Review article

Photo Dynamic Therapy in Oral Diseases

Sudhakara Reddy .R , a Ramya . Kotha , b Ramesh Tatapudi c , Subbarayudu Gudapati d , Sai Madhavai .N b Sai Kiran .Ch b

a Prof And Hod, Department Of Oral Medicine And Radiology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India.
b Department Of Oral Medicine And Radiology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India.
c Associate Professor, Department Of Oral Medicine And Radiology, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India.
d Reader, Department Of Prosthodontics, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India.

ABSTRACT

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Photodynamic therapy (PDT), also known as photoradiation therapy, phototherapy, or photochemotherapy, involves the use of a photoactive dye (photosensitizer) 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 in treatment of oral premalignant and malignant conditions and oral microbiological diseases (bacterial and fungal infection therapies,) and the photodynamic diagnosis (PDD) of the malignant transformation of oral lesions. The absence of genotoxic and mutagenic effects of PDT is an important factor for long-term safety during treatment. PDT also represents a novel therapeutic approach in the management of oral biofilms. Studies are now leading toward selective photosensitizers, since killing the entire flora leaves patients open to opportunistic infections. 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.

1. Introduction

Light has been used as a therapeutic agent for many centuries. In ancient Greece the sun was used in heliotherapy or the exposure of the body to the sun for the restoration of health. The Chinese used to treat such conditions as rickets, skin cancer and even psychosis. This use of light for treatment of various pathologies is referred as Phototherapy. The earliest use of photochemotherapy or the use of an exogenous photosensitizer to absorb light and render a therapeutic effect dates back to 1400 B.C. Indians used a drug called psoralens, obtained from plants to treat vitiligo. Since then many potential applications of using light for therapeutic purposes came in to the lime light. One such application of use of light energy is the

Various Nanotechnology Products

laser science The past decade has seen a veritable explosion of research into the clinical applications of lasers in dental practice. Once regarded as a complex technology with limited uses in clinical dentistry, there is a growing awareness of the usefulness of lasers in the armamentarium of the modern dental practice, where they can be used as an adjunct or alternative to traditional approaches.[1]

Lasers for can be used in two forms – photoactivated dye disinfection & photodynamic therapy [1] Von Tappeiner and Jodlbauer defined Photodynamic Therapy as the dynamic interaction among light, a photosensitizing agent, and oxygen resulting in tissue destruction [2] Synonyms for Photodynamic Therapy - Photoradiation Therapy ,Phototherapy or Photo Chemotherapy [3]
2. Historical Review:

In 1900 by Oscar Raab realized that the interaction between acridine (a dye) and visible light in the presence of oxygen killed paramecia [3]. Niels Finsen studies focused on the application of arc lamp in phototherapy. In 1903 he was awarded a Nobel Prize for this research [3].

The term 'photodynamic action' ('photodynamische Wirkung') was introduced in 1904 by one of the pioneers of photobiology: Professor Hermann von Tappeiner, director of the Pharmacological Institute of the Ludwig-Maximilians University in Munich [2].

The German physician Friedrich Meyer-Betz performed the pioneering study which was at first called photo radiation therapy (PRT) with porphyrins in 1913. He tested the effects of hematoporphyrin-PRT on his own skin. John Toth, as product manager for Cooper Medical Devices Corp, Cooper Lasersonics, acknowledged the "photodynamic chemical effect" of the therapy with early clinical argon dye lasers and wrote the first "white paper" renaming the therapy as "Photodynamic Therapy" (PDT). This was done to support efforts in setting up 10 clinical sites in Japan where the term "radiation" had negative connotations [3].

In 1942 Auler and Banzer from the University of Berlin discovered characteristic red fluorescence of porphyrins in rodent tumors. This discovery was a beginning of photodynamic diagnosis (PDD) [4].

The current era of PDT began with studies by R.L. Lipson and S. Schwartz at the Mayo Clinic in 1960 who observed that injection of crude preparations of hematoporphyrin led to fluorescence of neoplastic lesions. To gain an optimal tumor localizing preparation, Schwartz treated hematoporphyrin with acetic acid and sulfuric acid and obtained a porphyrin mixture that he termed "hematoporphyrin derivative" (HPD), which was used by Lipson et al. for tumor detection [5].

In 1976 Kelly and Snell performed the first experiments in PDT on humans. They investigated effects of hematoporphyrin derivatives (HpD) photodynamic therapy in case of bladder carcinoma in five patients [4].

In 1978 Thomas Dougherty carried out the first large experiment on humans. The clinical study comprised 25 patients with 113 tumours (both primary and metastatic). Results proved that PDT was very effective therapeutic method. In 1993, in Canada, the purified HpD was officially accepted as commercially available product termed Photofrin II [4].

Thomas Dougherty helped in expanding clinical trials and forming the International Photodynamic Association, in 1986 [3].

PDT was first approved by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions of the face or scalp [3].

3. Principles of Photodynamic Therapy:

Photodynamic therapy (PDT) is a medical treatment that utilizes light to activate a photosensitizing agent (photosensitizer) in the presence of oxygen. The exposure of the photosensitizer to light results in the formation of oxygen species, such as singlet oxygen and free radicals, causing localized photodamage and cell death [6].

Clinically, this reaction is cytotoxic and vasculotoxic. Depending on the type of agent, photosensitizers may be injected intravenously, ingested orally, or applied topically. The relative simplicity of the mechanism of activation of photosensitizers has stimulated considerable interest in PDT [6].

3.1. Photodynamic Reaction:

PDT involves three components: Light source, A photosensitiser, Oxygen

Figure 1 – basic components of photodynamic therapy – photosensitiser, oxygen and light source, interaction of these components results in photodynamic reaction.

A photosensitizer or its metabolic precursor is administered to the patient. Upon irradiation with light of a specific wavelength, the photosensitizer undergoes a transition from a low-energy ground state to an excited singlet state. Subsequently, the photosensitizer may decay back to its ground state, with emission of fluorescence, or may undergo a transition to a higher-energy triplet state [6].

There are two mechanisms by which the triplet-state photosensitizer can react with biomolecules:

Figure 2 – shows mechanism of photodynamic reaction - light source illuminates photosensitiser which is converted in to activated photosensitiser which in turn converts oxygen in to reactive oxygen species . Reactive oxygen species has toxic effects on tumor cells and microorganisms.

Photosensitizers are usually aromatic molecules which are efficient in the formation of long-lived triplet excited states in the photodynamic reaction. [8] More than 400 compounds are known with photosensitizing properties including dyes, drugs, cosmetics, chemicals and many natural substances.

The requirements of an optimal photosensitizer include photo-physical, chemical, and biological characteristics. An ideal photosensitizer should be non-toxic, and should display local toxicity only after activation by illumination. [6]

5. Advantages of Photodynamic Therapy[6]

Potential Advantages of Photodynamic Therapy over Conventional Anti-cancer therapies include that it

- Is non-invasive and convenient for the patient
- Can be performed in outpatient or day-case (inpatient) settings
- Can be targeted accurately and selectively in early or localized diseases

Although it cannot cure advanced disseminated disease, because illumination of the whole body is not possible, it can improve quality of life and lengthen survival.

Repeated doses can be given without the need for total-dose limitations.

Has moderate side-effects.

Can have excellent cosmetic results, and the healing process results in little or no scarring.

Can offer organ-sparing treatment worldwide, with very little investment in infrastructure.

6. Photodynamic Therapy in Oral Diseases:

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

7. Premalignant Lesions and Conditions:

7.1. LEUKOPLAKIA:

Oral leukoplakia, oral erythroplakia and oral verrucous hyperplasia are three common oral precancerous lesions. The high malignant transformation rate of oral premalignant lesions highlights the importance of early detection and treatment.

Traditional treatment for oral precancers is total surgical excision that always leads to scar formation. Photodynamic therapy is an effective treatment option for human precancerous lesions because it can be used repeatedly without cumulative side effects and results in little or no scar formation. [9]

The application of photodynamic therapy in oral leukoplakia significantly reduces the time of treatment in comparison with pharmacological methods involving vitamin A or active metabolites of vitamin A. Application of vitamin A requires 2 to 3 months to complete cure. [10]

In the case of multifocal leukoplakia, it is very often impossible to remove all pathological foci within a margin of intact tissue. Micro foci, which are invisible upon macroscopic examination, are usually eradicated after PDT. Eradication of microfoci considerably decreases risk of recurrences. In the case of lesion located on the skin of face or labial mucosa the PDT assures cosmetic effects which are very important in that localization. [4]

Delta aminolevulinic acid is very often used in the treatment of leukoplakia at concentration from 10 to 20%, 0.1% chlorophyll gel is being used too.

8. Erythroplakia and Verrucous Hyperplasia

Topical ALA-PDT using the 635-nm light-emitting diode (LED) light is very effective for treatment of oral verrucous hyperplasia (O VH) and oral erythroplakia (OEL) lesions. [9]

HSIN-MING CHEN ETAL (2005) tried to evaluate PDT protocol using the 635-nm laser light was with and found it to be effective for treatment of OEL and OVH lesions. [11]
Results of the study showed that the laser light-mediated topical ALA-PDT is very effective for OVH and OEL lesions. 20% ALA preparation was a gel form, which was adhesive to the oral mucosa, was partially resistant to the dilution of the saliva, and in turn helped the absorption of ALA from the mucosal surface.

The potential advantages of this study is that it used a fractionated protocol to deliver light treatment; the lesional epithelial cells might regenerate new protoporphyrin IX and obtain new oxygen during multiple 3-min resting periods, finally resulting in a more successful clinical outcome for OVH and OEL lesions.

The verrucous appearance of the OVH lesion provided a large area for good retention and absorption of ALA on the surface. In general, OVH and OEL lesions with smaller size, pink to red color, epithelial dysplasia, and thin surface keratin layer had better PDT outcomes than those corresponding lesions, respectively. Pink to red and dysplastic oral OVH and OEL lesions usually had thinner surface keratin layer, leading to diffusion of more ALA into the lesions. Furthermore, dysplastic OVH and OEL lesions usually had more permeable epithelium (due to wide intercellular spaces of the dysplastic epithelium); this also resulted in diffusion of more ALA into the lesions. In addition, the dysplastic epithelium may retain more ALA than the hyperplastic epithelium, and the thinner keratin layer may only have a minimal effect on the reduction of the light intensity. In addition, there are more epithelial cells in the cell division cycle in dysplastic OVH and OEL lesions than in non-dysplastic OVH lesions. Dysplastic epithelial cells in the cell division cycle are more susceptible to the destruction by PDT-generated singlet oxygen molecules and free radicals than those epithelial cells not in the cell division cycle. The sufficient photosensitizers and light dose finally resulted in a better clinical outcome for those OVH and OEL lesions with pink to red colour, epithelial dysplasia, and thinner surface keratin layer.

9. Verrucous Carcinoma

In a case report by (Hsin-Ming Chen et al. 2005), the efficacy of new treatment protocol of ALA PDT for an extroral verrucous carcinoma (VC) lesion at the right mouth angle and an intraoral VC lesion at the right buccal mucosa of a 56-year-old male area quid chewer and smoker was tested.

New topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT) protocol composed of multiple 3-min fractionated irradiations with a light emitting diode (LED) red light at 635 ± 5 nm for a total of 1000 s (fluence rate: 100 mW/cm2; light exposure dose: 100 J/cm2) after topical application of 2% ALA for 1.5 or 2 h has been used successfully for the treatment of oral verrucous hyperplasia.

The extroral tumour was cleared after six treatments of topical ALA-PDT and the intraoral tumour showed complete regression after 22 treatments of topical ALA-PDT. No recurrence of the VC lesion was found after a follow-up period of 6 months. It was suggested that PDT using a topical application of 20% ALA followed by multiple 3-min fractionated irradiations with an LED red light is also an effective and successful treatment modality for VC.

Treatment with a light of 635-nm wavelength can activate PpIX in lesional epithelial cells; PpIX, in turn, transfers energy from light to molecular oxygen, resulting in generation of reactive oxygen species (ROS). There are three possible mechanisms by which ALA-PDT mediates tumour destruction. Firstly, the ROS can kill tumour cells directly. Secondly, PDT can damage the tumour-associated vasculature, leading to thrombus formation and subsequent tumour infarction. Thirdly, PDT can also activate an immune response against tumour cells. The successful treatment of VC case with topical ALA-PDT could be at least partially because of ALA preparation and the new treatment protocol. The 20% ALA preparation used in this study was a liquid form at room temperature; it became a gel form at body temperature upon contacting the lesional oral mucosa because of a thermo responsive sol–gel transition of the vehicle. The gel form of ALA preparation was adhesive to the oral mucosa and partially resistant to the dilution of the saliva. This characteristic feature of ALA preparation, in turn, helped the absorption of ALA from the mucosal surface. In addition, the verrucous appearance of the VC lesion also provided a large area for good retention of ALA on the surface and for good absorption of ALA into cells.

10. Lichen Planus:

Lichen planus is a relatively common chronic inflammatory mucocutaneous disease. Although the cause is not well known, T-cell-mediated autoimmune phenomena are involved in the pathogenesis of lichen planus.[12]

The reported frequency of malignant transformation varies greatly from 0.4% to more than 5% over a period of 0.5 to more than 20 years. Treatment options for OLP are numerous, including topical, intralesional and systemic corticosteroids, topical cyclosporine and tacrolimus, topical and systemic retinoids, however, outcomes are often disappointing. So searching for new treatment modalities seems quite rational.

The exact mechanism of action of PDT is unclear. It would appear to act on hyper proliferating cells, such as those present in malignancies which selectively uptake the Photosensitizers. It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis in the hyperproliferating inflammatory cells, which are present in psoriasis and lichen planus. This may reverse the hyperproliferation and inflammation of lichen planus.[13]

One report of the use of PDT for hypertrophic lichen planus of the penis by Kirby et al. used ALA-mediated PDT twice for treating the lesion. The lesion had completely resolved after 4 weeks. At 6-month follow-up there was no recurrence.

In another study conducted by (Aghahosseini et al. 2005) methylene blue-mediated photodynamic therapy (MB-PDT) was used as a possible alternative method for the treatment of oral lichen planus (OLP). 26 OLP lesions were enrolled in this study. Patients were instructed to gargle a 5% methylene blue solution in water for 5 minutes. Ten minutes later, irradiation was performed by laser light (1463 nm, light exposure dose 120 J/cm2). Lesions were evaluated pre and post-operatively and at follow-up sessions by changes in sign and symptom (pain) scores, and size of...
lesions. Results showed that there was significant improvement in sign scores was achieved in 16 lesions. Four keratotic lesions disappeared completely. There was a statistically significant decrease in sign and symptom scores 1 week after treatment and at follow-up sessions up to 12 weeks. Average reduction in size of lesions was 44.3%. In conclusion MB-PDT seems to be an effective alternative treatment for control of OLP.

In another study conducted by Farzane Aghahosseini et al (2005) Before world patients with five oral lichen planus lesions were treated using topical PDT mediated by methylene blue (MB-PDT). Methylene blue was prepared 0.05 gr per 100 cc. Ten minutes prior to laser irradiation, patients gargled MB for 5 minutes. A diode laser (Lumina, Russia; 632 nm, CW) 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 cm². Large lesions were illuminated with multiple spots. A fluence of 100 J/cm² was used. The patients were followed up on sessions 3, 7, 15 days and 1 to 9 months after PDT. At the follow up sessions; lesions were examined to detect any residual lesion. Lesions were exactly measured and digital photographs were taken before PDT and at follow up session. Response rates were assessed clinically by amount of reduction in surface area of lesions. Clinical improvement was achieved in four lesions. Two lesions showed complete remission, and another two lesions had about 50% clinically improvement 3-9 months after a single session of PDT. No response detected in one lesion. MB-PDT blue seems to be an effective alternative treatment for control of OLP.[13]

11. Head and Neck Cancer

Squamous cell carcinoma of the larynx and oral cavity may be treated effectively with single-modality therapy. Because radiotherapy and limited surgical resection don’t yield excellent tumour control, the choice of therapy in early-stage laryngeal and oral cancers is often dictated by functional treatment outcomes, such as voice quality and swallowing function.[14]

The preferred treatment modality is surgery for early-stage oral cavity cancer and radiotherapy for early laryngeal cancer. However, irradiation and surgery may result in long-term morbidity. The limitation of surgical resection in the oral cavity and larynx is the necessity to remove vital functional tissue, such as part of the tongue in the oral cavity, which may affect speech and swallowing.

Radiotherapy to the oral cavity often results in long-term morbidities, such as xerostomia, dysphagia, loss of dentition, and risk of osteoradionecrosis. Dysphagia, loss of dentition, and risk of osteoradionecrosis.

Endolaryngeal laser surgery is also an effective treatment for early-stage laryngeal cancers, but it requires considerable expertise and technology. The reported long-term results of these treatment modalities are variable. An optimal treatment for moderate to severe dysplasia and early carcinomas of the oral cavity and larynx would be one that is safe, effective, repeatable, minimally invasive, and devoid of permanent sequelae.

12. Advantage of Photodynamic Therapy Over Conventional Treatment Modalities In Head And Neck Carcinoma:

The main advantage of PDT for dysplasia and early carcinoma of the larynx is the ability to preserve normal endolaryngeal tissue while effectively treating the lesion. This results in preservation of laryngeal function and voice quality. It may be performed in an outpatient setting using a single non-invasive light activation treatment, requiring a short duration of therapy. For selected recurrent carcinomas of the larynx that have failed conventional radiotherapy, PDT, and remove eliminate and add word eliminated eliminate the need for salvage surgery. PDT can be repeated without the additional permanent functional laryngeal impairment that can occur with repeated conventional laser surgery or cordectomy. PDT for dysplasia and CIS and primary T1 laryngeal carcinomas reserves radiotherapy for the treatment of recurrences and second head and neck primary cancers that may occur in this high-risk patient population. PDT spares the tissue architecture, providing a matrix for regeneration of normal tissue by leaving sub epithelial collagen and elastin intact, and spares noncellular supporting elements. A further important positive aspect of PDT is that it can be repeated. This attribute is significant because patients with head and neck cancer have an increased lifelong rate of development of second primary cancers in the upper aerodigestive tract.

Nestor R. Rigual,(2009) conducted a prospective trial to determine the response of dysplasia, carcinoma in situ (CIS), and T1 carcinoma of the oral cavity and larynx to photodynamic therapy with porfimer sodium was conducted Patients with primary or recurrent moderate to severe oral or laryngeal dysplasia, CIS, or T1NO carcinoma were included. Methodology included: Porfimer sodium, 2 mg/kg of body weight, was injected intravenously 48 hours before treatment. Light at 630 nm for photosensitizer activation was delivered from an argon laser or diode laser using lens or cylindrical diffuser fibers. The light dose was 50 J/cm² for dysplasia and CIS and 75 J/cm² for carcinoma. Response was evaluated at 1 week and at 1 month and then at 3-month intervals thereafter. Post treatment biopsies were performed in all patients with persistent and recurrent visible lesions. Of thirty patients enrolled, 26 were evaluable. Mean follow-up was 15 months (range, 7-52 months). Twenty-four patients had a CR, 1 had a PR, and 1 had NR Three patients with oral dysplasia with an initial CR experienced recurrence in the treatment field. All the patients with NR, a PR, or recurrence after an initial CR underwent salvage treatment. Temporary morbidities included edema, pain, hoarseness, and skin phototoxicity.[14]

In conclusion it can be stated that Photodynamic therapy with porfimer sodium is an effective treatment alternative, with no permanent sequelae, for oral and laryngeal dysplasia and early carcinomas.

13. Oral Microbial Diseases

Photodynamic therapy has been implicated against a great number of microbial species which include bacterial, viral and fungal organisms.
14. Viral Diseases:

The most literature on viral diseases that are treated with PDT regards warts or condylomata. Other viruses that were reported to be treated with PDT include molluscum contagiosum and herpes simplex.[15]

HERPES SIMPLEX VIRUS-1 (HSV-1) is a DNA virus that causes primary herpetic gingivostomatitis, mucocutaneous orofacial disease, and ocular disease. Recurrent lesions are common on the face and lips, and less common, intraorally. Occasional cases are caused by HSV-2, and HSV-1 may also present as a primary genital infection. The infection usually occurs in children, adolescents, and young adults. Transmission is via direct contact with infected secretions and the majority of primary infections are subclinical.[15]

Recurrent herpes labialis occurs in 20–40% of the population, and the lesions are commonly referred to as “cold sores” or “fever blisters.” Patients notice a prodrome of tingling, itching, or burning, followed by a papule that progresses to vesicular, crusted, and healing stages; the outer one-third of the lips are the most frequently affected areas.[10]

Arduino and Porter analyzed the published literature to evaluate the advantages and limitations of therapy for HSV-1 infection. These authors reported that topical application acyclovir (ACV) at 5% appears to be the accepted standard therapy for herpes labialis, being both effective and well-tolerated, although topical application of penciclovir 1% has also been proposed as a potentially useful treatment. Systemic ACV may be effective in reducing the duration of symptoms of recurrent HSV-1 infection, but the optimal timing and dosing remain unclear. Acyclovir and famciclovir may be of benefit in the acute treatment of severe HSV-1 disease in immunocompromised patients. There is also evidence that prophylactic oral ACV may reduce the frequency and severity of herpetic flares in immunocompromised patients.[15]

Another treatment option for HSV-1 is phototherapy. High- and low-power lasers either associated with PDT or not can be used. The choice of therapy should be made according to the stage of the lesion. When the lesion is at the vesicular stage, HPL or PDT must be used. When crusts have already formed, LPL at the red wavelength can be used, with the aim of accelerating the healing process. An infrared laser can also be used at the crusting stage when edema is present, or when there is no infectious process. High-power lasers can be used to rupture and drain vesicles. Furthermore, it is hypothesized that irradiation can reduce the quantity of virus present in the fluid, decreasing the frequency and duration of infections. The use of a water spray can reduce pain during irradiation, but some lasers, such as the Nd:YAG and diode lasers, do not have a cooling system.

Substances employed in photodynamic procedures to inactivate HSV include found protoporphyrin IX, hematoporphyrin derivatives, and aminolevulinic acid (5-ALA). When 5-ALA is exogenously supplied, protoporphyrin IX is converted to protoporphyrin IX, causing photodynamic damage to the underlying mucosa.[16]

The mechanism of virus inactivation involves binding of the dye to nucleic acid, absorption of light, generation of reactive oxygen species, and guanine oxidation in the viral genome. Research clearly demonstrated the effect of MB effectively against viruses. Also, MB shows strong absorption at the red end of the visible spectrum.

Juliana Marotti et al (2009) has reported the use of photodynamic therapy (PDT) as a treatment for herpes lesions, on four cases. The vesicles were carefully perforated with a sterilized needle so that the liquid could flow. A small cotton ball soaked in a 0.01% (m/V) methylene blue solution was placed over the lesion, and after 5 min, the excess dye was removed. The lesions were irradiated with a 660-nm LPL (Twin Laser; MM Optics São Carlos, Brazil) with a spot size of 0.04 cm², in continuous mode. Energy density was 120 J/cm², power output was 40 mW, for 2 min per point for 4.8 J/cm² of energy, in contact mode. The total delivered energy was 19.2 J, equally divided among four different points. After 24 h the patients returned and the phototherapy was performed with the same LPL, at an energy density of 3.8 J/cm², 15 mW power output, for a total of 0.6 J of energy, divided over the same four points. The phototherapy regimen was repeated after 72 hr and 1 week. No pain or discomfort was reported during treatment. Patients returned for follow-up appointments during the following 6 mo after treatment.

Treatment with low-level laser therapy can be considered as an option in the treatment of herpes labialis, and decreases the frequency of vesicle recurrence and provides comfort for patients. No significant acute side effects were noted and the lesions healed rapidly.[15]

Treatment of herpes labialis with PDT was effective, had no side effects, and when associated with laser phototherapy, accelerated the healing process.[10]

15. Bacterial Diseases

Photodynamic therapy has been used against a number of bacterial species. Its implications in bacteriology can be dated back to early 20th century. In 1990, it was demonstrated that Escherichia coli could be killed if pre treated with Methylene blue and exposed to white light. Helicobacter infection was eradicated with methylene and toluidine blue, using a copper vapor–pumped dye laser on ex vivo samples of ferret gastric mucosa, without damage to the underlying mucosa.[16]

16. Damage Caused By PDT to Bacteria:

There are two basic mechanisms that have been proposed to account for the lethal damage caused to bacteria by PDT: 1) DNA damage and 2) damage to the cytoplasmic membrane allowing leakage of cellular contents or inactivation of membrane transport systems and enzymes. Breaks in both single and double stranded DNA and the disappearance of the plasmid supercoiled fraction have been detected in both gram positive and negative organisms. The other causes of cell death include – alteration of cytoplasmic membrane proteins and disturbance of cell wall synthesis and the appearance of multi lamellar structure near the septum of dividing cells along with loss of potassium ions from the cells may be other possible ways of bacterial death.
The environmental factors surrounding the bacteria may influence the efficient binding of photosensitizers. Supercoiled fraction have been detected in both gram positive and gram negative.

A novel porphyrin-based photosensitizer, XF73, showed high efficacy at killing methicillin-resistant Staphylococcus aureus (MRSA) without damage to keratinocytes or eukaryotic cells. The investigators postulated a use for this photosensitizer to prevent MRSA infection in hospitals as well as for burns or other open wounds in vivo animal model was used to postulate that PDT might be a good therapeutic alternative for the treatment of osteomyelitis.[16]

17. Pulpal and Periapical Diseases

Apical periodontitis is a disease caused by bacteria, and, consequently, successful treatment of this condition is dependent on the effective elimination of intracanal bacterial populations. Although complete eradication of the infection in the entire root canal systems is the ideal goal to be reached, maximum reduction in bacterial counts to levels that are compatible with periodicidal tissue healing is the attainable goal in current clinical endodontics[18]

The issue as to whether or not the root canal treatment of teeth with apical periodontitis should be concluded in one or two visits is one of the greatest controversies in endodontics now a days. The establishment of treatment protocols that can predictably disinfect the root canals in one visit has the potential to help smooth this discussion.

In this regard, the idea of speeding up root canal disinfection while maintaining efficacy sounds interesting and should be pursued. In this regard, the use of laser technology arises as a possibility in endodontic therapy. In vitro and in vivo studies using PDT have shown that this approach has the potential to maximize root canal disinfection. However, while disclosing and confirming the excellent antibacterial potential of PDT, none of these studies have consistently examined the effectiveness of this procedure in supplementing bacterial elimination after chemomechanical procedures, which is the greatest potential use of this technology with regard to root canal disinfection.

Possible explanation for incomplete bacterial elimination may be the low concentration of available oxygen in the canals, especially in irregularities and in dentinal tubules. Under such conditions, the formation of cytotoxic oxygen derivatives may be precluded or minimized. In the clinical situation, conditions of low oxygen are expected to be still more critical. Also, the photosensitizer agent may have not diffused well into oxygen are expected to be still more critical. Also, the photosensitizer agent may have not diffused well into and adjunctive use of antibacterial disinfectants or various antibiotics have been conventional methods of the periodontal therapy[3]

The field of antimicrobial chemotherapy is one of constant challenge, particularly in view of the rapid evolutionary changes and wide variety of pathogens encountered. Of particular importance in this area has been the appearance of drug resistance in a wide range of pathogens leading to increased morbidity from infections which, in the past, had been trivial and easily treated[8] Amoxicillin resistance was occasionally observed in periodontal reservoirs due to the production of beta-lactamases. Preferably, this was detected in Prevotella sp. and Fusobacteria and not in A. actinomycetemcomitans.

Although several authors have reported the possibility of a lethal photosensitization of bacteria in vivo and in vitro, others have pointed out that Gram-negative bacterial species, due to their special cell wall, are largely resistant to PDT[8]

The cytotoxic product, usually cannot migrate > 0.02 mm after its formation, thus making it ideal for the local application of PDT without endangering distant molecules, cells, or organs.[3]

Wilson proved the effect of a cyanide photosensitizer on Gram-positive and Gram-negative species. On the other hand, Nitzan et al. and Bertolini et al. have reported a limited activity of porphyrin-containing photosensitizers toward Gram-negative bacteria. Meanwhile, attempts are being made to increase the permeability of the Gram-negative bacterial membrane to photosensitizers by using membrane active substances or by synthesizing special, positively charged photosensitizers that bind more easily to the bacterial membrane.[3]

Microorganisms in gelatinous matrix are less accessible to antibiotics. Using antimicrobial agents to treat periodontitis with out disruption of biofilm ultimately results in treatment failures. It is difficult to maintain therapeutic concentrations at the target site and target organisms can develop resistance to drugs. This resistance is minimized by using PDT. Polysaccharides present in extracellular matrix of oral biofilm are highly sensitive to singlet oxygen and susceptible to photodamage. Breaking the biofilm may inhibit plasmid exchange involved in transfer of antibiotic resistance and disrupt colonization. PDT is effective against antibiotic resistance bacteria. Antioxidant enzymes produced against some oxygen radicals but not against singlet oxygen.[3]

PFGT: PDT was shown to have in vitro effects against Tinea rubrum at dosages of ALA of 1 to 10 m mol and 10 to 14 days of incubation. Diode laser was effective in activating toluidine blue-induced PDT of Candida species at low levels. Interdigital tinea pedis was treated successfully with 29% ALA in Eucerin cream and 75 J/cm2 red light.[18]

19. Histological Changes after Photodynamic Therapy

Nuclear area (NA), coefficient of variation of the nuclear area (NACV) as well as proliferating cell nuclear antigen (PCNA) of tumour are useful indicators in assessing the effect on tumor on PDT[19].
Masataka Uehara et al. (2010) conducted a study to analyze the morphological change of cell nuclei and the change of proliferating activity of oral malignancy and epithelial dysplasia between before and after photodynamic therapy in order to predict recurrence.

The mean NA after PDT was significantly lower than that before PDT in the nonrecurrent group. However, there was no significant difference in mean NA before and after PDT in the recurrent group. There were no significant differences in NACV before and after PDT in either the nonrecurrent or recurrent group. Furthermore, the PCNA labelling indices of the specimens after PDT was significantly lower than that before PDT in both the nonrecurrent and the recurrent group.

Mean nuclear area in the biopsy specimen after photodynamic therapy is likely to be a predictive marker for the recurrence of oral squamous cell carcinoma or epithelial dysplasia subjected to photodynamic therapy, while coefficient of variation of the nuclear area and proliferating cell nuclear antigen labelling indices are less helpful in predicting the recurrence of such lesions.[19]

20. Future Perspectives and Conclusion

During the past 30 years, PDT has been employed in the treatment of many tumour types, and its effectiveness as a curative and palliative treatment is well documented. But why is its role in other disciplines still marginal? In general, it is difficult to persuade clinicians to use a new technique when standard treatments yield a high response rate. Although lasers have become much less expensive, the setup of a new PDT centre remains costly.[10]

Long-term comparisons show that PDT is cost effective for palliative treatment of head and neck cancer and treatment of Barrett's esophagus and high-grade dysplasia. The issue of cumbersomeness, difficult-to-use laser equipment has now been dealt with, and simple pre programmed menus assist the physician with treatment.

The main drawback against using PDT as frontline therapy lies in the fact that large randomized trials have not yet been done. 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.

Experimental demonstrations of the important contribution of vascular-mediated damage to tumour destruction, and the correlation seen between drug levels in the plasma at the time of illumination and PDT efficacy, might have clinical implications. If the vasculature, rather than tumor cells, is the main target for PDT damage, then optimal illumination times should be when the plasma drug levels are high.

New clinical protocols could reduce drug-light intervals, and, if they show an improvement in outcome, then drug dose might also be decreased, which would result in less generalized phototoxicity.

Research into selective delivery of photosensitizers by conjugation to antibodies, use of liposomes as carrier and delivery systems, or new photosensitizers with a more specific tumor localization and faster clearance is also warranted. It is also worthwhile to explore the possibilities of combining PDT with other therapies. It has already been shown that the combination of PDT with doxorubicin, mitomycin C, modulators of the immune system, and inhibitors of angiogenesis resulted in superior PDT responsiveness.

As our understanding of the best ways to combine these therapies in increases, it is to be expected that further improvements in the clinical application of PDT will be seen.

Conflict of Interest: NONE

21. References


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