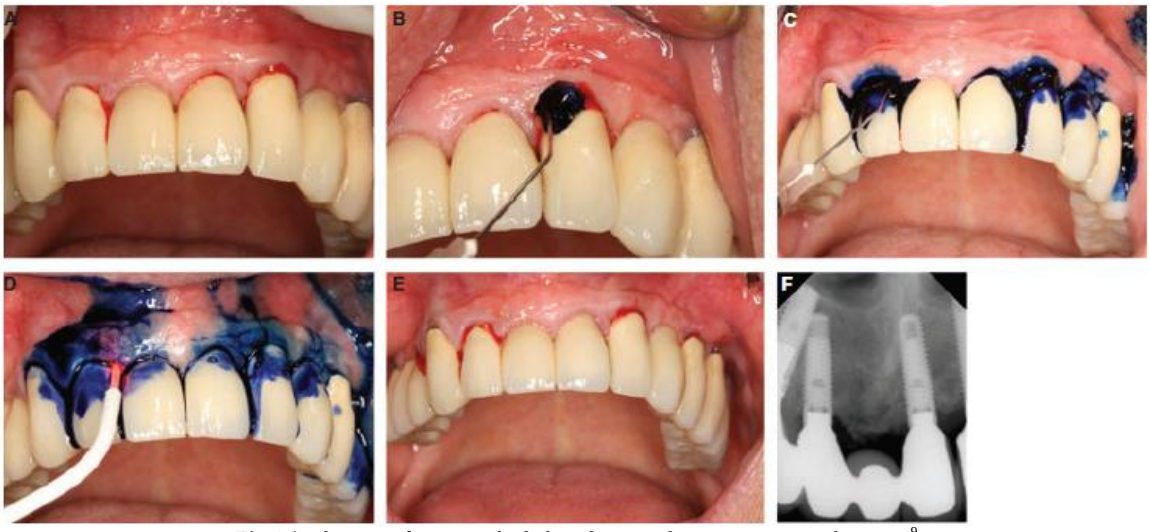


Fig:6 Application of antimicrobial photodynamic therapy in peri-implant site. [9]

Clinical application of antimicrobial photodynamic therapy in the treatment of peri-implantitis

(A) The clinical situation before nonsurgical peri-implant therapy and antimicrobial photodynamic therapy of a 32-year-old patient. The clinical parameters at implant #22 were a probing pocket depth of 5 mm and relative attachment level of 5 mm with bleeding on probing.

(B) Application of the photosensitizer. The photosensitizer applied was a Phenothiazine Chloride (HELBO Blue Photosensitizer, HELBO Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). The photosensitizer was placed in the peri-implant pocket for 3 mins.

(C) After application of the photosensitizer.

(D) Irradiation with the diode laser. Laser irradiation was performed with a diode laser of 670 nm wavelength at 75 mW of power output (HELBO TheraLite Laser, HELBO Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). Laser irradiation was performed for 1 min.

(E) The clinical situation 6 months after therapy. The treated site showed limited clinical improvement with the peri-implant pocket remaining and bleeding on probing occurring after therapy. Nonsurgical treatment of a peri-implant pocket using antimicrobial photodynamic therapy monotherapy did not improve the treated site.
(F) Radiograph of the treated implant before treatment.

Several studies have demonstrated bactericidal and detoxification effects of high-level lasers on contaminated dental implant surfaces[22]. High-level lasers have been used successfully in the surgical management of peri-implantitis. However, in nonsurgical therapy, high-level lasers have shown limited clinical efficacy. Moreover, following the application of some lasers, surface alterations (such as melting and carbonization) have been observed on the treated titanium surface.

Antimicrobial photodynamic therapy was recently proposed as an adjunctive for bacterial elimination in the treatment of periimplantitis, based on its successful application in the treatment of periodontitis. Currently, one in vitro, four animal and two clinical studies are available reporting the various effects of application of antimicrobial photodynamic therapy as an adjunctive to the treatment of peri-implantitis.

In an in vitro study, Hass et al in 1997.[23] examined the efficacy of antimicrobial photodynamic therapy in killing bacteria associated with peri-implantitis, such as A. actinomycetemcomitans, P. gingivalis or Prevotella intermedia (P. intermedia), which adhered to titanium plates with different surface characteristics. The plates were incubated with those bacteria and then subjected to four different treatments:

(i) photodynamic therapy (toluidine blue O + diode laser);
(ii) no treatment;
(iii)laser light alone; and
(iv)toluidineblue O alone.

None of the smears obtained from the plates subjected to photodynamic therapy showed bacterial growth of any of the microorganisms, while in the other treatment groups all three species of bacteria were detected after treatment. Scanning electron microscopic analysis showed that antimicrobial photodynamic therapy led to bacterial cell destruction without damage to the titanium surface. In an animal study using dogs, Hayek et al. in 2005 compared the effects of antimicrobial photodynamic therapy (paste-based Azulene + 50 mW diode laser) with those of a conventional technique, which included mucoperiosteal flap surgery and irrigation with chlorhexidine, on microbial reduction following ligature-induced peri implantitis. Periodontal pathogens, such as Prevotella ssp., Fusobacterium ssp. And Streptococcus beta-haemolyticus, were effectively reduced by photodynamic therapy to a level equivalent to that achieved by conventional treatment. The authors emphasized the favorable application of the photosensitizer in a paste base instead of in liquid solution, which allows it to be removed easily after treatment without any compromise in esthetics.

Similar antimicrobial results were also obtained by Shibli et al 2003, who reported that antimicrobial photodynamic therapy (toluidine blue O + 50 mW diode laser) could reduce the bacterial count of P. intermedia, P. nigrescens, Fusobacterium spp. And beta-hemolytic Streptococcus in ligature-induced peri-implantitis of dogs and, in some samples, complete elimination of those bacteria could be obtained.

In a clinical case-series study, Haas et al. in 2000 investigated the clinical effects of treatment of antimicrobial photodynamic therapy (toludine blue O + diode laser) in combination with guided bone regeneration using autogenous bone grafts on 24 implants diagnosed with peri-implantitis in 17 patients. They reported that 21 implants out

of 24 showed improvements in the bone defect after a mean observation period of 9.5 months. Dortbudak et al in 2001 examined the effectiveness of antimicrobial photodynamic therapy in treating contaminated implant surfaces by evaluating the remaining levels of A. actinomycetemcomitans, P. gingivalis and P. intermedia.

Microbiological samples on 15 patients diagnosed with peri-implantitis were taken from the same implants before and after application of toluidine blue O alone and then after the application of laser light (photodynamic therapy). Significant decreases of all species of bacteria were observed following photodynamic therapy by comparison with baseline levels.

In another study, Shibli et al. in 2003 evaluated the efficacy of antimicrobial photodynamic therapy associated with guided bone regeneration for the treatment of ligature-induced peri-implantitis in dogs, using implants with different surface characteristics. They reported that antimicrobial photodynamic therapy may be effectively applied for decontamination of implant surfaces and that bone defect fill and re-osseointegration could be achieved by its combination with guided bone regeneration. Furthermore, in a case report Schuckert et al. in 2006 demonstrated effective bone regeneration within bone defects around implants affected by peri-implantitis following surgical therapy using photodynamic therapy (tolonium chloride + 100 mW diode laser) to decontaminate the implant surface and the application of recombinant human bone morphogenetic protein-2.

Thus, the results of the previous studies indicate that the application of antimicrobial photodynamic therapy can effectively reduce the prevalence of pathogens on implant surfaces without causing any side effects on the implant and bone surfaces. However, in vivo and clinical studies are very limited and significant clinical effects of antimicrobial photodynamic therapy have not yet been demonstrated. De Angelis et al in 2012 investigated the effectiveness of adjuvant light activated disinfection in the treatment of peri-implantitis in a 4 month RCT and reported that the use of adjuvant PDT with mechanical cleaning did not improve any clinical outcomes up to 4 months Bassetti M 2013 studied anti-infective therapy of peri-implantitis with adjuvant PDT ot LDD in a 12 month RCT and observed that NSPT with adjuvant PDT was equally effective in reduction of mucosal inflammation as with adjuvant delivery of minicycline microspheres up to 12 months and hence PDT can be presented as an alternative to LDD. Deppe H et al in 2013 reported that PDT could stop bone resorption in moderate peri-implantitis defects but not in severe defects and contraindicated the use of PDT alone since surgical treatment is considered mandatory in sever peri-implantitis cases.

Other applications of photodynamic therapy

Apart from the conventional use in cancer treatment and the use as an antimicrobial therapy, PDT has a wide range of application. Mainstream uses for photodynamic therapy (PDT) in dermatology include nonmelanoma skin cancer and its precursors, acne vulgaris, photorejuvenation, and hidradenitis suppurativa. Photodynamic therapy has found its greatest success in the treatment of cancer, age-related macular degeneration, actinic keratosis and Barretts esophagus. The application of photodynamic therapy for targeting pathogenic microbes in wound infections has been explored in animal models. Photodynamic therapy with topical application of ALA is used offlabel for the treatment of acne vulgaris and has been employed for clinical use as an antifungal agent[24].

Conditions treated by photodynamic therapy[24]

Nonmelanoma Skin cancer	Other neoplasia	Inflammatory / Immune disorders	Infectious disorders	Miscellanious
Actinic keratosis	Dermatologic	Acene vulgaris	HPV	Laser assisted hair removal
Basal cell CA	Cutaneous T cell lymphoma	Psoriasis	MRSA	
Squamous cell CA	Non dematologic	Lichen Planus	Osteomyelitis	
Actinic Chelitis	Vulvular neoplasia	Scleroderma	Mollouscum contageousm	
DSAP	Anal carcinoma Barrets Oesophagus	Alopecia areata Darier's disease Macular degeneration of retina	Oral candidiasis	

Advantages of antimicrobial photodynamic therapy

One of the greatest hits of photodynamic therapy is the double selectivity obtained by targeting the PHOTO SENSITIZER, derived from its high affinity for microbial cells, and the light, implying that only the infected area is irradiated and, consequently, treated. However, many other advantages can be found compared to antimicrobial drugs[15]:

Practical advantages: APDT is safe for human tissue as the PHOTO SENSITIZER typically shows a higher affinity against microbial cells. The results are instantaneous while antibiotics take several days to act. It can be used to treat damaged or dead tissue, e.g. burns.

Effective: The therapeutic window of APDT is broader than other antimicrobial therapies, even against pathogenic biofilms. Because of the high reactivity of ROS, secreted virulence factors can be destroyed as these are commonly proteins, enzymes or aminoacid residues. Besides, APDT cannot easily induce the development of microbial resistance

Potential risks in photodynamic therapy

A critical issue when applying novel techniques relates to their clinical safety. The risks and side effects of antimicrobial photodynamic therapy are basically classified into two categories: one relates to the effect of light energy itself; and the other is related to the photosensitizer and the photochemical reaction (lethal photosensitization).Concern regarding short-term and long-term changes of biological tissues, including the periodontium, when novel technique may offer the following advantages compared with other forms of periodontal therapy (scaling, mouthwashes and surgery): [25]

(i) rapid and painless application of light;
(ii) selectivity in its effect;
(iii) full penetration of dental plaque by light;
(iv) limited penetration of light into gum tissue;
(v) absence of phototoxicity to human cells;
(vi) no effects on taste; and
(vii) Possible clinical and microbiological benefit with minimal impact on natural microbiota.

Antibody-targeted antibacterial approaches using photodynamic therapy

Antibodies conjugated with photosensitizers have been used to target Staphylococcus aureus. Selective killing of P. gingivalis was achieved in the presence of Streptococcus sanguinis (previously S. sanguis) or in human gingival fibroblasts using a murine monoclonal antibody against P. gingivalis lipopolysaccharide conjugated with toluidine blue O. In two studies, bacteriophages were used as vehicles to deliver the photosensitizer tin(IV) chlorine e6 to the surface of S. aureus strains. This led to approximately 99.7% killing of microorganisms[26].The combination of pulsed laser energy and absorbing gold nanoparticles selectively attached to the bacterium for killing of microorganisms is a new technology that was introduced recently.

Nanoparticle-based antimicrobial photodynamic therapy

Incomplete penetration of methylene blue in oral biofilms may become greater in a clinical setting, where both the photoactive compound and light should be applied for periods of up to 15 min. Therefore, one of the ways to overcome these deficiencies is to develop delivery systems that significantly improve the pharmacological characteristics of methylene blue. Recently, we proposed the encapsulation of methylene blue within poly (D,Llactide- co-glycolide) (PLGA) nanoparticles (150– 200 nm in diameter) that may offer a novel design of nano-platform for enhanced drug delivery and photodestruction of oral biofilms[25].

Application of antimicrobial photodynamic therapy in the treatment of peri-implant disease

Treatment of peri-implantitis has become an interesting topic among clinicians and researchers. In the treatment of peri-implantitis, it has been proven that complete eradication of the causative bacteria, which are similar to the pathogens responsible for the development of periodontal disease, and disinfection and detoxification of the diseased implant surface, as well as of the periimplant pockets, are essential to achieve effective healing with regeneration of the lost bone around the affected implants.

Conventional mechanical methods are apparently ineffective for complete debridement of the bone defect as well as of the contaminated microstructured implant surface. Thus, adjunctive application of systemic or local antibiotics and antiseptics has been generally recommended (Roos-Jansaker 2003).[9]

However, because of the potential problems related to antibiotics (such as resistance) and antiseptics, as mentioned previously, and the generally insufficient effect of the antimicrobial agents for bacterial eradication as well as poor results of re-osseointegration following their adjunctive application during nonsurgical and surgical therapy of peri-implantitis, novel approaches are still necessary in the treatment of peri-implant diseases.

Antimicrobial photodynamic therapy seems to be a unique and interesting therapeutic approach towards the treatment of periodontitis and peri-implantitis. The results of a number of in vitro, in vivo and clinical trials clearly demonstrate the effective and efficient bactericidal effect of antimicrobial photodynamic therapy. The potential applications of photodynamic therapy to treat oral conditions seem limited only by our imagination. Applications appear not only the common oral diseases of dental caries and periodontal disease but also the conditions of oral cancer, peri-implantitis, endodontic therapy, candidiasis etc. Low toxicity and rapidity of effect are qualities of photodynamic therapy that are enviable.

CONCLUSION

Antimicrobial photodynamic therapy may hold promise as a substitute for currently available chemotherapy in the treatment of periodontal and peri-implant diseases. At this time in history, it is difficult to know where light will lead us in the oral cavity but the promise is clear and the opportunities are visible.

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