Review Article

Photodynamic Therapy in Periodontics: An Innovative Therapy with Dynamic Rays

Rajsi Jain[1], Praveen Kudva[1], Rakesh Kumar[2]

[1]Department of Periodontics and Implantology, Jaipur Dental college, Jaipur, [2]Department of Neurosurgery, SMS Medical College, Jaipur, Rajasthan, India.

Abstract:
Periodontal disease is a multifactorial disease associated with destruction of supporting periodontal tissues of the tooth caused by certain periodontopathogenic species of bacteria or their toxic products by means of a biofilm formation. The conventional methods to treat periodontal diseases are the mechanical removal of the biofilm and adjunctive use of antibacterial disinfectants or various antibiotics. The disadvantages of these conventional methods range from lack of patient compliance, inaccessible areas to instrumentation, microbial resistance in the biofilm, systemic side effects, and failure on the antibiotics to act on non perfused areas, allergy and limitation of spectrum of microorganisms affected. As a result there is pronounced interest and keenness in the development of alternatives like photodynamic therapy to conventional methods of treating periodontal disease. This review article provides a general insight of use of photodynamic therapy in medicine and dentistry. To our knowledge, this article coves all the detailed aspects of photodynamic therapy which are not yet covered in a single review article.
Keywords: photodynamic therapy, periodontopathic bacteria, biofillm

Corresponding Authors: Dr. Rajsi Jain, 4-kh-2, housing board, Shastri Nagar, Jaipur, Rajasthan, 302016, India, Email id: jrajsi26@gmail.com

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INTRODUCTION:

Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photo chemotherapy, involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen. PDT has emerged in recent years as a new non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses[1].

HISTORY:

The concept of treatment with light and photoactive compounds can be traced back over 6000 years to the ancient Egyptians who used light-sensitive substances (psoralens) by crushing leaves of plants related to parsley[2].

Raab in 1900 first studied photodynamic reaction using cultures of Paramecium and acridine an organic dye[3]. The essential involvement of light and oxygen in the process was shortly thereafter demonstrated by von Tappeiner, who coined the term 'photodynamic'[4]. Friedrich Meyer-Betz performed the pioneering study which was at first called photo radiation therapy (PRT) with porphyrins in 1913. Wilson et al. (1993) proved the effect of cyanide photosensitizer on Gram-negative and Gram-positive species. PDT was first approved by the Food and Drug Administration in 1999. Thereafter, in the recent past many combinations of lasers and photosensitizers were tried with varying successes.[5]

PRINCIPLES BEHIND PHOTO-DYNAMIC THERAPY:

PDT is based on the principle that a photosensitizer binds to the target cell and can be activated by light of a suitable wavelength. During this process, free radicals are formed which then produce an effect that is toxic to the cell. The photosensitizer has selectivity for prokaryotic cells. By irradiation with light in the visible range of the spectrum the dye is excited to its triplet state, the energy of which is transferred to molecular oxygen. The product formed is the highly reactive singlet oxygen capable of reacting with biological systems and destroying them. Only the first excited state with energy of 94 kJ/mol (22 kcal/mol) above the ground state is important, the second excited state does not react.[6]

MECHANISM OF ACTION:

The three components of photodynamic therapy are oxygen, photosensitizer and light. When a photosensitizer is administered to the patient and irradiated with a suitable wavelength, it goes to an excited state from its ground state. This excited state can then decay back to its ground state or form the higher energy triplet state. The interaction between biomolecules and triplet state photosensitizers can be of two types as follows:

Type I: It involves electron/hydrogen transfer directly from the photosensitizer, producing ions, or electron/ hydrogen removal from a substrate molecule to form free radicals. These radicals react rapidly with oxygen, resulting in the production of highly reactive oxygen species.

Type II: The reactions produce electronically excited and highly reactive state of oxygen known as singlet oxygen. In PDT, it is difficult to distinguish between the two reactions mechanisms. A contribution from both types I and II processes indicates that the mechanism of damage is dependent on both oxygen tension and photosensitizer concentration. In this process free radicals are formed which then produces an effect that is toxic to the cell. The half-life of oxygen radicals is only about a few nanoseconds hence this cytotoxic molecule can diffuse only up to 20 nm in cells. Thus, these photosensitizers localize in the mitochondria, plasma membrane, endoplasmic reticulum and Golgi complex at concentrations sufficient for mediating cytotoxicity. Due to the very short half-life of oxygen radicals, measured in nanoseconds, this cytotoxic molecule can diffuse only up to 20 nm in cells[5]. Also the reactive end products of this pathway results in a rapid cyto- and vasculotoxicity which are the basis of PDT. Research in a number of laboratories has demonstrated the potential of PDT as a treatment for localized microbial infections. PDT has shown to be active against both Gram-positive and Gram-negative organisms[7]. Tim Maisch et al. (2004) studied the general photobiological and photochemical aspects and stated he photodynamic activity to induce cell damage or death is determined by five important photophysical/ photochemical properties including the following:

1. An overall lipophilicity and ionization of the photoreactive dyes
2. The molecular extinction coefficient
3. Quantum yield of the triplet state formation UT
4. Redox potentials of the excited states of the PS red or PST red, if the reaction follows the type I mechanism
5. The quantum yield of the singlet oxygen generation, if the reaction occurs by a type II photosensitization.[8]

PHOTOSENSITIZERS:

A photosensitizer is a chemical compound which when administered to the patient is taken up selectively by the diseased tissue and readily undergoes photo excitation when lased with a suitable wavelength transferring its energy to other molecules causing

destruction of pathologic tissues and microorganisms.

Ideal requisites of photosensitizers

1. No dark toxicity.
2. Preferential uptake & retention in diseased tissue.
3. Minimal or no skin sensitivity.
4. Rapid clearance
5. Limited in vivo stability for rapid clearance from normal tissue.
6. High absorption in the red region of the visible spectrum with high extinction coefficient (E ≥/50 000 M-1 cm-1) is also an important criteria to increase the number of photons absorbed and to take advantage of the increase in the penetration depth of light into tissue at longer wavelengths.
7. The absorption band of the sensitizer should not overlap the absorption bands of other chromophores present in the tissues.[6]

Classification of photosensitizers

Photosensitizers can be grouped as follows (Mark Wainwright 1998)[9]

- Cationic-azinephotosensitizers- Phenothiazinium
- Macrocyclic photosensitizers- Porphyrin
- Natural product photosensitizers
- Naturally occurring photosensitizers
- Acridines
- Cyanines and merocyanine

Generation Photosensitizers

- First generation- Photofrin, hematoporphyrin derivatives
- Second generation- 5-aminolevulinic acid, benzoporphyrin derivative, lutetium texaphyrin, temoporfin (mTHPC), tinethyl-etiopurpurin, talaporfin sodium andFoscan®
- Third generation: Biologic conjugates (e.g. Antibody conjugate, liposome conjugate)

Methylene blue, toluidine blue, and acridine orange are potent photosensitizers. Riboflavin is a potent photosensitizer absorbing at wavelength 450 nm. Degradation products formed upon illumination are lumichrome and lumiflavin, both with photosensitizing properties. Riboflavin was suggested for antibacterial and antiviral decontamination of blood conserves and plasma or cell concentrates. Activity and function of the blood conserves remain largely unaffected during this treatment. Chlorophyll is a photosensitizer absorbing light maximally at 683 nm. Tetracyclines used as antibiotics in periodontal diseases are effective photosensitizers producing singlet oxygen.

Light source:

PDT requires a source of light that activates the photosensitizer by exposure to low-power visible light at a specific wavelength. Human tissue transmits red light efficiently, and the longer activation wavelength of the photosensitizer results in deeper light penetration. Consequently, most 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). This limits the depth of necrosis and/or apoptosis and defines the therapeutic effect. As a result, larger solid tumors cannot be uniformly illuminated, because of the limited depth of light penetration.[4] The total light dose, the dose rates, and the depth of destruction vary with each tissue treated and with each photosensitizer .In the past, photosensitizer activation was achieved via a variety of light sources, such as argon-pumped dye lasers, potassium titanyl phosphate or neodymium:yttrium aluminum garnet pumped dye lasers, and gold systems are complex and expensive. At present, diode laser systems that are easy to handle, portable, and cost-effective are used predominantly. For treatment of larger areas, non-coherent light sources, such as tungsten filament, quartz halogen, xenon arc, metal

halide, and phosphor-coated sodium lamps, are in use. Recently, non-laser light sources, such as light-emitting diodes, have also been applied in PDT.These light sources are much less expensive, small, lightweight and highly flexible.[8]

Applications in Medical Field:

Medical applications of photodynamic therapy include treatment of cancer, psoriasis, actinic keratosis, rheumatoid arthritis, age related macular degeneration, treatment of brain tumors etc. Broadly, it represents an alternative antibacterial, antifungal, and antiviral approach for drug-resistant organisms including bacteria that grow in the biofilm.[9] Currently, PDT is being applied mostly in the treatment of cancer however, several studies have shown that PDT also has antimicrobial properties. Photodynamic antimicrobial chemotherapy (PACT) represents an alternative antibacterial, antifungal, and antiviral treatment for drug-resistant organisms. Photodynamic therapy (PDT) has been investigated extensively, both experimentally and clinically, as an adjunctive treatment in the neuro-oncological field. It is based on the more selective accumulation of a photo sensitizer in malignant than normal tissue with low systemic toxicity.[10] It is unlikely that bacteria would develop resistance to the cytotoxic action of singlet oxygen or free radicals. Bacteria that grow in biofilms, implicated in diseases like cystic fibrosis (Pseudomonas aeruginosa) are also susceptible to PDT.[8]

Application in Dentistry:

Applications of PDT in dentistry are growing rapidly in the treatment of oral cancer, as well as bacterial and fungal infections, and the photodynamic diagnosis of the malignant transformation of oral lesions. Applications of photoactivated disinfection (Based on Wilson & Wilson) [11]

- Treating periodontal pockets.
- Plaque infected cervical regions of teeth & implants.
- Disinfecting carious dentin prior to restoration.
- Destroying cariogenic microbes for caries treatment and prevention.
- Disinfecting root canals.
- Disinfecting oral tissues prior to and during surgery.
- Treating oral candidiasis in immunocompromized patients.
- Treating denture stomatitis

PDT could be an alternative approach to reduce bacteria in dental caries. Use of PDT added to conventional endodontic treatment leads to a further major reduction of microbial load and PDT is an efficient treatment to kill multidrug resistant microorganisms. PDT also has positive effects in orthodontic patients not only immediately after multibanding, but also for preventing pain during treatment Possibly PDT can be used in the future to modify the growth and development of facial structures in humans. Topical 5 Amino levulenic acid (ALA) based PDT has been used to treat premalignant and malignant lesions in the oral cavity. PDT of the oral mucosa causes superficial necrosis, leaving little scarring and no cumulative toxicity. 5‐ALA–based PDT appeared to be an effective treatment for oral leukoplakia.[10]

Applications in Periodontics:

An adjunct in non surgical periodontal treatment: In patients with chronic periodontitis, clinical outcomes of conventional subgingival debridement can be improved by adjunctive PDT. Various studies were done with different time period like 3 and 6 months and they used clinical parameters like probing depth, clinical attachment level and bleeding on probing and showed clinically significant improvement in all parameters using photodynamic therapy as an adjunct to scaling and root planning.[12]

Effect on periodontal microbes: To evaluate a new approach to kill periodontopathogenic bacteria using PDT, it was concluded that PDT with chlorine e6 is advantageous for suppressing periodontopathogenic bacteria. Various studies have shown that Gram-positive bacteria are most susceptible to PDT. Photo-killing of Gram negative bacteria is also possible. However, experiments were published showing PDT resistant Gram-negative bacteria. This resistance can be overcome by cell wall modification or by the selection of appropriate sensitizing dyes. Special interest is concentrated on PDT effects in bacteria resistant to antimicrobial drugs. Antimicrobial PDT not only kills the bacteria, but may also lead to the detoxification of endotoxins such as lipopolysaccharide. These lipo-polysaccharide treated by PDT do not stimulate the production of proinflammatory cytokines by mononuclear cells. Thus, PDT inactivates endotoxins by decreasing their biological activity. In an animal study, it was found that PDT was useful in reducing the redness, bleeding on probing, and Porphyromonas gingivalis.[13]

Non-surgical treatment of aggressive periodontitis: A study on 10 patients with aggressive periodontitis, in a split-mouth design to compare PDT using a laser source with a wavelength of 690 nm associated with a phenothiazine photosensitizer or scaling and root planning (SRP) with hand instruments to compare the CAL at baseline and three months after treatment with an automated periodontal probe, concludes that PDT and SRP show similar clinical results in the non-surgical treatment of aggressive periodontitis. PDT resulted in improved clinical parameters and decrease in Tumor necrosis factor-α (TNF) and the ligand for receptor activator of NF-κB (RANKL) levels when used as a monotherapy in aggressive periodontitis compared with SRP.[14]

Effect on periodontal structure: Researchers at São Paulo State University found that using PDT was an effective method to minimize destruction of periodontal tissue which can accompany treatment for periodontal diseases. In a rat population, PDT did minimal damage to periodontal tissues, in comparison to other techniques including SRP and antibiotic therapy. The amount of cementum that must be removed is also 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 immunosuppresion) and for those who display high resistance to antibiotic therapy.[15]

Effect on wound healing: complete wound healing was achieved faster in sites receiving LPT (within 18–21 days) than in control sites (within 19–24 days). In particular, the evidence from in vivo studies indicates that LPT may be beneficial in enhancing periodontal healing after Gingivectomy, scaling, root planning, and intrabony defect surgery. PDT has a biostimulatory effect on human osteoblast like cells during the first 72 h after irradiation. PDT can promote an increase in collagen fiber deposition, as well as in the amount of well organized bone trabeculae after 30 days of induced bone defect healing. The effects of LPT on the bone healing process in surgically created bone cavities were evaluated using a biochemical assay. The results indicated that LPT acts by affecting calcium transport during new bone formation.[16]

Effect on pain and hypersensitivity management: LPT has been suggested as an alternative method for postoperative pain control. Compared to oral analgesics and nonsteroidal anti-inflammatory drugs, LPT can be advantageous because the therapeutic

window for its anti-inflammatory action overlaps with its ability to improve tissue repair. Some authors describe a possible stabilization of nerve cell membranes, probably due to the more stable conformation of the lipid bilayers induced by LPT, and the associated integral proteins of the nerve cell membrane. Several mechanisms are proposed to explain the decrease in pain after LPT in Dentinal Hypersensitivity (DH). The positive effects are mainly attributed to the formation of tertiary dentin and the reduction in sensory nerve activity. Although information on the neurophysiological mechanism is not yet conclusive, it is postulated that LPT mediates an analgesic effect related to the depolarization of C-fiber afferents.[17]

Effect on anti-inflammatory potential: It has been reported that LPT is able to reduce gingival inflammation and metalloproteinase 8 (MMP-8) expression when applied after SRP, as well as to reduce inflammatory cells on histology. Ozawa et al. showed that LPT significantly inhibits the increase in plasminogen activity induced in human periodontal ligament cells in response to mechanical tensile force. Plasminogen activity is capable of activating latent collagenase, the enzyme responsible for cleaving collagen fibers. LPT also effectively inhibits prostaglandin E2 (PGE2) synthesis. The findings of a study suggest an inhibitory effect of LPT irradiation on interleukin (IL)-1β and interferon (IFN)-γ production and a stimulatory effect on platelet derived growth factor (PDGF) and transforming growth factor (TGF)-β. These alterations may be responsible for the anti-inflammatory effects of LPT and its positive effects on wound healing.[18]

Effect of PDT on periodontal bone loss in dental furcations: The use of PDT in furcation involvement in induced periodontitis shows some advantages over the use of conventional antimicrobials, such as the reduced need for flap procedures and shorter treatment time; as local therapy, with lack of micro flora disturbance in other sites of the oral cavity.[19]

Photodynamic therapy in Implantology: Laser PDT can be used in implantology to promote osseointegration and to prevent peri-implantitis. Studies have shown that laser photobiomodulation can be successfully used to improve bone quality around dental implants, allowing early wearing of prostheses. The results of a study showed significant differences on the concentration of calcium hydroxyapatite on irradiated and control specimens and concluded that infrared laser photobiomodulation does improve bone healing. The percentage of bone fill and re-osseointegration also improved with photobiomodulation. Data suggest that lethal photosensitization may have potential in the treatment of peri-implantitis.[20]

Advantages of photodynamic therapy[21]:

1. Minimally invasive technique with least collateral damage to normal cells enhances results and superior healing.
2. Exceedingly efficient broad spectrum of action, since one photosensitizer can act on bacteria, virus, fungi, yeasts, and parasitic protozoa.
3. Efficacy independent of the antibiotic resistance pattern of the given microbial strain.
4. The therapy also causes no adverse effects such as ulcers, sloughing or charring of oral tissues.
5. Lesser chance of recurrence of malignancy.
6. Economical to use.

Adverse effects[22]

The risk and side effects of antimicrobial PDT are basically

Classified into two categories.

1. Relates to the effect of light energy.
2. Relates to the photosensitizer and the photo chemical 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 regard to photosensitizers and photochemical reactions, it is important to apply antimicrobial photodynamic therapy to stain and kill selectively the targeted bacteria without adversely affecting the surrounding periodontal tissues. PDT has the potential of promoting genotoxic effects, including induction of DNA strand breaks, chromosomal aberrations and alkylation of DNA. However, porphyrin molecules also possess antimutagenic properties, with ALAPDT delaying photocarcinogenesis in mice.ALA-PDT has a low frequency of severe adverse effects, achieves a good cosmetic outcome, and has a low risk of carcinogenicity.[23]

Future Directions:

The improvement of phototherapeutic effects was enabled mostly by chemical derivatization of the dyes allowing better cellular uptake. Specific targeting is also possible by coupling the dyes with antibodies specific for cell-wall constituents as reported for P. gingivalis or S. aureus. PDT will not replace antimicrobial chemotherapy, but may improve the treatment of oral infections, accelerating and lowering the cost of the treatment[24]. Development of new photosensitizers, more efficient light delivery systems, and further studies are required to establish the optimum treatment parameters.

Conclusion:

The future of PDT will depend on the interactions between clinical applications and technological innovations. Allison et al[9] have described PDT as the therapy that "is truly the marriage of a drug and a light", and as a result, only interdisciplinary research approaches can overcome all the difficulties and challenges of PDT.

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