Review Article

Photodynamic therapy in periodontitis - A short review

D. Shruthi, Antonette Rhea*

ABSTRACT

Periodontal disease is caused by dental plaque biofilms. Periodontitis is a common disease that causes tooth loss, and chronic inflammation induced by bacterial infection which is the major cause of periodontium destruction. The treatment for periodontitis depends on removal of periodontopathogens and their toxic products. Photodynamic therapy (PDT) is a powerful laser-initiated photochemical reaction, involving the use of a photoactive dye (photosensitizer) activated by light of a specific wavelength in the presence of oxygen. PDT is based on the principle that a photoactivable substance that is a photosensitizer binds to the target cell and can be activated by light of suitable wavelength. The mechanism of PDT is based on the principle that a photoactivable material that is a photosensitizer binds to the target cell or microorganisms and can be activated by light of an appropriate wavelength. Most of the studies that are done revealed that PDT is most effective on combination with conventional scaling and root planning method. The reason for this review is to understand and provide information about PDT and extend knowledge of advanced laser therapy. The aim and objective of this review are to provide comprehensive information about PDT and its role in periodontitis.

KEY WORDS: Antimicrobial, Periodontitis, Photosensitizer, Photoactive dye, Wavelength

INTRODUCTION

Periodontal disease which is caused by dental plaque is characterized by the clinical signs of inflammation and loss of periodontal tissue support. The mechanical removal of the biofilm and adjunctive use of antibacterial disinfectants, antibiotics have been the conventional methods of periodontal therapy till date.[1] The removal of plaque and the reduction in number of infectious organisms can be impaired at sites with difficult access. The possibility of development of resistance to the antibiotics by the target organisms has led to the development of a new antimicrobial concept with fewer complications.[2] Periodontitis is an infectious polymicrobial disease affecting the attachment apparatus of the teeth.[3] The various periodontal pathogens which are susceptible in the disease progression includes Aggregatibacter (formerly Actinobacillus) *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia* (previously forsythensis), Campylobacter rectus, and *Treponema denticola*.[4]

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The application of light energy (phototherapy) has been considered as a novel treatment approach in periodontics.[5] The major advantages of photodynamic therapy (PDT) are that it is a specific therapy targeting cells, it has no collateral effect, it is initiated only on exposure to light. Its use will not lead to the selection of resistant bacterial species.[6]

PDT was introduced in medical practice as therapy for inactivation of microorganisms on the basis of photosensitizer attachment to target cells, and it can be activated by a suitable wavelength of light.[7] PDT utilizes singlet oxygen and free radicals which are produced by a light-activated photosensitizer to kill microbes. The photochemical system is initiated by light or a low-electricity laser at an applicable wavelength to excite the photosensitizer.[8] Suitable dye sensitizers for PDT are mainly porphyrinoid compounds, including chlorine, bacteriochlorins, phthalocyanines, and related structures.[9] These exist as colored compounds or dyes as these compounds have extended conjugation and absorb light in the visible region.[10] The aim of this review is to provide comprehensive information about PDT and its role in periodontitis.

Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** Antonette Rhea, Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, Poonamallee High Road, Chennai - 600 077, Tamil Nadu, India. Phone: +91-9176645343. E-mail: arhea.a@gmail.com

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HISTORY OF PDT

Phototherapy initially originated in Ancient Greece, Egypt, and then in India but later disappeared from many centuries and came into practice only after being rediscovered at the beginning of 20th century by western civilization. The Danish physician, Niels Finsen, was the first who introduced the contemporary PDT.[11] Oscar Raab, a medical student working with Professor Herman von Tappeiner in Munich first reported the concept of cell death being induced by the interaction of light and chemicals which has been recognized for 100 years. He discovered that the combination of light and acridine red had a lethal effect on a species of paramecium named Infusoria.[12] Von Tappeiner coined the term "photodynamic action" and demonstrated that oxygen was essential by doing subsequent work in the laboratory. In 1911, Hausmann in Vienna performed his first studies of the biological effects of hematoporphyrin and reported on the effect of hematoporphyrin and light on a paramecium, red blood cells and described skin reactions in mice that are exposed to light after hematoporphyrin administration.[13] In 1913, Friedrich Meyer-Betz, to determine whether the same effects could be induced in humans as well as mice, he injected himself with 200 mg of hematoporphyrin and subsequently noticed prolonged pain and swelling in light-exposed areas.[14] Dougherlg and Marcus renamed as "photodynamic therapy."[15] In 1999, the Food and Drug Administration approved the PDT to treat precancerous skin lesions of the face or scalp.[16]

COMPONENTS OF PDT

PDT involves three components such as visible light, a nontoxic photosensitizer, and oxygen.[17] PDT is based on the principle that a photoactivatable substance that is a photosensitizer binds to the target cell and can be activated by light of suitable wavelength.[18] The photosensitizers are mostly activated by red light with mild penetration depth from 0.5 cm to at least 1.5 cm of wavelength between 630 and 700 nm.[19] Light systems for the therapy: Diode laser systems, non-coherent light sources, and non-laser light sources include light-emitting diodes.[20] Photosensitizers in antimicrobial PDT (APDT), which include porphyrins, phthalocyanines, and phenothiazines (e.g., toluidine blue O and methylene blue), act and affect both Gram-positive and Gram-negative bacteria by bearing a positive charge.[21] The ideal PDT photosensitizers have characteristics that are similar to the pure form of known chemical composition. It should be easily synthesized from the available precursors and also easily reproducible; high singlet oxygen quantum yield (Φ); strong absorption in the red region of the visible spectrum (680–800 nm) with a high extinction coefficient (εmax), e.g., 50,000–100,000 M/cm. Effective accumulation in tumor tissue and possession of low dark toxicity for both photo sensitizer and its metabolites. It should also be stable and soluble in the body's tissue fluids, and poses easy delivery to the body via injection or other methods and should be excreted from the body upon completion of treatment.[22]

MECHANISM OF PDT

The mechanism of PDT is based on the principle that a photoactivatable material that is a photosensitizer binds to the target cell or microorganisms and can be activated by light of an appropriate wavelength.[23] A photosensitizer when irradiated with light of certain wavelength, ground state is activated to highly energized triplet state. The excited photosensitizer has a longer lifetime, which results in interactions with surrounding molecules, and generally, it is assumed that at the triplet state the generation of cytotoxic species occurs. The triplet-state photosensitizer reacts with biomolecules using two different pathways such as type 1 and type 2.[24]

Type I: It includes the transfer of electron/hydrogen directly from the photosensitizer, production of ions, or removal of electron/hydrogen to form free radicals from a substrate molecule. These radicals react rapidly with oxygen which results in the production of highly reactive oxygen species (superoxide, hydroxyl radicals, and hydrogen peroxide).

Type II: In this type of reaction, the triplet state the photosensitizer reacts with oxygen to produce an excited and highly reactive state of oxygen known as singlet oxygen which can interact with a large number of biological substrates which can induce oxidative damage on the cell membrane and cell wall.[25]

The antimicrobial effect low-power lasers are achieved by association with extrinsic photosensitizers, which results in the production of highly reactive oxygen species that cause damage to membranes, mitochondria, and DNA, culminating in the death of the microorganisms [Figure 1].[26]

APPLICATION OF PDT

PDT is widely applied in the management of dental caries, oral and mucosal infection, endodontic infection, peri-implantitis, and periodontitis.[27] Application of PDT in dentistry includes diagnosis of malignant oral lesions, treatment of premalignant and malignant lesions, and photodynamic antimicrobial chemotherapy of bacterial and fungal infections.[17] Pathogenic periodontal microorganisms such as *P. gingivalis*, *P. intermedia*, *Fusobacterium nucleatum*, and *Parvimonas micra* have been destroyed by photodynamic action. The reduction of the biological activities of the key virulence factors,

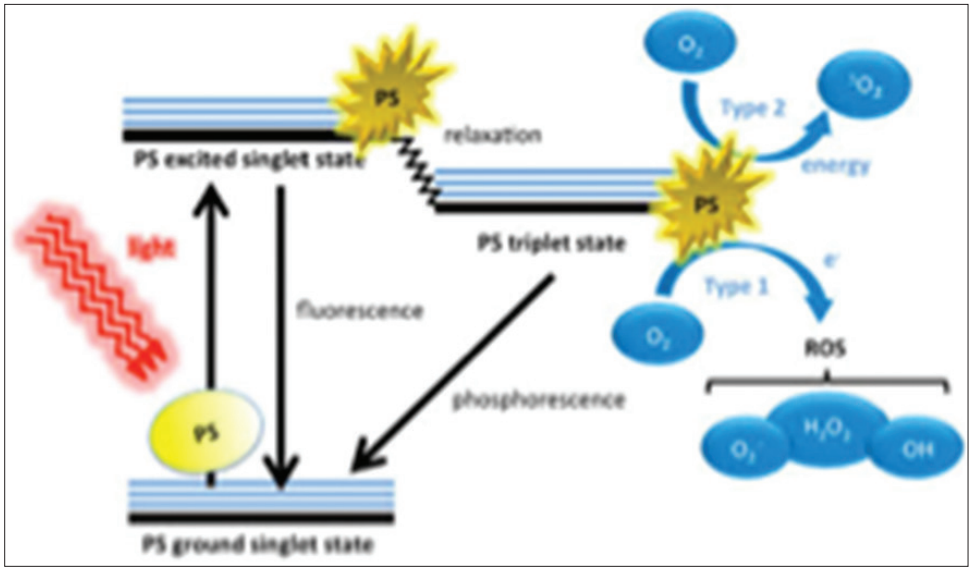

Figure 1: Mechanism of photodynamic therapy

such as lipopolysaccharide and proteases, may act as an additional benefit.[28] Photodynamic inactivation of Candida albicans in a murine model of oral candidiasis has been noted.[29] PDT is lately being recognized as an appealing, non-invasive and alternative treatment method for precancerous lesions and superficial cancers. PDT has many benefits while as compared with conventional treatment modalities. It has, additionally, been used for the photoinactivation of microbes. There may be an growing hobby within the practical application of antimicrobial photodynamic therapy (APDT) in many branches of dentistry, mainly in periodontology, for the management of such situations as chronic periodontitis or peri-implantitis.[30]

PDT IN PERIODONTITIS

PDT can be considered as adjunctive to conventional mechanical therapy. It has an effective bacterial eradication property and is simple technically. Its antimicrobial efficiency has been demonstrated in various studies. According to Kömerik *et al.*, PDT not only kills bacteria but it also leads to detoxification of endotoxins such as lipopolysaccharide.[31] Moore *et al.* in their study have found that species such as *P. gingivalis, P. intermedia*, *Prevotella nigerscens,* and *Prevotella melaninogenica* accounts for increased bleeding tendency of long-lasting gingivitis and development of periodontitis.[32] Soukos *et al.* in their study have shown that broadband light from 380 to 520 nm was effective to achieve a reduction in the growth of *P. gingivalis* and Prevotella spp.[33] Novaes *et al.* investigated the effects of PDT and scaling and root planning (SRP) in the subgingival microbiological composition associated with aggressive periodontitis. The study indicated that PDT is more effective in reducing the growth of *A. actinomycetemcomitans* than SRP but was less effective in reducing the growth of red complex periodontal pathogens than SRP.[34] Chitsazi *et al.* studied about the effect of single sessions of PDT on the improvement of clinical parameters and evaluated effects of five sessions of PDT. The study showed a significant decrease in periodontopathogen *A. actinomycetemcomitans* after treatment of periodontitis by PDT after SRP.[35] Wavelength of light and photosensitizer used in PDT also plays major role in the eradication of microorganisms; this is explained by various studies. Chan *et al.* demonstrated light based bactericidal modality to eliminate periodontal pathogens, in which cultures of *A. actinomycetemcomitans, F. nucleatum*, *P. gingivalis*, *P. intermedia,* and Streptococcus sanguis were exposed to He-Ne laser at various wavelengths in presence and absence of methylene blue as a photosensitizer. The study showed that irradiation of methylene blue treated bacteria with 665 diode laser was most effective that during 30 s exposure time, average bacterial death rates were to be 71–88% and the bactericidal rate increased as 90–100% during 60 s of exposure time.[36] However, most of the studies that are done reveals that PDT is most effective on combination with conventional SRP method. Sgolastra *et al.* in their study found that PDT was effective when used as an adjunct to conventional SRP and there was no evidence of effectiveness for the use of PDT as an alternative to SRP.[37] Azarpazhooh *et al.* in their study also showed that PDT as an independent treatment was not superior to SRP and was effective on a combination of SRP.[38] Atieh *et al.* study also revealed that PDT on combination with SRP had effective results in reducing periodontitis.[39]

Limitation of PDT

Despite of many advantages and beneficial effects, photodynamic therapy still poses certain limitations. It

can be used to limited sites where light can reach and activate photosensitizer. The drugs used for PDT can also lead the patient who undergoes therapy sensitive to light for some time and may also cause allergic reactions; thus, precautions must be taken before and after therapy. PDT cannot be used in patients with certain blood diseases such as porphyria.[9] The free radicals which are formed during activation are found to be toxic to bacteria, hence making it useful for the treatment of localized microbial infections.[30]

CURRENT STATUS AND FUTURE OF PDT

A number of clinical trials and follow-up have now been reported, and PDT has shown to have potential role in treating periodontal and endodontic problems. It has been proved by various *in vitro*, *in vivo*, microbial studies that PDT has good results against periodontal disease. Various studies on photosensitizer that is used in PDT have been done to make the therapy safe and less adverse reactions. Future studies will undoubtedly be toward development of photosensitizer with less side effects, more efficient, decreased duration of photosensitivity. Studies on these fields of PDT will make it an efficient form of treatment in practice.

CONCLUSION

APDT seems to be a unique and interesting therapeutic approach toward periodontal therapy. It is an attractive option as a noninvasive and low-cost treatment approach in the field of Periodontology, with confirmed safety. Although many studies assessing the effectiveness of APDT have not so far indicated superiority compared to conventional periodontitis treatment, PDT adjunctive to SRP improves clinical and microbial parameters. PDT may be useful as an alternative therapeutic strategy for residual pocket treatment in supportive periodontal maintenance.[23] Further randomized long-term clinical studies and meta-analyses are necessary to demonstrate the beneficial effects of antimicrobial photochemical therapy and their conventional methods.

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