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PHOTODYNAMIC THERAPY- A LITERATURE REVIEW

Oral Medicine

Dr. Mudita Rawal MDS (OMDR). Private Practice,Ahmedabad,Gujurat, India.

Dr.PratikChandrakantMalusare* MDS 2 Senior Lecturer, Oral medicine & Radiology Department ,G.D Pol Foundation Y.M.T Dental College, Kharghar, Navi Mumbai. *Corresponding Author

ABSTRACT

Photodynamic therapy also known as Photoradiation therapy, Phototherapy or Photochemical therapy involves the use of a photoactive dye known as photosensitiser that is activated by exposure to light of a specific wavelength in the presence of oxygen. 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: the treatment of oral cancer, bacterial and fungal infection therapies, and the photodynamic diagnosis of the malignant transformation of oral lesions. PDT has shown potential in the treatment of oral leukoplakia, oral lichen planus, and head and neck cancer. PDT is being also tested in the case of eradication of microbia which colonized root canals and dental plaque. The absence of genotoxic and mutagenic effects of PDT is an important factor for long-term safety during treatment. The application of a Photodynamic therapy might be a new, potent tool in dental disorders.

KEYWORDS

INTRODUCTION:

Photodynamic therapy (PDT) is a minimally invasive therapeutic modality used in the management of various cancerous and pre-malignant diseases. It involves the systemic administration of a non-toxic photosensitizing (PS) drug, which accumulates in host and tumor cells, and subsequent illumination of the tumor site with visible light, corresponding to the appropriate photosensitizer absorption wavelength (Figure 1).1

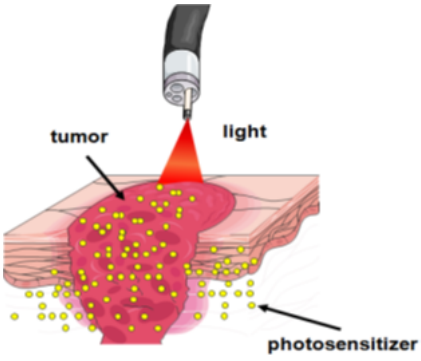

Figure 1. Overview of PDT. Following photosensitizer administration it undergoes systemic distribution and selectively accumulates in the tumor. Illumination activates the photosensitizer and in the presence of molecular oxygen triggers a photochemical reaction that culminates in the production of O2.

Photodynamic therapy (PDT) is a treatment modality that uses cytotoxic-free radicals produced from the administration of a light-sensitive drug known as a photosensitizer (PS), with a light of an appropriate wavelength. It is also known as Photoradiation therapy, Phototherapy or Photochemical therapy. The word photodynamics means the application of dynamics of photons of light on the biological molecules. Von Tappeiner coined the term 'photodynamic'.2 It as a medical treatment that utilizes light to activate a photosensitizing agent in the presence of oxygen results in the formation of toxic oxygen species causing localized photodamage and cell death. These cytotoxic species, including singlet oxygen and free radicals, induce direct oxidative damage to cellular organelles, destruction of microvasculature, and promotion of apoptosis. It is a minimally invasive and minimally toxic technique that has been used clinically to treat a plethora of medical conditions including skin diseases, localized infections, age-related macular degeneration, as well as premalignant and malignant disorders (Hopper, 2000; Kaiser et al, 2009). Although PDT has been used in the treatment for oral diseases for more than 20 years, its use is still underutilized to its true potential. This review aims at providing comprehensive and critical viewpoints of the use of PDT in oral diseases. Apart from PDT one can distinguish two other light involving therapies: 1) phototherapy in which ultraviolet A (UV−A) and B (UV−B) light are being used without any photosensitizer and 2) photochemotherapy consisting of ultraviolet A (UV−A) light and psolarens (natural photosensitive compounds).

BASIC PRINCIPLE:

Photodynamic therapy is divided into following two stages-

FIRST STAGE- Light-sensitive Photosensitizer is administered systemically-intravenously or orally, or applied topically and a certain period of incubation time is allowed for the sensitizer to accumulate in the target tissue.

SECOND STAGE- Light of appropriate wavelength is irradiated onto the target that leads to the activation of the PS generating free radicals and highly reactive forms of oxygen which are cytotoxic.

MECHANISM OF ACTION (figure2)

A photosensitizer is a chemical compound (usually a dye) that can be excited by light of specific wavelength (visible or infra-red light). The agent or its metabolic product is administered (injected or applied externally) to the patient and gets accumulated in the targeted tissues (cancer cells). The tissue is then exposed to the light activating the dye from its ground singlet state to an excited singlet state which then undergoes an intersystem crossing forming a longer lived excited triplet state. In the presence of endogenous oxygen, an energy transfer then takes place from this activated agent to the oxygen molecule forming excited singlet state oxygen or other reactive oxygen species (ROS), causing a rapid and selective destruction of the target tissues. There are two mechanisms for this process.

1. Type I reaction involving electron 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 (superoxide, hydroxyl radicals, and hydrogen peroxide).
2. Type II reaction producing the electronically excited and highly reactive state of oxygen known as singlet oxygen.2

In PDT, it is difficult to distinguish between the two reactions mechanisms. Usually it involves a contribution from both the 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. It may also mediate tumor destruction indirectly by vascular damage through photochemical oxygen consumption or by stimulation of the host response. A massive

invasion of inflammatory cells during and after PDT has been observed in murine tumor models.

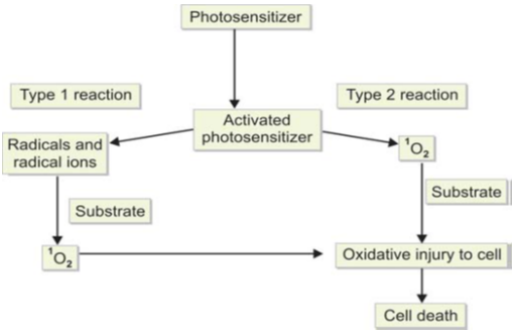

Figure2 : Mechanism of action

COMPONENTS OF PHOTODYNAMIC THERAPY

1. A photosensitizer
2. A light source
3. Tissue oxygen

PHOTOSENSITIZER:

Photosensitization is the process of transferring the energy of absorbed light to the desired reactants through the use of a substance capable of absorbing light (photon), called a Photosensitizer (PS).

The various agents can be grouped under 3 Generations.

First generation include Photofrin (most extensively used) and hematoporphyrin derivatives (HPD). Porfimer sodium, or Photofrin®, a haematoporphyrin derivative (HpD) was the first PS that was approved for its clinical use in PDT . However, these PSs were associated with poor light absorption and significant side effects such as skin photosensitivity (O'Connor et al, 2009). To overcome these disadvantages, second-generation PSs were developed.

Second generation include 5-aminolevulinic acid (ALA), benzoporphyrin derivatives (BPD), temoporfin and talaporphin sodium . Foscan is the most potent amongst them. The relative advantages of second-generation PS as compared to that of first generation are their chemical purity, higher yields of singlet oxygen, greater tumour specificity and increased penetration depths into tissues (Gomer, 1991).

Third-generation photosensitizers have been introduced in which PSs are attached to various modifiers such as monoclonal antibodies, nanoparticles, liposomes and polymers, which may target the specific receptors expressed on certain tumours or enhance its tumour affinity (Moser, 1998). However, these are not currently commercially available.

Currently only 3 agents have been approved by FDA - Porfimer sodium, ALA and Vertoporfin. Foscan is in used only in European countries.

AMINOLEVULINIC ACID

5-Aminolevulinic acid is an endogenous amino acid which is synthesized in mitochondria from glycine and succinyl CoA (Ishizuka et al, 2011). It is a biological precursor in the heme pathway that is converted to the endogenous PS protoporphyrin IX (PpIX) (Peng et al,1997b). Application of exogenous ALA bypasses internal feedback mechanisms that are governed by concentration of free heme(figure 3) and leads to intracellular accumulation of photosensitizing concentrations of PpIX (Kennedy and Pottier, 1992). Cells in rapid division tend to accumulate more ALA-derived porphyrins owing to the low activity of ferrochelatase and low iron levels - resulting in a build-up of PpIX in these cells (Peng et al, 1997a). This causes tissue-specific photosensitization of ALA-induced PpIX that forms the basis of its use as a PS in PDT. PpIX has fluorescent properties that can be used to detect its synthesis within the target cells (Webber et al, 1997). Leunig et al (1996, 2001) demonstrated the selective uptake of topically applied ALA in oral premalignant and malignant tissues, as well as the use of ALA-induced PpIX fluorescence in monitoring the response to the therapy (Leunig et al, 2000). ALA can be activated under a light source at 635-nm wavelength (Triesscheijn et al, 2006). It is water soluble and can be administered systemically or locally. For systemic application, ALA is usually given at a dose of 30-60 mg/kg orally followed by light administration at 635 nm, 4 h later at 150 J/ cm. For topical application, a preparation of 10-20% of ALA is commonly used to apply on the target lesion. It is rapidly cleared from the body (within 24 hrs) after systemic or topical administration, thus considerably decreasing the systemic side effects of phototoxicity. Two topical ALA-based drugs, Levulan® and Metvix® (methyl ester derivative of ALA), have received approval from the FDA .4

Requirements of an optimal photosensitizer should include following characteristics:5

1. Highly selective tumor accumulation : targetibility
2. Low toxicity and fast elimination from the skin and epithelium
3. High quantum yield of singlet oxygen production in vivo
4. Cost effectiveness and commercial availability
5. High solubility in water, injection solutions, and blood substitutes

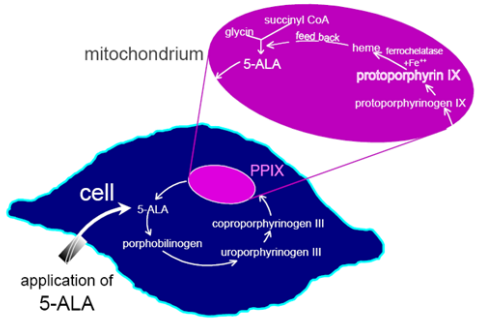

Figure3: Protoporphyrin IX induced by topical ALA

LIGHT SOURCE-

PDT requires a source of light that activates the photosensitizer by exposure to low-power visible light at a specific wavelength. The selection of light sources relies on the characteristics of the tumour (location, depth, size, and accessibility of lesion); types of PS (absorption spectra and mode of administration); cost; and the availability of light delivery systems. The source of light chosen must exhibit appropriate emission characteristics that match the maximum absorption wavelength range of the administered PS to produce adequate Reactive oxygen species for tissue damage (Plaetzer et al, 2009). 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).

There are 3 light systems for the therapy:-

1. Diode laser systems: easy to handle, portable and cost-effective.
2. Non-coherent light sources: preferred for treatment of larger areas and include tungsten filament, quartz halogen, xenon arc, metal halide and phosphor-coated sodium lamps.
3. Non-laser light sources include lightemitting diodes (LED). They are economical, light weight and highly flexible.[5]

OXYGEN:

Cytotoxic effects seen in PDT are oxygen dependent (Lee See *et al,* 1984). When PS absorbs a photon, it activates the molecules from their ground state to a short-lived excited state (singlet state) and a relatively long-lived excited state (triplet state) (Henderson and Dougherty,1992). PDT cytotoxicity occurs through two major photooxidative reaction pathways –type I and type II as discussed above. The radius of action of singlet oxygen is restricted to <0.02 um during its brief lifetime (Moan and Berg, 1991). Tissue damage is therefore restricted only to the structures in the vicinity of its production, which in tum is dependent on the penetration depth of the light used to activate the Photosensitizer.[4]

PHOTODYNAMIC THERAPY IN DENTISTRY:

With the invention of many modern photosensitizer, appropriate illumination devices photodynamic therapy has spread its application into dentistry and oral diseases. Recently most research is directed in this aspect and advances are being made to achieve a standardised protocol for various oral diseases.

1.Premalignant lesions and conditions:
Leukoplakia: The application of PDT in oral leukoplakia reduces the time of treatment in comparison with pharmacological methods involving vitamin A and its active metabolites .It requires 2 to 3 months to complete cure.[6] Delta−aminolevulinic acid 10%-20% or 0.1% chlorophyll gel can be used.

Erythroplakia and verrucous hyperplasia : Chen et al (2005)[7] used topical 20% ALA gel at 635 nm wavelength in oral erythroplakia and oral verrucous hyperplasia which resulted in complete regression of lesions after 6 treatments once a week.

Oral lichen Planus: Aghahosseini F et al (2006)[8] used Methylene blue-mediated photodynamic therapy (MB-PDT) in 26 OLP patients resulting in significant decrease in sign and symptom scores in 16 patients. Four keratotic lesions disappeared completely 1 week after treatment and at follow-up of 12 weeks. Average reduction in size was 44.3%.

2.Head and neck cancers-
Photofrin and foscan are most commonly used Photosensitizer in head and neck cancers. Nester R Rigual (2009)[9] conducted PDT in 30 patients with primary or recurrent moderate to severe oral or laryngeal dysplasia,carcinoma in situ, T1N0 carcinoma using Porfimer sodium 2mg/kg IV . 48 hrs after injecting Photosensitizer the tumour was irradiated using light of 630 nm. Evaluation was done in 1 week , 1 month and 3 months intervals. Out of 30 patients, 24 showed complete response, 1 showed partial response and 1 showed no response.

3.Oral microbial diseases-
Viral diseases- Juliana Marotti et al (2009)[10] reported use of PDT in treatment of herpes labialis in 4 cases. Vesicles were perforated with sterilised needle. Cotton ball socked in 0.01% methylene blue solution was placed over the lesion which was irradiated with 660 nm light. Phototherapy was repeated after 24 hrs, 72 hrs and 1 week. Complete response was noted on follow up appointments with no recurrence upto 6 months.

Oral candidiasis- Karla Bianca et al (2014)[11] treated pseudomembranous candidiasis on palate with weekly methylene blue 0.01% and irradiation with diode laser (660nm) on the entire palate. After 6 sessions, on examination there was complete resolution of candidiasis.

4.Applications in Endodontics –
PDT has shown to be effective against Gram positive as well as Gram-negative endodontic pathogens. Methylene blue and toluidine blue seem to be the ideal photosensitizers for canal sterilizations. PDT has shown to be effective against Grampositive as well as Gram-negative endodontic pathogens. In particular E.faecalis which has shown high resistance to the conventional debridement techniques due to limitations of mechanical debridement of instruments and lack of penetration of irrigants. Research has shown high susceptibility to phenothiazinium PDT in which up to 99.99% reduction in bacterial count was seen.[12]

Procedure- 0.5 ml toluidine blue (50 µg/ml) is injected inside the canal and allowed towait for 5 minutes followed by irradiation using a 50 mW diode laser (Ga-Al-As) at a wavelength of 633 nm with an endodontic diffuser fiber of 200 µm for 1 to 2 minutes or methylene blue 50 µg/ml can be used with 670 nm wavelength.[13]

5.Applications in Periodontics-
Phenothiazinium photosensitizers have shown to be safe and highly effective for periodontal infections. The photosensitizer is first injected in the periodontal pocket and allowed to pigment for 2 minutes. Then the fiber is inserted 1 mm short of the pocket and lased by moving from side to side toward the coronal third. It has been proven that PDT has found an adjunctive role in peri-implantitis.[14] PDT may be an effective way to treat the bacteria linked to periodontal diseases and could provide a better option than antibiotics or other mechanical methods for treating periodontal diseases and may prove to be a promising alternative to conventional periodontal therapy in near future.

ADVANTAGES OF PDT-
- Minimally invasive technique
- Can be performed in outpatient or day-care settings.
- More economical than radiation and surgical therapy for cancer patients.
- Lesser chance of recurrence of malignancy
- Faster post-op healing with no long term side effects.

- **LIMITATIONS-**
- Light needed to activate photosensitizer cannot penetrate more than 1cm of tissue depth using standard laser and low powered LED technology.
- Less effective in treatment of large tumors and metastasis.
- May leave many people very sensitive to light post therapy
- Cannot be used in people allergic to porphyrins.[15]

CONCLUSION
There is a great need to develop an evidence based approach to the use of PDT for the treatment of oral diseases. It would be prudent to say that there is an insufficient evidence to suggest that PDT is superior to the traditional modalities . Further, randomized long term clinical studies and meta analysis are necessary to demonstrate the beneficial effect of photodynamic therapy in comparison with conventional methods.

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