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RESEARCH ARTICLE

PHOTODYNAMIC THERAPY

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ABSTRACT

Photodynamic therapy (PDT) is treatment modality involving the administration of photosensitizing compound, which selectively accumulates in the hyperproliferative target cells followed by local irradiation with visible light of lesion. Eventually target tissue will be damaged by necrosis and apoptosis. The transfer of energy from the activated photosensitizer to available oxygen results in the formation of toxic oxygen species, such as singlet oxygen and free radicals. These very reactive chemical species can damage proteins, lipids, nucleic acids, and other cellular components. Applications of PDT in dentistry are growing rapidly in treatment of oral premalignant and malignant conditions. PDT also represents a novel therapeutic approach in the management of oral biofilms. This review emphasis on the various fundamental aspects of photodynamic therapy and the research done till date in treating various oral lesions using this new therapeutic approach.

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INTRODUCTION

Photodynamic therapy (PDT) is a medical treatment modality that utilizes light to activate a photosensitizing agent (photosensitizer) in the presence of oxygen. It has been used against bladder cancers, brain cancers, breast cancers, gynecological malignancies and colorectal cancers. It is also called as Photoradiation therapy, phototherapy, or photochemotherapy. (Ramya *et al*., 2012) It involves the use of a photoactive dye (photosensitizer) that is activated by exposure to light of a specific wavelength in the presence of oxygen. Treatment using light and light activated compounds is referred back from ancient times. Egyptians used Psoralenswith Sunlight to treat Sunburns. Ancient Indians used *Psoraleacorylifolia*with light to treat vitiligo. First medical use was by Jesionek and Tappeiner in 1905 who used it to treat Basal Cell Carcinoma. Von Tappeiner coined the term "Photodynamic". He defined PDT as the dynamic interaction among light, a photosensitising agent and oxygen resulting in tissue destruction. (Nikhil VishwasKhandge *et al*., 2013)

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History

- 1900 –Raab reported that combination of archidine orange and ultraviolet light could destroy living organisms. (Raab, 1900)
- 1920 Policard - tumor tissue was inherently more fluorescent than healthy tissue. (Policard, 1924)
- 1950 - Ronchese attempted to activate endogenous fluorescent molecules in tumor tissue to delineate its boundaries more accurately. (Ronchese, 1954)
- 1960 Winkelman used synthetic porphyrins (tetraphenylporphines) to detect tumor tissue. (Winkelman, 1967)
- 1970 Dougherty rediscovered that fluorescein diacetate could photodynamically destroy T A-3 cells *in vitro.* (Dougherty, 1974)
- 1976 Weisshaupt *et al* identified the cytotoxic product of photochemical reaction to be singlet oxygen. (Weishaupt *et al*., 1976)
- After several years, Photofrin was produced

Components: (Dougherty *et al*., 1998)

It has 3 components - Light, photosensitizer and oxygen. Exposure of the photo sensitizer to light results in the

formation of oxygen species, such as singlet oxygen and free radicals, causing localized photo damage and cell death. Clinically, this reaction is cytotoxic and vasculotoxic. Depending on the type of agent, photosensitizers may be injected intravenously, ingested orally or applied topically.

Mechanism: (Živilė Lukšienė *et al*., 2003)

When administered to patients upon irradiation with specific wavelength photosensitizer goes from low-energy ground state to excited singlet state. Subsequently then goes to ground state with decay and there is emission of fluorescence or goes directly to high level- triplet state. Triplet state can react with endogenous oxygen to produce singlet oxygen and other radical species, causing a rapid and selective destruction of the target tissue. Two mechanisms by which the triplet-state photosensitizer can react with biomolecules. First- 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. Second- produces the electronically excited and highly reactive state of oxygen known as singlet oxygen. In PDT, it is difficult to distinguish between the two reactions mechanisms.

Types of Photosensitizers (Nikhil VishwasKhandge *et al*., 2013)

Table 1: Types of photosensitizers

Photosensitizers	*Examples*
Phenothiazine dyes	Methylene blue (MB) and toluidine Blue O (TBO; Tolonium chloride)
Phthalocyanine dyes	Aluminum disulphonated phthalocyanine, cationic Zn(II)-phthalocyanine, naphthalocyanine
Chlorophyll platform	Chlorins_Purpurins_Bacteriochlorins
Porphyrins	HPD (hematoporphyrin derivative), Photofrin® and ALA (5-aminolevulinic acid), texaphyrins, BPD (benzoporphyrin derivative)
Xanthenes	Erythrosin
Monoterpene	Azulene

Table 2: Generations of photosensitizers

Generation	*Photosensitizers*
First generation	Photofrin, hematoporphyrin derivatives (HPDs)
Second generation	5-aminolevulinic acid (ALA), benzoporphyrin derivative (BPD), lutetium texaphyrin, temoporfin (mTHPC), tinethyletiopurpurin (SnET2), talaporfin sodium (LS11) and Foscan® (mTHPC)
Third generation	Biologic conjugates (e.g. Antibody conjugate, liposome conjugate)

Photosensitizers (ps) - ideal requisites (Mubeen, Kavitha, 2011)

- Selectivity/targetibility
- High quantum yields of singlet oxygen
- Toxicity
- Administration
- Amphilicity
- Activation
- Elimination
- Fluorescence
- Mutagenicity
- Integrative ability
- Cost effectiveness
- Commercial availability

Light Source (Reddy *et al*., 2009; Konopka and Goslinski, 2007; Steiner, 2006)

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. Three light systems

- Diode laser systems
- Noncoherent light sources
- Nonlaser light sources include (LED).

Applications

Applications of Photoactivated Disinfection (Wilson, 1993)

- Treating periodontal pockets
- Plaque-infected cervical regions of teeth and 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 immune compromised patients
- Treating denture stomatitis.

PDT in oral pre-malignancies and malignancies

PDT in leukoplakia (Mubeen and Kavitha, 2011)

ALA is converted to Protoporphyrin IX in situ. Due to the limited depth of topical ALA, and the limited light penetration at 635 nm, the use of ALA is restricted to superficial lesions. Topical ALA-PDT is an effective treatment modality for management of Oral Verrucous Hyperplasia, Oral Leukoplakia, Oral Erythroleukoplakia.

PDT in oral lichen planus (Aghahosseini *et al*., 2006)

Topical PDT mediated by methylene blue (MB-PDT) is used. Ten minutes prior to laser irradiation, patients gargled MB for 5 minutes. A diode laser (632 nm) was used as light source. The lesions and 1 cm of their surrounding marginal zone were illuminated with a spot size of 2.5-3 cm^2. Large lesions were illuminated with multiple spots. Fluence of 100 J/cm2 was used. 50% complete remission has been reported.

PDT in oral malignancies (Biel, 2002; Pass, 1993; Mang *et al*., 2006)

Photofrin and Derivatives were used. Injected intravenously, 2 mg/kg in an outpatient setting and after 48 hrs, the tumour is illuminated at 630 nm. Excellent results were demonstrated. Foscan PDT has an efficient role in the treatment of primary oropharyngeal cancers, recurrent & second primary oral carcinomas. 0.15 mg/kg and activation with laser light at 652 nm. 5-Aminolevulinic Acid can also be used.

PDT potential indicative diseases

Oncologic

- Actinic keratosis
- Bowen's disease
- Superficial Basal Cell Carcinoma/Squamous Cell Carcinoma
- Nevoid Basal Cell Carcinoma syndrome
- Keratoacanthoma
- Kaposi's sarcoma
- Cutaneous metastases
- Cutaneous T Cell Lymphoma, XerodermaPigmentosum and actinic cheilitis

Nononcologic

- Psoriasis vulgaris
- Human papiloma virus-associated dermatoses
- Condylomataacuminata
- Mycosis fungoides (topical ALA-3. PDT with Nd-YAG laser).
- Lip dysplasia (nicotine abuse)
- Actinic cheilitis.

Photodynamic Antimicrobial Chemotherapy (PACT) (Mark Wainwright, 1998)

Emergence of antibiotic resistant strains, such as methicillin resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecalis, stimulated a search for alternative treatments. Development of resistance to PACT unlikely, since, in microbial cells, singlet oxygen and free radicals interact with several cell structures and different metabolic pathways. PACT is equally effective against antibiotic-resistant and antibiotic susceptible bacteria.

Advantages of PDT (Konopka and Goslinski, 2007)

- Minimally invasive technique
- Exceedingly efficient broad spectrum of action
- Efficacy independent of the antibiotic resistance.
- No adverse effects such as ulcers, sloughing or charring of oral tissues.
- Lesser chance of recurrence of malignancy.
- Economical to use.

Limitations of PDT (Konopka and Goslinski, 2007)

- Penetration depth not more than 1.5cm of tissue.
- Leaves many people very sensitive to light post therapy (photosensitivity)
- Cannot be used in people allergic to porphyrins.
- Lack of accurate dosimetry and suitable illumination devices.

Conclusion

PDT has shown its potential in the management of early stage oral malignancies with a very good outcome and with excellent functional and cosmetic results.

The development of new, more tumour-specific photo-sensitizers and light delivery systems still more improve its efficacy and thus the future of PDT depends on interactions between clinical applications and technological innovations.

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