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REVIEW ARTICLE

Photodynamic Therapy: A Targeted Therapy in Periodontics

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ABSTRACT

Advances in research are provided by techniques that were forgotten for many decades and innovative procedures to clinical application. With the increase of microbial resistance and development of lighting devices with safe and accurate delivery of energy, today professionals can count on therapies to manage pathogens in different fields of dentistry, especially periodontics and peri-implantitis. When the therapeutic resources have been exhausted, other alternatives can be considered, as the antimicrobial photodynamic therapy. Photodynamic therapy is a novel noninvasive therapeutic approach with increased pathogen and site specificity. Photodynamic therapy involves use of photosensitizer that is activated by exposure to light of specific wavelength to form toxic oxygen species thereby causing localized photo damage and cell death. Application of photodynamic therapy in periodontics, such as pocket debridement, gingivitis, aggressive periodontitis continue to evolve into a mature clinical treatment modality, and is considered as a promising novel approach for eradicating pathogenic bacteria in periodontitis.

Keywords: Antimicrobial photodynamic therapy, Laser, Periodontitis, Photosensitizer.

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INTRODUCTION

Recent advances in technology have led to a constant drive to develop novel approaches for the treatment of periodontal diseases. The need to find more optimal treatment protocols for periodontal disease is a long-term goal for periodontal researchers and clinicians. Periodontal disease caused by dental plaque is characterized by the clinical signs of inflammation and loss of periodontal tissue support. The mechanical removal of this biofilm and adjunctive use of antibacterial disinfectants and antibiotics have been the conventional methods of periodontal therapy. But, the removal of plaque and the reduction in the number of infectious organisms can be impaired in sites with difficult access. The possibility of development of resistance to antibiotics by the target organism has led to the development of a new antimicrobial concept with fewer complications.[1]

Since the beginning of the 1990s, the application of light energy (in other words, phototherapy) has been considered as a novel treatment approach in periodontics. Dental lasers have been used as an effective means of decontamination of periodontal pockets over a period of 20 years. Lasers possess high bactericidal properties and they have demonstrated effective killing of oral pathogenic bacteria associated with periodontitis and peri-implantitis.[2] In spite of the substantial bactericidal effects of high-level lasers, there is limited clinical evidence to demonstrate clearly that lasers can produce a greater reduction in the number of subgingival bacteria than that achieved using traditional mechanical therapy. Also, the use of high-level lasers usually results in irreversible thermal damage to the surrounding periodontal tissues.

Recently, a new type of noninvasive phototherapy for bacterial elimination, called photodynamic therapy, has been introduced, which uses low-level laser light. Unlike high-level lasers, photodynamic therapy can selectively target the bacteria without potentially damaging the host tissues. Photodynamic therapy has been extensively studied in the laboratory, and clinical trials have been recently initiated in the field of periodontics and peri-implant therapy. In this review article, an overview on the existing clinical evidence on the effects of photodynamic therapy in the treatment of periodontal and peri-implant diseases is presented and discussed.

Antimicrobial Photodynamic Therapy

The photodynamic therapy (PDT), photodynamic inactivation (PDI) and, more recently, antimicrobial photodynamic therapy (aPDT) is a treatment indicated for the destruction of pathogenic cells, in tumors, whether bacterial, viral, fungal or inflammatory clinical conditions, with the use of photosensitizing (PS) substances and sources of light in low wavelengths as well as low doses, compatible with this action. Photodynamic

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therapy was introduced in medical therapy in 1904 as the light-induced inactivation of cells, microorganisms or molecules and 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.[3]

One target is host mammalian tissue in the treatment of cancers. It has been shown that the photosensitizers have a selective affinity for tumor or vascular tissue, and after excitation by light they produce cytotoxic effects, which may lead to cell death or tissue destruction by necrosis or apoptosis.[4] The other target recently broadly discussed in the microorganism. The microorganism is an important target in the treatment of local oral infections, and photodynamic therapy has been introduced as an important novel disinfection therapy in the field of dentistry. Theoretically, neither the photosensitizer nor the light alone can induce an efficient cytotoxic effect on the cells. The photosensitizer is generally applied in the targeted area by topical application, aerosol delivery or interstitial injection. The light that activates the photosensitizer must be of a specific wavelength with a relatively high intensity.[5] With the discovery and development of lasers that are collimated, coherent and monochromatic, this therapy proved to be a great evolution because it became possible to utilize a homogeneous intensive light with low-level energy that was suitable for activation of the photodynamic reaction.

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 controling the amount of light applied to activate the reaction. Using this simple procedure, bacteria can be eradicated in a very short period of time.

Mechanisms involved in Antimicrobial Photodynamic Therapy

The knowledge of the preferred uptake and accumulation of some dyes into tumor tissues stimulated the introduction of PDT into clinical practice. Photodynamic therapy involves three components: light, a photosensitizer and oxygen. The photosensitizer is administered to the patient, and upon irradiation with light of a specific wavelength, the photosensitizer undergoes a transition from a low energy ground state to an excited singlet state. Subsequently, the photosensitizer may decay back to its ground state with the emission of fluorescence or may undergo a transition to a higher energy triplet state. The triplet state photosensitizer can react with biomolecules in two different pathways: type I and II[4] (Fig. 1).

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.

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, 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.

Singlet oxygen has a short lifetime in biological systems (<0.04 ms) and a very short radius of action (0.02 μm).[6] Because of the limited migration of singlet oxygen from its

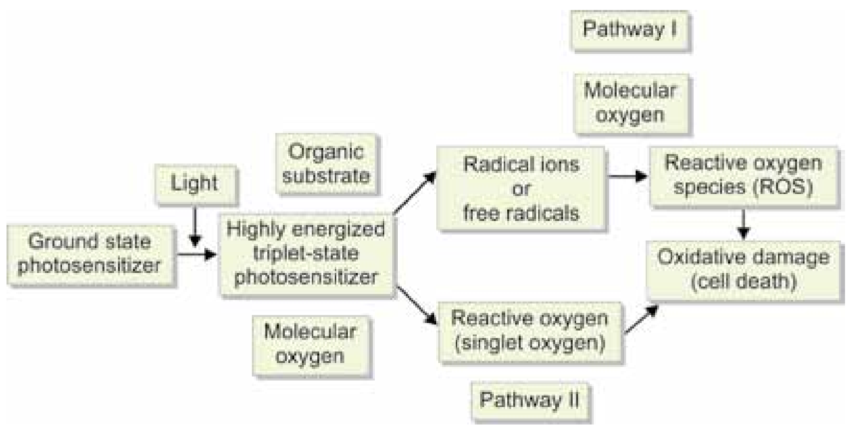

Fig. 1: Mechanism of photodynamic antimicrobial reactions at the molecular level. After irradiation with light of a specific wavelength, the photosensitizer in the ground state is converted to a highly-energized triplet state. The triplet-state photosensitizer follows two different pathways (I and II) to react with biomolecules. Pathway I involves the production of ions or electron/hydrogen removal from an organic substrate molecule of the cells to form free radicals. Pathway II involves the production of a highly reactive state of oxygen, known as singlet oxygen which reacts with the surroundings as a result of its high chemical reactivity. The free radicals and the singlet oxygen convey toxic or lethal effects to the bacterial cell by damaging the cell membrane and the cell wall

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.[7]

Photosensitizing Agents and the Wavelengths used in Periodontal and Peri-implant Therapy

Photodynamic therapy is based on the principle that a photoactivable substance (the photosensitizer) binds to the target cell and can be activated by light of a suitable wavelength. In antimicrobial photodynamic therapy, the particular photosensitizers employed are toluidine blue O and methylene. With respect to antimicrobial photodynamic therapy, it has been demonstrated that methylene blue and toluidine blue O are very effective photosensitizing agents for the inactivation of both Gram-positive and Gram-negative periodontopathic bacteria.[8] It is still a point of debate that Gram-negative organisms seem to be generally more resistant to photodynamic therapy than Gram-positive bacteria, as a result of the differences in the outer membrane structures of both types of bacteria.[9] However, studies have shown that photosensitizers, such as toluidine blue O and methylene blue, which undergo a pronounced cationic charge, can bind to the outer membrane of Gram-negative bacteria and penetrate bacterial cells,[10] demonstrating a high degree of selectivity for killing microorganisms compared with host mammalian cells. Therefore, toluidine blue O and methylene blue have been the photosensitizers of choice in the treatment of periodontitis and peri-implantitis. However, toluidine blue O seems to exhibit a greater ability for killing Gram-positive and Gram-negative bacteria than methylene blue.

PDT requires a sources of light to activate the photosensitizer by exposure to low power visible light at a specific wavelength. In the past, photosensitizer activation was achieved by a variety of light sources, such as argon lasers, potassium titanyl phosphate or neodymium-doped:yttrium, aluminum and garnet (Nd:YAG) lasers. Currently, however, the light sources of a specific wavelength mostly applied in photodynamic therapy are those of helium-neon lasers (633 nm), gallium-aluminum-arsenide diode lasers (630-690, 830 or 906 nm) and argon lasers (488-514 nm). Recently, non-laser light sources, such as light-emitting diodes, have been suggested as new light activators in photodynamic therapy as light-emitting diode devices are more compact and portable, and the cost is much lower compared with that of traditional lasers. In the early 1990s, Dobson and Wilson[11] showed that low-level helium-neon laser irradiation with toluidine blue O or methylene blue was effective for killing *P. gingivalis*, *F. nucleatum*, *A. actinomycetemcomitans* and *S. sanguinis*.

Applications of Photodynamic Therapy in Periodontics

Treatment of periodontal disease and peri-implantitis has become an interesting topic between clinicians and researchers. With the extensive increase in placement of dental implants, the number of implants affected by peri-implantitis has also been increasing in clinical practice. 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,[12] and disinfection and detoxification of the diseased implant surface as well as of the peri-implant pockets, are essential to achieve effective healing with regeneration of the lost bone around the affected implants. PDT can be considered as an adjunctive to conventional mechanical therapy. The technical simplicity and effective bacterial eradication are the two reasons why photodynamic therapy is extensively studied in periodontics. Antimicrobial PDT not only kills the bacteria, but may also lead to the detoxification of endotoxins, such as lipopolysaccharide. These lipopolysaccharides treated by PDT do not stimulate the production of proinflammatory cytokines by mononuclear cells. Thus, PDT inactivates endotoxins by decreasing their biological activity.[13]

In a randomized clinical trial performed in 2007 by Andersen et al,[14] 33 patients suffering from chronic periodontitis were randomly placed in three groups. In group 1, PDT, in group 2, scaling and root planing (SRP+) PDT (diode laser) and, in the control group, SRP alone was applied. The results of this study showed that the addition of PDT to SRP from a statistical point of view significantly improved the clinical attachment level (CAL) and the probing pocket depth (PPD). Only one study, by De Oliveira et al,[15] 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 and 60 mW diode laser) or scaling and root planing. Laser application was performed for 10 seconds per site after 3 minutes of residence time of the photosensitizer. Three months later, both treatment procedures gave comparable clinical outcomes, as evidenced by PPD reductions and clinical attachment level gains, suggesting a potential clinical effect of photodynamic therapy as an alternative to scaling and root planing.

In a case report, Schuckert et al[16] demonstrated effective bone regeneration within bone defects around implants affected by peri-implantitis following surgical therapy using photodynamic therapy (tolonium chloride and 100 mW diode laser) to decontaminate the implant surface and the application of recombinant human bone morphogenetic protein 2.

Noro Filho GA et al,[17] in a split mouth randomized clinical trial in 2012, randomly placed 12 patients infected with HIV, and with antecedent of chronic periodontitis in two groups, SRP and aPDT, as an adjunctive treatment (660 nm wavelength and photosensitizer: methylene blue). In the evaluation performed, after 6 months improvements in CAL and PPD were observed and they concluded that the combination of SRP and aPDT can have more benefits in the treatment of these patients.

On interpreting the data from the various controlled clinical studies, it becomes obvious that in patients with chronic periodontitis, aggressive periodontitis and peri-implantitis, the adjunctive use of PDT to scaling and root planning may result in greater clinical attachment level gains, reduction in bleeding on probing and PPD. PDT has advantage, such as reducing the treatment time, no need for anesthesia, destruction of bacteria, inactivation of endotoxins, and unlikely development of resistance by the target bacteria and no damage to the adjacent host tissues. The multiple use of PDT compared to its use as a single dose is more effective. Considering that the effective role of laser in the treatment of periodontal diseases has been proven, it is suggested that different types of photosensitizers, lasers, wavelengths and powers been compared in order to obtain the best and most effective clinical results. Number of sessions, durations and frequencies are other laser characteristics that have to be evaluated to determine the best possible configuration and periodicity.

Even though PDT has no routine use in daily practice, there are potential benefits for this therapy beyond mechanical debridement. The amount of cementum that must be removed is reduced significantly, which allows for better tissue regeneration without an increased risk of hypersensitivity. Furthermore, PDT's antibacterial effects are advantageous for patients with systemic diseases (such as cardiovascular diseases, diabetes, and immunosuppression), may be especially relevant for pregnant women, because, a high prevalence of *Prevotella intermedia* is associated within the second trimester, in pregnancy-associated periodontitis and for those who display high resistance to antibiotic therapy.[18] PDT cannot perform the various applications of other lasers during the surgical stage of periodontal therapy (i.e. incision, excision, or carbonization), but it may improve both the wound healing mechanisms and the regenerative potential of cells. Additional research is necessary to examine these possibilities.

ADVERSE EFFECTS

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 is related to the effect of light energy itself, and, the other is related to the photosensitizer and the photochemical reaction.

The potential inadvertent irradiation of the patients eyes must be strictly avoided during treatment, even though the laser power employed is very low. The use of protective glasses by the patient, the operator and the assistant is recommended. During treatment with high level lasers, thermogenesis occurs as a result of the interaction of the laser with the tissues. PDT, as a low level therapy, using a diode laser with short irradiation time, does not produce any thermal changes within the gingival tissues and root surfaces.

With respect to the photosensitizers and photochemical reactions, it is important to know if the targeted bacteria can be killed by the application of antimicrobial photodynamic therapy without the occurrence of any adverse effects in the surrounding periodontal tissues. Research performed *in vitro* and, in animal models, suggests that the adverse effects on host tissues may not be a problem, because, the photosensitizer concentrations and light energy doses necessary to kill the infecting microorganism have little effect on adjacent host tissues.[19] Luan et al[20] reported that no necrotic or inflammatory changes were found in periodontal tissues following photodynamic therapy treatment, suggesting that antimicrobial photodynamic therapy is a safe therapy that does not damage the adjacent normal tissues.

PERSPECTIVES AND FUTURE DIRECTIONS

Antimicrobial photodynamic therapy seems to be a unique and interesting therapeutic approach toward the treatment of periodontitis and peri-implantitis. The numerous *in vitro* studies have clearly demonstrated the effective and efficient bactericidal effect of PDT. There is a great need to develop an evidence-based approach to the use of PDT for the treatment of periodontitis and peri-implantitis. It would be prudent to say that there is an insufficient evidence to suggest that PDT is superior to the traditional modalities of periodontal therapy. Development of new photosensitizers, more efficient light delivery systems, and further studies are required to establish the optimum treatment parameters. Antimicrobial photodynamic therapy may hold promise as a substitute for currently available chemotherapy in the treatment of periodontal and peri-implant diseases.

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