REVIEW ARTICLE

SCOPE OF PHOTODYNAMIC THERAPY IN THE FIELD OF PERIODONTICS: A REVIEW

ABSTRACT

Photodynamic therapy (PDT) is a form of phototherapy using nontoxic light-sensitive compounds that are exposed selectively to light, whereupon they become toxic to targeted malignant and other diseased cells. It involves the use of low power lasers with appropriate wavelength to kill micro organisms treated with a photosensitizer drug. PDT could be a useful adjunct to mechanical as well as antibiotics in eliminating periopathogenic bacteria. Applications of photodynamic therapy in dentistry are growing rapidly for the treatment of oral cancer, bacterial and fungal infections and photodynamic diagnosis of malignant transformation of oral lesions, and are recognized as a treatment strategy which is both minimally invasive and minimally toxic.

Keywords: photodynamic therapy, photosensitizers, gingivitis, periodontits, peri-implantitis, Flap surgery, microbial resistance, systemic antibiotics.

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INTRODUCTION

Photodynamic therapy (PDT) is an effective and innovative microbicidal method which involves the combination of a non-toxic dye (photosensitizer) and a visible light source. It shows a great microbicidal effect in addition to better access to sites that are inaccessible to conventional therapy. The use of PDT as an antimicrobial control method has local and specific effects, and also selectiveness for the pathogens[(1)]. The word photodynamics means the application of dynamics of photons of light on the biological molecules[(2)]. Photodynamic therapy (PDT) matured as feasible medical technology in 1980s at several institutions in the world basically as a treatment for cancer. Photodynamic ther-

apy (PDT) has emerged in recent years as a non – invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses[3]. This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light – mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species, predominantly singlet oxygen[4].

Most modern PDT applications involve three key components[5]: a photosensitizer, a light source and tissue oxygen. The wavelength of the light source needs to be appropriate for exciting the photosensitizer to produce reactive oxygen species. The combination of these three components leads to the chemical destruction of any tissues which have either selectively taken up the photosensitizer or have been locally exposed to light.

HISTORY

The origin of light as a therapy in medicine and surgery are 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. 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. [3]

A German physician Friedrich Mayer-Betz performed the first study, with what was first called photoradiation therapy (PRT) with porphyrins in 1913 in humans. But it was John Toth, who acknowledged the photodynamic chemical effect of the therapy with early clinical argon dye asers and renamed it as photodynamic therapy (PDT). It received even greater interest as Thomas Dougherty formed the International Photodynamic Association. Its use first started in dermatology (1992), then oncology (1995), and recently in microbiology (1996) [6]. PDT was approved by the Food and Drug Administration in 1999 to treat precancerous skin lesions of the face or scalp.[4,7] The first light sources used in PDT were conventional lamps with no-coherent and polychromatic light, and a strong thermal component associated with light emission. They were later replaced by light-emitting diodes and low-level diode lasers[1].

MECHANISM OF ACTION

The basis of PDT is the interaction of light with photosensitive agents to produce an energy transfer and a local chemical effect. Here, many photosensitizers work together to harvest light energy to produce chemical reactions. Of the many photosensitizers that have been used in PDT, each has its own unique excitation properties. Usually, the photosensitizer is excited from a ground singlet state to an excited singlet state. It then undergoes intersystem crossing to a longer-lived excited triplet state. One of the few chemical species present in tissue with a ground triplet state is molecular oxygen. When the photosensitizer and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitizer to relax to its ground singlet state, and create an excited singlet state oxygen molecule. Singlet oxygen is a very aggressive chemical species and will very rapidly react with any nearby biomolecules. Ultimately, these destructive reactions will kill cells through apoptosis or necrosis. PDT can be considered a form of targeted singlet oxygen chemotherapy, where the targeting is achieved with the combination of the photosensitizer (functioning as a catalyst) and intense light.

PHOTOSENSITIZER

Requirements of an optimal photosensitizer include following characteristics:

1. Biologically stable [1,8]
2. Must be photochemically efficient [1,8]
3. Selectively retained in the target tissue [1,8]
4. Low toxicity and fast elimination from the skin and epithelium[6]
5. Should have minimal toxicity to other than the target area [1,8]
6. High quantum yield of singlet oxygen production in vivo[6]

7. Cost effectiveness and commercial availability[6]

8. High solubility in water, injection solutions, and blood substitutes[6]

9. Storage [9]

More than 400 compounds are known with photosensitizing properties including dyes, drugs, cosmetics, chemicals and many natural substances.[10] Most of the sensitizers used for medical purposes belong to the following basic structures:

· Tricyclic dyes with different meso-atoms. Acridine orange, proflavine, riboflavin, methylene blue, fluorescein, eosine, erythrosin, rose bengal.

· Tetrapyrroles. Porphyrins and derivatives, chlorophyll, phylloerythrin, phthalocyanines.

· Furocoumarins. Psoralen and its methoxy-derivatives xanthotoxin, bergaptene.

ADVANTAGES OF PDT[6]

Therapy has only localized effects as the photosenstizer is selectively absorbed at a greater rate by target tissues, can be performed in outpatient or day-case settings[16], is more economical than radiation and surgical therapy for cancer patients, shows faster post-operative healing with no long term side effects, less invasive and can be repeated many times at the same site if needed, unlike radiation[6].

PDT presents some advantages over conventional antibiotic therapy, such as rapid elimination of target microorganisms (within seconds or minutes, depending on energy density and power used) and absence of maintenance of high concentrations of dye on lesions during hours or days as observed in conventional therapy. Due to production of singlet oxygen and free radicals, which are responsible for mediating bacterial killing, the development of resistance to lethal photosensitization by the target organisms would be a very unlikely event. Another advantage relates to the restriction of antimicrobial effects to the lesion through careful application of the dye and light source, without affecting the adjacent normal microflora. Also, PDT acts eliminating disease-causative microorganisms and their virulence factors[1].

LIMITATIONS[6]

Light needed to activate photosensitizer cannot penetrate more than 1cm of tissue depth using standard laser and low powered LED technology and hence is less effective in treatment of large tumors and

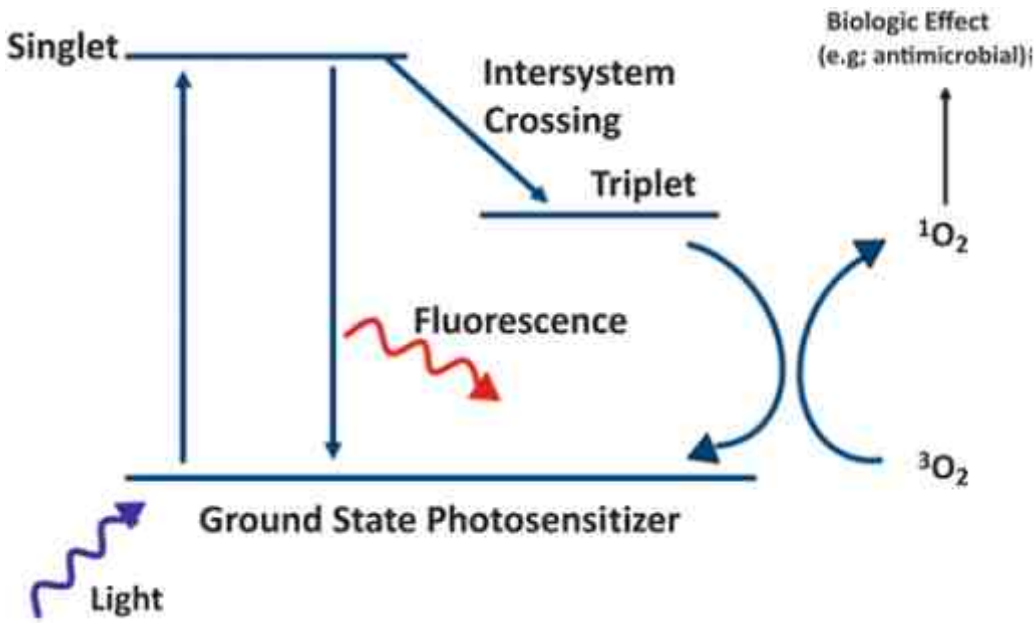

Figure1. Principles of PDT[15].

metastasis. It may leave many people very sensitive to light post therapy and cannot be used in people allergic to porphyrins.

Application of photodynamic therapy in dentistry.

Photodynamic therapy has been used in (i) photodynamic diagnosis of malignant transformation of oral lesions, (ii) treatment of premalignant and malignant oral lesions, (iii) chemotherapy (PACT) of bacterial and fungal infections, (iv) prevention of alveolar ostitis and postextraction pain, (v) decontamination of implant surface and prevention and treatment of peri-implantitis, (vi) endodontic treatment[13].

Photodynamic antimicrobial chemotherapy therapy[4]

Antimicrobial PDT can be considered as an adjunctive to conventional mechanical therapy. The liquid photosensitizer placed directly in the periodontal pocket can easily access the whole root surface before activation by the laser light through an optical fiber placed directly in the pocket.[17] As a result of the technical simplicity and the effective bacterial killing, the application of PDT in the treatment of periodontal diseases has been studied extensively. 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 pro-inflammatory cytokines by mononuclear cells. Thus, PDT inactivate endotoxins by decreasing their biological activity.[4]

It has been demonstrated that bacteria associated with periodontal disease can be killed through photosensitization with toulidine blue O by irradiating with helium – neon soft laser. Data from an *in vitro* study indicated that PDT could kill bacteria organized in a biofilm. In an animal study, it was found that PDT was useful in reducing the redness, bleeding on probing, and porphyromonas gingivalis levels.[18]

Yilmaz *et al*. randomly assigned a total of 10 patients to receive repeated application of scaling and root planing with photodynamic therapy the other groups were receiving only scaling and root planing, photodynamic therapy, and oral hygiene instructions. Methylene blue served as the photosensitizer and was used as a mouth rinse. Significant clinical and microbiological improvement was seen within groups receiving scaling and root planing with photodynamic therapy and the scaling and root planing alone. However, improvement in groups receiving photodynamic therapy alone, as well as those receiving only oral hygiene instructions, did not reach significant levels. The reduced effectiveness of PDT may be the due the application of PDT from the external surface of the gingiva.[19]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; [20] 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 has advantages such as reducing the treatment time, no need for anesthesia, destruction of bacteria in a very short period of time (<60 seconds), unlikely development of resistance by the target bacteria, and avoidable damage to the adjacent host tissues. Further studies using larger sample sizes are warranted to confirm these results[10].

An Adjunct In Non Surgical Periodontal Treatment[10]

Twenty-four subjects with chronic periodontitis were randomly treated with scaling and root planning followed by a single episode of PDT (test) and scaling and root planing alone (control). Gingival recession, and clinical attachment level (CAL) were measured at baseline and three, six months after therapy and it was concluded that the additional application of a single episode of PDT to scaling and root planing failed to result in an additional improvement in terms of pocket depth reduction and CAL gain, but it resulted in a significantly higher reduction in bleeding scores compared to scaling and root planning alone. Although mechanical removal of the

periodontal pathogens is the current gold standard of treatment in periodontics, antibiotics are also known to be effective. The use of antibiotics to destroy microorganisms (MO) selectively represents one of the most revolutionary progresses made in scientific medicine, resulting in the treatment and sometimes complete eradication of earlier incurable diseases. However, bacteria have developed resistance mechanisms against antimicrobial drugs which were previously highly effective. Besides, bacteria replicate very rapidly and a mutation that helps a MO to survive in the presence of an antibiotic will quickly become predominant in the microbial population. The use of photoactivable compounds or photo sensitizers (PS) to cause photodestruction of oral bacteria has been demonstrated, indicating that photodynamic therapy (PDT) could be a useful alternative to mechanical means as well as antibiotics in eliminating periopathogenic bacteria. Antimicrobial photodynamic therapy (aPDT) represents a potential alternative methodology to inactivate microbial cells and has already shown to be effective *in vitro* against bacteria, fungi, viruses, and protozoa.[13,21,22]

EFFECTS OF PHOTODYNAMIC ANTIMICROBIAL CHEMOTHERAPY ON ORAL BIOFILMS

A wide range of persistent human infections are due to microbial biofilms. Periodontal diseases result from accumulation of subgingival bacterial biofilms on tooth surfaces. Although mechanical removal of the periodontal pathogens is the current gold standard of treatment, antibiotics are also known to be effective. However, development of resistance in the target organisms is a problem associated with the use of such drugs. The use of photoactivatable compounds or photosensitizers (PS) to cause photodestruction of oral bacteria has been demonstrated, indicating that photodynamic therapy (PDT) could be a useful alternative to mechanical means as well as antibiotics in eliminating periopathogenic bacteria. The antimicrobial activity of photosensitizers is mediated by singlet oxygen, which, because of its high chemical reactivity, has a direct effect on extracellular molecules. Thus, the polysaccharides present in EMP of a bacterial biofilm are also susceptible to photodamage. Such dual activity, not exhibited by antibiotics, represents a significant advantage of PACT. Breaking down biofilms may inhibit plasmid exchange involved in the transfer of antibiotic resistance, and disrupt colonization. The photosensitive compounds are topically applied in the gingival sulcus and the laser is used to activate the compounds and complete the disinfection. Studies done by Braun et al., 2008 in patients with chronic periodontitis showed better clinical outcomes when PDT was used along with conventional therapy.[6,23]

Effect of PDT on Periodontal Bone Loss in Dental Furcations.[10]

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. PDT is also beneficial during the maintenance of periodontal therapy because it may act on the biofilm and eliminate the need for the removal of additional root substance by mechanical retreatment. Thus, the patient may experience less dentinal hypersensitivity. This therapy also serves as an adjunct to mechanical therapy in sites with difficult access.

Effect of a PDT on peri-implantitis

Peri-implantitis seems to occur in 5-10% of all implant cases. In this way, photodynamic therapy can be used successfully to decontaminate the implant surface.[13, 24] 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 hydrxyapatite 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.[25]

One of the most interesting developments over the last years has been the introduction of the 9.6-µm CO_2 laser. It has been shown in the recent literature that the use of this new device can preserve tissue, with almost no adverse effects at the light microscopic level. Intraoperatively used PDT or peri-implant care of ailing implants with the CO_2 laser seems to be more of value than the conventional methods. Data suggest that lethal photosensitization may have potential in the treatment of peri-implantitis.[13,24]

CONCLUSION

Antimicrobial PDT seems to be a unique and interesting therapeutic approach towards periodontal therapy[4]. PDT application has an adjunctive benefit besides mechanical treatment at sites with difficult access (e.g. furcations, deep invaginations, concavities). Necessity for flap operations may be reduced, patient comfort may increase and treatment time decrease. PDT removes the biofilm in residual deep pockets during maintenance; no more root substance is removed by mechanical retreatment. Thus the patient may experience less dentinal hypersensitivity. PDT may decrease the risk of bacteremia, which routinely occurs after periodontal treatment procedure.[10] Antimicrobial photodynamic therapy may hold promise as a substitute for currently available chemotherapy in the treatment of periodontal and peri-implant diseases[4]. Its nonsurgical profile improves the comfort of treatment and thus makes the process more attractive to patients. Its ease of use makes it suitable for dentists.

Treatment regimens still have to be optimized and standardized for better therapeutic effectiveness. Severe side effects have been reported when using inappropriate PDT schedules.

Appropriate choices of drug type and dose, light wavelength, and drug-light interval can improve the efficacy and safety of PDT. Furthermore, careful attention to the physics and dosimetry of light will help to minimize toxicity[16].

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