The Journal of Dental Panacea 2023;5(1):17–20

Content available at: https://www.ipinnovative.com/open-access-journals

The Journal of Dental Panacea

Journal homepage: https://www.jdentalpanacea.org/

Review Article

Photodynamic therapy in dentistry: A literature review

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ARTICLE INFO

Article history:
Received 19-11-2022
Accepted 09-12-2022
Available online 08-04-2023

Keywords:
Dentistry
Light Source
Oxygen
Photodynamic Therapy
Photosensitizer

ABSTRACT

Photodynamic therapy is a relatively new non-invasive treatment modality that involves photosensitizers, specific wavelengths of light, and the generation of singlet oxygen and reactive oxygen species. Applications of photodynamic therapy in dentistry are growing rapidly and is slowly reaching all specialties. The present literature review aims to discuss the basic mechanism of photodynamic therapy, its application in various branches of dentistry and its limitations.

1. Introduction

Photodynamic therapy (also known as PDT, photo radiation therapy, or photochemotherapy) has rapidly evolved as a therapeutic method over the years. It is in use since the 1960s in a variety of medical specialties and is described as "the light induced inactivation of cells, microorganisms, or molecules."[1] PDT is a minimally invasive technique utilizing photosensitizers (PS) in the form of chemical agents, specific wavelengths of light, and production of singlet as well as reactive oxygen species to target undesirable eukaryotic cells or pathogenic microorganisms.[2]

1.1. History

The first description of the theoretical foundations and applications of PDT go back to the ancient Egyptians. They believed that only the sun had a healing capacity for few dermatologic diseases such as vitiligo, psoriasis and skin cancer.[3] Today, sunlight (or light) is used as a therapeutic tool. This practice of doing so is known as photo therapy or heliotherapy. The Greeks were also among the first few to use light therapy in the history of mankind.[4]

The foundation of modern phototherapy was first laid by Danish scientist Niels Finsen in the 1890s. Niels Finsen studied a wide range of light sources that ranged from small active beams to ultraviolet radiation. In the 1960s at the Mayo Clinic, PDT was studied by Lipson and Schwartz who further accelerated the same by doing pioneer work in both research as well as clinical applications by Dougherty et al.[5]

PDT was then subsequently accepted by the World Food and Drug Administration (FDA) in 1999 for treating precancerous skin lesions present on the face/scalp. PDT has been suggested to be useful in nearly all aspects and specialties of medicine, and the number of possible applications is increasing daily.[2]

1.2. Mechanism of PDT

A PDT contains three components: Light, Photosensitizers (PS), and Oxygen.[6] This process involves excitation of PS by light (a physical process) and subsequent interaction of the excited PS with various cellular substrates and molecular oxygen. A photochemical reaction then occurs, ultimately

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https://doi.org/10.18231/j.jdp.2023.004

leading to cell death.[2]

1.3. Photosensitizers

PS is a macrocyclic compound with a heterocyclic structure similar to chlorophyll and heme. Depending on the type of drug used, PS is injected intravenously into the bloodstream (where it reaches the target site), taken orally, or applied topically to the area to be treated. They are generally divided into three main families.

The first generation PS was launched in the 1970s and early 1980s. Most of these compounds are cyclic tetrapyrroles and include substituted derivatives of porphyrins, chlorins and bacteriochlorins. However, the clinically relevant compounds are most commonly structural derivatives of hematoporphyrin.[7] High aggregation propensity, lack of specificity, poor solubility in physiological fluids, and cutaneous phototoxicity constitute some drawbacks of the generation. Therefore, most first generation PS are not suitable for use with PDT.[2]

Second-generation PS (e.g., verteporfin, talaporfin, temoporfin) were developed in the late 1980s to improve the efficacy of first-generation drugs in addition to better pharmacokinetic properties and reduced toxicity.[7] In addition, these PSs yield higher $^1O_2$ yields compared to first-generation compounds.[8] These molecules include core or structurally modified or substituted porphyrins, bacteriochlorins, chlorins, phthalocyanines, or other macrocycles. Chemically, the presence of fused aromatic rings in these molecules lengthens the p-conjugation, a desirable property for PS molecules.[9]

The 3rd generation PS is the most recently developed medically important compound. Derivatives of second-generation PS compounds have different functional groups that can be added by different synthetic strategies and have several advantages.[7] In principle, these are second-generation PS compounds conjugated with biological molecules or having built in "photo-quenching" property. These photosensitizers are activated only at specific target sites (proteins, receptors, etc.).[10]

1.4. Light source

A basic requirement for a PDT light source is to match the activation spectrum (electron absorption spectrum) of PS (usually the longest wavelength peak) and generate sufficient light intensity at that wavelength. The specific wavelength (630-800 nm) light sources mainly used in PDT today are the helium neon laser (633 nm), the gallium aluminum arsenide diode laser (630-690, 830, or 906 nm), and the argon laser (488 to 514 nanometers). The wavelengths of these sources range from visible light, through the blue of argon lasers, or the red of helium-neon and gallium-aluminum-arsenide lasers, to the infrared of some diode lasers.[11]

Diode lasers have become a popular source for PDT because they are easy to use, inexpensive, and portable. The laser light used in PDT has several advantages. It can provide the right amount of light, is monochromatic, has high efficiency and high potency, providing an intrusive optical transmission device via optical fiber.[12]

Laser systems based on light-emitting diodes (LEDs) have become an emerging light source for PDT due to their low cost, portability, and overall ease of use. Another advantage of LED-based systems is that the tips of these emitting fibers can be shaped differently and a light applicator (or diffuser) can be used to achieve uniform scattering.[13]

1.5. Role of oxygen

Oxygen is the last element needed for photodynamic reactions. The photodynamic process begins with excitation of a photosensitizer by a light source, followed by photochemical reaction of the agitated PS with cellular substrates or molecular oxygen, eventually leading to cell death. In the presence of intracellular oxygen, photoactivated photosensitizers react with molecules by electron or hydrogen transfer, leading to the formation of free radicals (type I reactions) or energy transfer to oxygen (type II reactions) to produce singlet oxygen. Both pathways can lead to cell death.[14]

2. Applications of PDT in Dentistry

2.1. Oral medicine

PDT has shown promise as a tool for treating precancerous and malignant lesion of the oral cavity.[15] Local application of photosensitizer 5-aminolevulinic acid (ALA) has been employed as an investigatory tool for diagnosing oral lesions, in a procedure known as ALA-based photodynamic diagnosis. ALA is applied topically to suspicious lesion sites following which it accumulates and increases tissue fluorescence of the lesion. Malignant and non-malignant lesions can be distinguished by a measurable difference in fluorescence levels between normal and precancerous tissue.[16]

Antimicrobial PDT has shown good results in the management of oral candidiasis. In an in vitro study, Photofrin®-mediated PDT was successfully used to target Candida species.[17] PDT has also shown success in the management of lesions caused by herpes simplex virus (or HSV). PDT using methylene blue as a photosensitizer is considered a viable option for treating herpes labialis.[18]

2.2. Oral and maxillofacial surgery

PDT is an effective treatment method pertaining to early-stage precancerous lesions and tumors of the head and neck region. Advantages of PDT are based on its minimal

invasiveness and ability to selectively destroy tumors while sparing healthy tissue.[6] Compared with conventional treatment options, PDT has an added advantage as the number of sessions is not limited, and after effects of PDT are not severe and last only for a brief time period.[19]

Alveolar osteitis and post-extraction pain can also be managed and prevented with the aid of PDT. A study by Saini R et al. (2016) found that the lower incidence of alveolar osteitis after PDT is an emerging treatment modality for prevention of the condition.[20]

2.3. Endodontics

Studies have supported using PDT in combination along with conventional chemo mechanical formulations. A reduction of bacteria from 37.6% to 100% has been observed which further supports the claim that PDT can be considered an alternative method in conjunction with contemporary root canal disinfection.[21] It has been shown to be highly effective as an antibacterial agent when used against both Gram positive as well as Gram negative bacteria of endodontic relevance, especially Enterococcus faecalis.[22]

Additionally, PDT may also prove to be beneficial as an adjunct to conventional canal therapy in cases of chronic periodontitis. One study (2008) performed root canal treatment (RCT) in two visits using polyethyleneimine (PEI) as a photosensitizer along with a fiber optic diode laser. Results showed that PDT as an adjunct to treatment minimized the presence of periodontal pathogens logarithmically. As a whole, this indicates that the use of PDT in RCT enhances the antimicrobial efficacy.[23]

2.4. Pediatric dentistry

Preservation of deciduous teeth demonstrating pulpal changes due to either caries or trauma is indeed a challenge in pediatric dentistry. Approximately 75% deciduous teeth having carious defects show pulpal involvement owing to thin enamel & dentin, less mineralization of enamel, and existence of pronounced pulp horns below the cusp in primary teeth compared to permanent teeth. In this context, PDT is a promising approach for disinfecting dentin. PDT was also shown to be efficacious against both antibiotic-resistant and antibiotic-sensitive bacteria.[24]In 2014, de Sant'Anna reported that PDT offers good long-term results when used along with conventional treatment in pediatric patients with diabetes.[25]

2.5. Periodontology

Progression of periodontitis and periodontal tissue ruination can be significantly diminished by the application of antimicrobial photodynamic therapy. Oral bacteria residing in plankton cultures and plaque swabs were shown to be susceptible to antimicrobial photodynamic therapy. Moreover, photodynamic therapy can induce bacterial cell death and eventually reduce bacterial counts in S. mutans, S. sobrinus, S. sobrinus and S. Sanguini biofilms in cases where toluidine blue O or erythrosine were employed as PS.[1] A study by Anderson *et al*. (2007) concluded that the group that receiving a combination of PDT with scaling demonstrated promising results with the absence of bleeding on probing and decreased pocket depth.[26]

Peri-implantitis refers to an inflammatory reaction affecting the bone and tissue around dental implants. Peri-implantitis is a result of bacterial contamination and colonization of and around the implant surface.[27] Results of full PDT treatment with both photosensitizers and laser light has shown a significant reduction in bacterial load.[28]

3. Limitations of PDT

Although PDT has many benefits, adverse events have also been reported. Methylene blue when used as a PS in root canal therapy can cause tooth staining and discoloration.[29] Attempts have been made to conquer this shortcoming. It was concluded that 2.5% sodium hypochlorite when used at the time of root canal irrigation and preparation prevented tooth staining associated with the use of MB.[30]

Another drawback is that PS is viscous and can strongly penetrate dentin. A chemical smear layer may be formed that promotes occlusion of the dentin tubules, which may lead to microleakage and reduced adhesive strength of the root canal filling material to the dentin. Bacterial species and their mode of growth have been found to affect susceptibility to PDT in a dose-dependent way.[31] In addition, dentin, dentin matrix, dental pulp tissue, bacterial lipopolysaccharides, and bovine serum albumin can reduce the antibacterial effects of PDT.[32]

Furthermore, PDT is an ablative method and doesn't allow for histopathological diagnosis. Persistent cutaneous photosensitivity for several days with some PSs restricts PDT as a treatment option. Also, PDT has not shown much promise in treating big tumors. This is because light is unable to penetrate deeply into large pathologies. PDT also cannot be used to treat cancer that has already metastatized.[33]

4. Conclusion

Photodynamic antimicrobial therapy is a growing treatment modality, especially in scenarios where minimally invasive dentistry and prevention are at the forefront of dental goals. According to the available literature, the use of PDT in dentistry is promising and can be considered in the prevention and management of oral diseases, both as a sole therapeutic agent and as a complementary tool.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Sachdeva A. Photodynamic therapy in dentistry: A literature review. *J Dent Panacea* 2023;5(1):17-20.