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ROLE OF PHOTODYNAMIC THERAPY IN PERIODONTITIS

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ABSTRACT

The etiology of periodontitis is multifactorial and the anatomical complexity of tooth roots serves as niches for bacterial deposits, making eradication of periodontopathogens more difficult both mechanically and chemically. Also, the fact that conventional treatment such as scaling and root planing (SRP) does not completely eliminate periodontal pathogens, led to the use of various adjuvant treatments modalities. A novel noninvasive photochemical approach for infection control, namely photodynamic therapy, has received much attention in the treatment of oral diseases. Three nontoxic ingredients namely visible harmless light, a photosensitizer and oxygen are involved in this therapy. It is based on the principle that a photosensitizer binds to the target cells which when activated by light of a suitable wavelength results in the production of singlet oxygen and other very reactive agents that are extremely toxic to certain cells and bacteria. This article highlights the role of photodyanamic therapy in periodontitis.

Key words: Antimicrobial, periodontitis, photodynamic therapy, photosensitizer.

INTRODUCTION

The application of light energy (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[1]. Lasers possess high bactericidal properties and have demonstrated effective killing of oral pathogenic bacteria associated with periodontitis and peri-implantitis[2]. Most high-level lasers exhibit bactericidal effects by thermal denaturation or direct ablation or destruction of bacterial cells and have been applied in nonsurgical or surgical periodontal and peri-implant therapies.

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Besides damaging the bacterial cells, the use of high-level lasers results in irreversible thermal damage to the surrounding periodontal tissues, excessive ablation or thermal coagulation, carbonization or necrosis of the root, the gingival connective tissue, the bone and the pulp tissues, depending on the type of laser employed[3].Photodynamic therapy is a new type of noninvasive phototherapy for bacterial elimination, which uses low-level laser light and selectively targets the bacteria without potentially damaging the host tissues[1].

Historical perspective of photodynamic therapy

The origin of light as a therapy in medicine and surgery has been traced from antiquity to the modern day. Phototherapy began in ancient Greece, Egypt and India, but disappeared for many centuries, only being rediscovered by the Western civilization at the beginning of the 20th century. The use of contemporary photodynamic therapy was first reported by the Danish physician, Niels Finsen (1901). He successfully demonstrated photodynamic therapy by employing heat – filtered light from a carbon – arc lamp (The Finsen

Lamp) in the treatment of a tubercular condition of the skin known as Lupus Vulgaris. Niels Finsen won a nobel prize for his work on phototherapy in 1903. [1,4]

The concept of cell death induced by the interaction of light and chemicals was first reported by Osar Raab[5] a medical student working with Professor Herman Von Tappeiner in Munich. During the course of his study on the effects of acridine on paramecia cultures, he discovered that the combination of acridine red and light had a lethal effect on infusoria, a species of paramecium. Subsequent work in the laboratory of Von Tappeiner (1907) coined the term "Photodynamic action" and showed that oxygen was essential. Much later, Thomas Dougherty and co-worker[6] at Roswell Park cancer institute, Buffalo, New York, clinically tested Photodynamic therapy. In 1978, they published striking results in which they treated 113 cutaneous or subcutaneous malignant tumors and observed a total or partial resolution of 111 tumors. The active photosensitizer used in this clinical trial was called Hematoporphyrin Derivative. It was John Toth, who renamed it as Photodynamic therapy.

Photodynamic therapy was approved by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions of the face or scalp. PDT has emerged in recent years as a new non - invasive therapeutic option.

Components of PDT

Photodynamic therapy basically involves three non-toxic ingredients: visible harmless light, a nontoxic photosensitizer and oxygen. (Figure 1) It is based on the principle that a photosensitizer (i.e. a photoactivatable substance) binds to the target cells and is 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 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[1].

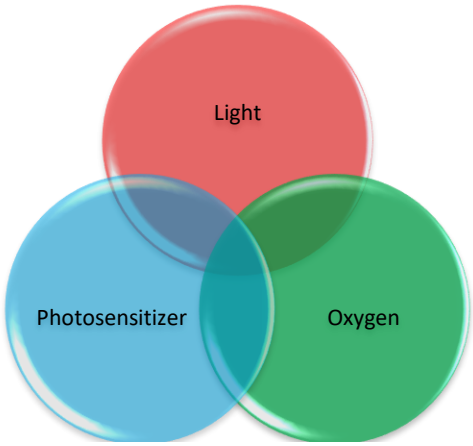

Figure 1: Basic components of photodynamic therapy

Light

Sources of light include a range of lasers, helium - neon lasers (633 nm), gallium - aluminum - arsenide diode lasers (630-690, 830 or 906 nm) and argon laser (488-514nm), the wavelength of which range from visible light to the blue of argon lasers, or from the red of helium-neon laser to the infra red area of diode lasers. Non-laser light sources like light emitting diode (LED) and light cure units. Photosensitizers are activated by red light between 630 and 700 nm corresponding to a light penetration depth from 0.5 cm (at 630 nm) to 1.5 cm at (700 nm) which is sufficient for periodontal treatment.[7] The total light dose, dose rates and the depth of destruction vary with each tissue treated and photosensitizer used[8].

Photosensitizers

A photosensitizer is a dye substance that is absorbed by the microorganism, cell or tissue allowing it to interact with the light. An optimal photo sensitizer must possess photo-physical, chemical and biological characteristics. The sensitizers used for medical purposes belong to the following basic structure: [7]

1. Tricyclic dyes with different meso-atoms E.g.: Acridine orange, proflavine, riboflavin, methylene blue, fluorescein and erythrosine.
2. Tetrapyrroles. E.g.: Porphyrins and derivatives, chlorophyll, phylloerythrin and phthalocyanines.
3. Furocoumarins. E.g.: Psoralen and its methoxyderivatives, xanthotoxin and bergaptene.

In antimicrobial PDT, photosensitizers used are toluidine blue O and methylene blue. Both have similar chemical and physicochemical characteristics. The positive charge seems to promote the binding of the photosensitizer to the gram-negative bacterial membrane and leads to its localized damage, resulting in an increase in its permeability. Methylene blue interaction with the anionic lipopolysaccharide macromolecule of gram-negative bacteria results in the generation of methylene blue dimers, which participate in the photosensitization process [9,10]

Mechanism of action

The bactericidal effect of photodynamic therapy is explained by two potential, but different, mechanisms namely the DNA damage and the damage caused to the cytoplasmic membrane of the bacteria by cytotoxic species generated by antimicrobial photodynamic therapy. After irradiation with light of a specific wavelength (lasers), the photosensitizer at ground state is activated to a highly energized triplet state. The longer lifetime of the triplet state enables the interaction of the excited photo sensitizer with the surrounding molecules resulting in the generation of cytotoxic species. There are two different pathways (type I and II) to react with biomolecules. [1,11]

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 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 and result in irreparable biological damage [11]. (Figure 2)

In the type II reaction, the triplet-state photosensitizer reacts with oxygen to produce a highly reactive state of oxygen, known as singlet oxygen ($^1O_2$), which interacts with a large number of biological substrates due to 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 µs) and a very short radius of action (0.02 µm) that causes limited migration of singlet oxygen from its site of formation leading to a localized response and making it ideal for application at localized sites without affecting distant molecules, cells or organs. The process of antimicrobial photodynamic therapy is generally mediated by a type II reaction, which is accepted as the major pathway in microbial cell damage.[11,12] (Figure 2)

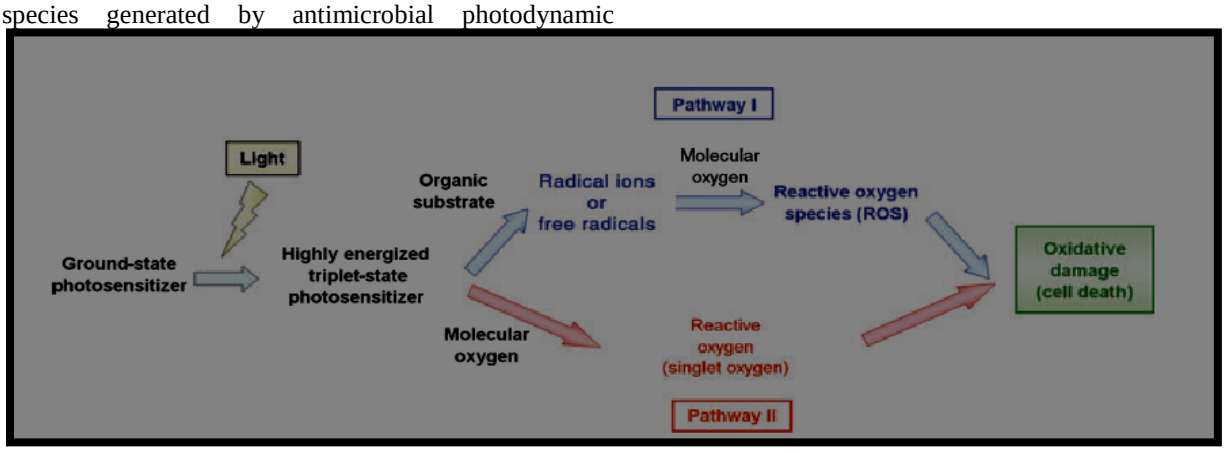

Figure 2: Mechanism of photodynamic antimicrobial reaction at the molecular level[1]

Photodynamic therapy in the treatment of oral diseases

Applications of photodynamic therapy in dentistry include photodynamic diagnosis of malignant oral lesions, treatment of premalignant and malignant oral lesions and photodynamic antimicrobial chemotherapy (PACT) of bacterial and fungal infections. The various uses are as follows: [1, 13]

1. Treatment of different types of oral solid tumors
2. Treatment of psoriasis, actinic keratosis
3. Treatment of inflammatory diseases like rheumatoid arthritis
4. Age related macular degeneration
5. Superficial precancerous oral lesions, such as oral leukoplakia, oral erythroleukoplakia, oral verrucous hyperplasia and lichen planus.
6. Treatment of Bacterial, fungal and viral infections of the oral cavity.
7. Treatment and prevention of dental caries.
8. As an adjunct to conventional endodontic disinfection treatment to destroy the bacteria that remain even after irrigation with sodium hypochlorite
9. Effective in the destruction of Candida albicans, which is responsible for oropharyngeal candidiasis
10. Elimination of bacteria in supragingival and subgingival plaque.
11. As an adjunctive for bacterial elimination in the treatment of periimplantitis

Photodynamic therapy and Periodontitis

Biofilm in oral cavity causes two of the most common diseases, dental caries and periodontal diseases. An effective approach of periodontal therapy is to change the local environment to suppress the growth of periodontal pathogens. Using antimicrobial agents to treat periodontitis without disruption of the biofilm ultimately results in treatment failures. It is difficult to maintain therapeutic concentrations at the target sites and target organisms can develop resistance to drugs. This resistance is minimized by using PDT. Polysaccharides present in extracellular matrix of oral biofilm are highly sensitive to singlet oxygen and susceptible to photodamage. Breaking the biofilm may inhibit plasmid exchange involved in transfer of antibiotic resistance and disrupt colonization[14,15] Photodynamic antimicrobial chemotherapy could be an ideal complement to conventional scaling and root planing. However, bacterial eradication from dental plaque-derived biofilms is still at a lower level compared to the planktonic condition. In the study conducted by Fontana et al [16] photodynamic therapy eliminated approximately 63% of bacteria in the planktonic phase as compared to 32% of bacteria in biofilms, derived from the same plaque samples.

During inflammation there is venous stagnation and reduced oxygen consumption by tissues. This decrease in oxygen level and change in pH enhances the growth of anaerobic species. PDT improves tissue blood flow in the microcirculatory system and reduces venous congestion in gingival tissues. Furthermore, PDT increases oxygenation of gingival tissues by 21–47 per cent which in turn decreases the time and speed of oxygen delivery and utilization, thus normalizing oxygen metabolism in periodontal tissues [17]

The pathogenesis of periodontal diseases is explained on the basis of the virulence factors possessed by the periodontopathogens that cause activation of macrophages, production of interleukin-1, release of prostaglandin E_2, which are potent stimulators of bone resorption. Endotoxin on root surface inhibits fibre reattachment on cementum. PDT causes the inactivation of the various virulence factors secreted by micro-organisms. [18]

Upon interpretation of the data from various controlled clinical studies, the adjunctive use of PDT to scaling and root planning in the treatment of patients with chronic periodontitis, aggressive periodontitis and peri-implantitis, resulted in greater clinical attachment level gains, reduction in bleeding on probing and probing pocket depths. Azarpazhooh et al[19] conducted a systemic review and concluded that photodynamic therapy as an independent therapy or as an adjunct to SRP was not superior to control treatment than SRP. A meta-analysis was performed by Sgolastra et al[20] which suggested that the use of aPDT as an adjunct to conventional treatment provides short-term benefits in terms of CAL gain and pocket depth reduction (at 3 months after treatment) thereby confirming the safety of PDT.

PDT has advantage such as reducing the treatment time (<60seconds), no need for anesthesia, destruction of bacteria, inactivation of endotoxins, non-invasive local therapy, reduced risk of bacteraemia after periodontal debridement and no damage to the adjacent host tissues[14,21].

Current status and future perspectives

In the dental field, photodynamic therapy is approved for the palliative treatment of patients with advanced head and neck cancer and in the treatment of various oral lesions. Photo-activated disinfection system, PAD™ (Denfotex Light Systems Ltd, Inverkeithing, UK), is used for the disinfection of root canals. The PAD™ consists of toluidine blue O solution and a 100 mW diode laser that emits light at 635 nm. Toluidine blue O (12.7 mg/l) is applied in the root canals for 60 seconds followed by exposure to light via a fiberoptic for 2 min. Photodynamic therapy rapidly eliminates microorganisms unlike the conventional therapy[22].
Recently, in Canada, the product called Periowave (http://www.periowave.com) was commercialized by Ondine Biopharma Corporation (http://www.ondinebiopharma.com) for the treatment of periodontitis. The Periowave product consists of a laser system with a custom-designed handpiece and patient treatment kits of methylene blue. A kit that includes phenothiazine chloride for clinical photodynamic therapy is now available in Austria, Germany, Switzerland and the UK (Helbo; Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria). Similar kits that include toluidine blue O are also available from other companies, including Denfotex Ltd., Dexcel Pharma Technologies Ltd., SciCan Medtech AG and Cumdente GmbH[22].(Figure 3,4)

The application of these kits is very simple and convenient. Methylene blue is applied directly in the dental pockets for 60 seconds followed by exposure to red light via a fiberoptic probe for 60 seconds per pocket or per tooth (10s per site, six sites in total). In the majority of the studies, photodynamic therapy was used as an adjunct to scaling and root planing. (Figure 5)

Figure 3: Periowave

Figure 4: Helbo® T-Controller
(From: www.bredent-medical.com)

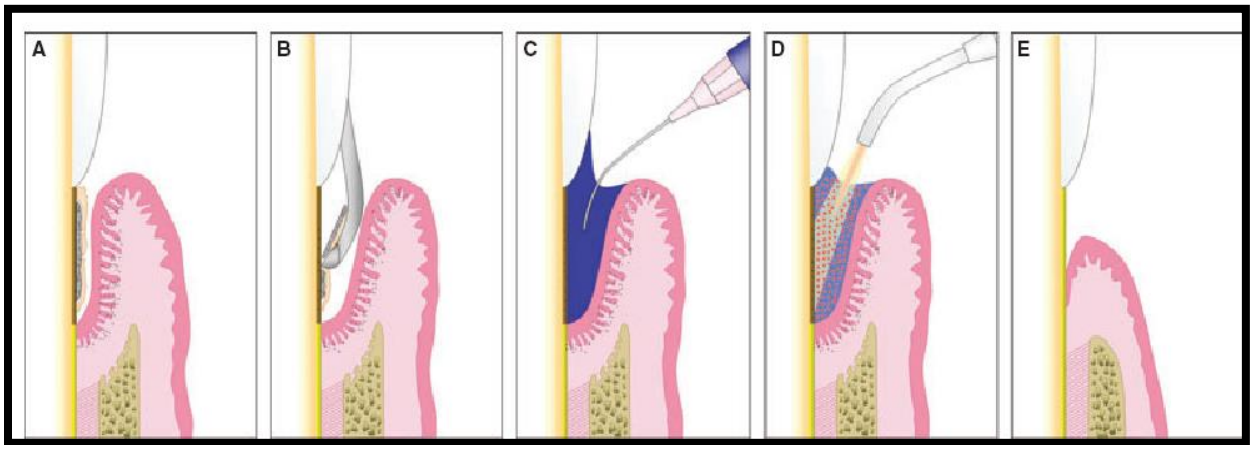

Figure 5: Steps of application of photodynamic therapy in the treatment of periodontitis.
(A) Periodontally diseased site before treatment. (B) Mechanical debridement using hand curettes. (C)Application of the photosensitizer via syringe at the diseased site that contains residual bacteria. (D) Photosensitization is performed using an intensive light by a special tip applied in the pocket. Singlet oxygen and other very reactive agents that are toxic to bacteria are produced, resulting in photochemical disinfection of the periodontal pocket. (E) Improved wound healing in the treated site.[1]

CONCLUSION

Antimicrobial photodynamic therapy is likely to be an attractive option as a non-invasive treatment approach in the field of periodontology, with confirmed clinical safety. Antimicrobial photodynamic treatment has been reported to be effective as an adjunct to conventional therapy to destroy bacteria in sites where there is limited access for mechanical instrumentation as a result of the anatomical complexity of the roots. Also, further randomized long-term clinical studies and meta-analyses are necessary to demonstrate the beneficial effects of antimicrobial photochemical therapy and their real advantages in comparison with conventional methods. Only then antimicrobial photodynamic therapy will hold promise as a substitute for currently available chemotherapy in the treatment of periodontal and peri-implant diseases.

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