Photodynamic Therapy - A New Ray of Hope in Periodontics

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ABSTRACT

Microbial biofilm in the oral cavity is the primary etiology for periodontal disease. It has been found that the growth of bacteria in dental plaque biofilm imparts to them an increased resistance to antimicrobial agents as compared to bacteria grown in suspensions and adherent cultures. Hence there is pronounced interest and keenness for the development of alternate therapeutic modalities, one such approach is the photodynamic therapy (PDT). This review provides an overview of PDT in the management of periodontal disease. Also new frontiers of antimicrobial PDT research have been discussed. Thus, the available knowledge of PDT should encourage a more clinically oriented application of this technique.

Keywords: Antimicrobial Therapy, Bacterial Resistance, Periodontal Disease, Photodynamic Therapy, Photosensitizers.

INTRODUCTION

Periodontal disease is a chronic inflammatory disease resulting in destruction of the supporting structures of teeth in response to various periodontopathogens.[1] Conventional periodontal therapy is unable to completely remove all pathogens, partially due to the various tooth-related anatomic factors such as furcation, cervical enamel projection etc.[2] Also these pathogens have been found to invade the pocket lining epithelium and the adjoining connective tissue.[1,4] The major drawbacks of adjunctive chemotherapy are the difficulties experienced in maintaining stable therapeutic concentration and the strong possibility of the development of resistance to antibiotics by the target organisms.[3]

The origin of light as a therapy in medicine and surgery has been traced from antiquity to the modern day. Phototherapy began in ancient Greece, Egypt and India, but disappeared for many centuries. At the beginning of 20th century it was rediscovered by the Western civilization. The use of contemporary photodynamic therapy was first reported by the Danish physician, Niels Finsen in 1901.[4] He successfully demonstrated photodynamic therapy by employing heat-filtered light from a carbon –arc lamp [also known as The Finsen lamp] in the treatment of a tubercular condition of the skin known as lupus vulgaris.[4] Raab et al. first showed the killing of protozoa paramecium caudatum in the presence of acridine orange when irradicated with light in the visible range of the light spectrum.[5]This combination of two non-toxic elements-dye and light- in an oxygenated environment includes damage and total destruction of microorganism. In 1904, Jodlbaner and Von Tappeiner coined the term photodynamic to describe oxygen-dependent chemical reactions induced by photosensitization which could inactivate bacteria.[6] Photodynamic therapy[PDT] has emerged in recent years as a non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi and viruses.[7]

Photosensitizers

The first approved photosensitizer was Hematoporphyrin derivative for the treatment of refractory superficial bladder cancer.[8] Antimicrobial photosensitizer such as porphyrins, phthalocyanines and phenothiazines [eg: toluidine blue O and methylene blue] which bear a positive charge, can directly target both gram-negative and gram-positive bacteria. Following exposure to light, the activated photosensitizer [in the exited triple state] can follow one of the two pathways[9] (Figure 1).

The type I pathway involves electron –transfer reactions from the photosensitizer triple state with the participation of a substrate to produce radical ions that can react with oxygen to produce cytotoxic species, such as superoxide, hydroxyl and lipid-derived radicals.[10]

The type II reaction involves energy transfer from the photosensitizer triplet state to ground state molecular oxygen to produce exited state singlet oxygen, which can oxidize many biological molecules such as protein, nucleic acid and lipid and leads to cytotoxicity.[11] Singlet oxygen, probably the major damaging species in photodynamic therapy has a diffusion distance of approximately 100nm and a half-life of<0.04 µs.[12] The various photosensitizers and their clinically used treatment kits have been elaborated in table 1.

Ideal properties of photosensitizer for antimicrobial photodynamic therapy[13]

1. A high quantum yield of triplet state to obtain large concentration of the activated drug.
2. High singlet oxygen quantum yield
3. High binding affinity for microorganisms.
4. A broad spectrum of action.
5. Low binding affinity for mammalian cells to avoid the risk of photo destruction of host tissues.
6. Low propensity for selecting resistant bacterial strains.
7. Minimal risk of promoting mutagenic processes
8. Low chemical toxicity.

Applications of photodynamic therapy

Photodynamic therapy due to its antimicrobial effects has been tested in various periodontal diseases.

1. Chronic Periodontitis

In the early 1990s, Dobson and Wilson showed that low level helium-neon laser irradiation with toluidine blue O or methylene blue was effective for killing P. gingivalis, F. nucleatum, A.

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actinomycetemcomitans and S.sanguinis.[14] Analysis of a number of in vitro studies supports the contention that antimicrobial photodynamic therapy with specific photosensitizer and light source is effectively bactericidal for periodontal pathogens.[15,16] Recently, several animal studies have been performed to help clarify the clinical response to antimicrobial photodynamic therapy in chronic periodontitis.[17,18] These animal studies carried out in ligature-induced periodontitis have reported reduction in microbial load following antimicrobial photodynamic therapy.[17,18] In vivo studies have proven its effects in suppressing periodontopathogens, reducing signs of inflammation and its safety aspect.[17,18]

Clinically in several randomized controlled trials carried out in chronic periodontitis patients, antimicrobial photodynamic therapy along with scaling and root planing (SRP) has been compared with SRP alone in chronic periodontitis patients. These studies report improvement in clinical parameters either similar to SRP or comparatively better than conventional therapy.

2. Aggressive Periodontitis

Photodynamic therapy as an adjunct has been found to be effective in treatment of aggressive periodontitis. Goulart R de et al. evaluated the photo inactivation of A. actinomycetemcomitans by RB [Rose Bengal dye] in planktonic and biofilm cultures. The PDT caused 45% of reduction in the biofilm without damage to the gingival fibroblast cells. The reduction of bacteria was dependent on RB concentration and irradiation time. The MB and Er:YAG [methylene blue and Erbium Yttrium Aluminium Garnet] have been also effective against A. actinomycetemcomitans. However, Er:YAG is more efficient at killing these bacterial cells in planktonic [75%] and biofilm [77%] than MB [50 and 54% respectively].In summary, RB, Er:YAG or MB could be an efficient option for pocket decontamination in aggressive periodontal diseases.[26]

de Oliveira RR et al. conducted a clinical study in ten patients with a clinical diagnosis of aggressive periodontitis. They were treated in a split-mouth design study to either photodynamic therapy[PDT] using a laser source with a wavelength of 690 nm associated with phenothiazine photosensitizer or scaling and root planning[SRP] with hand instruments and evaluated in terms of clinical outcomes after 3 months evaluation, the plaque scores were reduced and remained low throughout the study. A significant reduction of gingival index and bleeding index occurred in both groups after 3months.[27]

Photosensitizer	Commercially available treatment kits
Methylene blue	Periowave
Phenothiazine chloride	Helbo, photodynamic system GmbH and Co. KG, Grieskirchen, Austria.
Toluidine blue O	Denfotex Ltd, Dexcel pharma technologies Ltd.

Table-1: The Various Photosensitizer In Clinical Use Along With Their Treatment Kit.[9]

3. Peri-implantitis

Recently, several studies carried out on the contaminated dental implant surface have demonstrated bactericidal and detoxification effects of high-level lasers on the contaminated dental implant surface. In an in vitro study, Hass et al. examined the efficacy of antimicrobial photodynamic therapy in killing of bacteria associated with peri-implantitis, such as A. actinomycetemcomitans, P. gingivalis or P. intermedia, which adhere to titanium plates with different surface characteristics.[28] Hayek et al. compared the effects of antimicrobial photodynamic therapy [paste-based Azulene+50 mW diode laser] in dogs with ligature- induced peri-implantitis with that of a conventional technique, which included mucoperiosteal flap surgery and irrigation with chlorhexidine.[29]

In a clinical case-series study, Haas et al. investigated the clinical effects of treatment with antimicrobial photodynamic therapy [toluidine blue O + diode laser] in combination with guided bone regeneration using autogenous bone graft on 24 patients. They reported that 21 implant out of 24 showed improvements in the bone defects after a mean observation period of 9.5 months.[30]

Risks and Precautions of PDT

There are various risks associated with this therapeutic modality

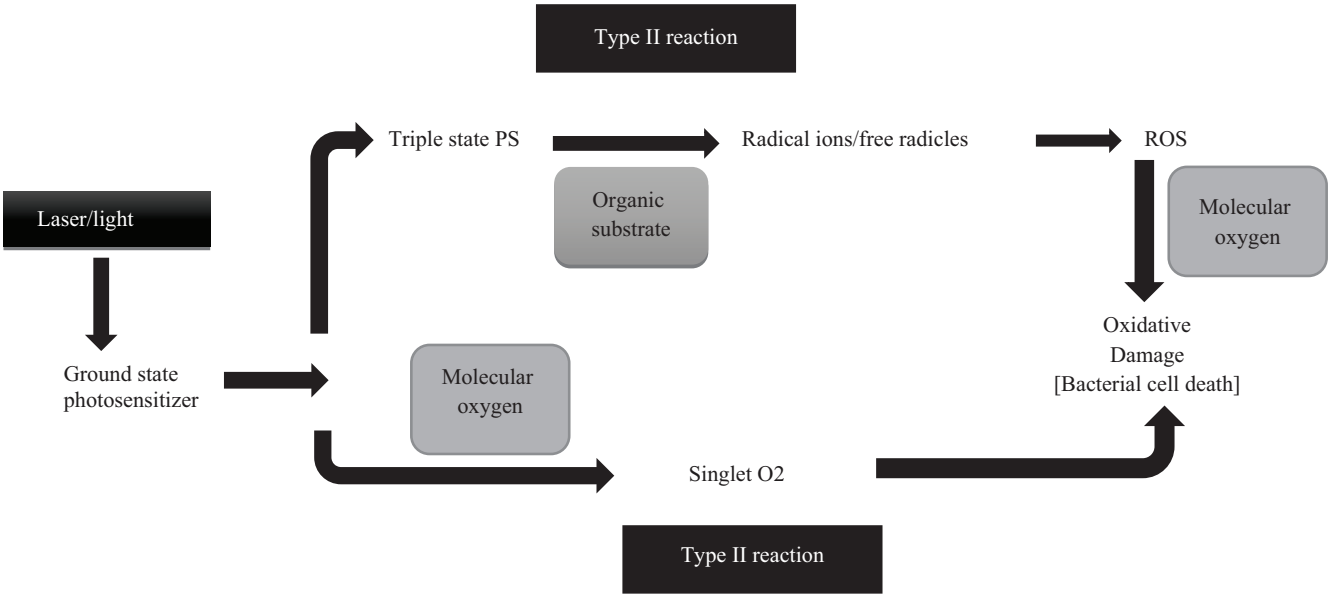

Figure-1: Mechanism of Photodynamic Therapy

Auther and year [reference]	Type of study	Light [wave length]	Photosensitizer	Light parameters and time of exposure method of irradication	Period of Observation	Results
Yilmaz et al. 2002[19]	RCT	Diode laser (685 nm)	MB	30 mW (5 Hz), Pulsed 71 s per each papillary region over gingiva	32 days	No additional clinical and microbiological improvement
Andersen et al. 2007[20]	RCT	Diode laser (670 nm)	MB (Periowave Kit)	150 mW, CW 60 s per site into periodontal pockets	3 months	Significant clinical improvements over SRP
Christodoulides et al. 2008[21]	RCT	Diode laser (670 nm)	MB (Helbo Blue Kit)	75 mW 60 s per tooth into periodontal pockets	6 months	PD reduction and CAL gain comparable to SRP Significantly higher reduction in BOP than SRP
Compos GN et al. 2013[22]	RCT	Diode laser [660]	MB	60 mw 60 s per tooth into periodontal pocket	3 months	Significantly higher PD reduction and CAL gain compared to the sites treated by conventional SRP alone.
Luchesi VH et al. 2013[23]	RCT	Diode laser [660nm]	MB	60 mW 1 min per site into periodontal pocket	6 months	No clinical benefits for class II furcation, but reduction in pro-inflammatory cytokines and a reduction in periodontopathogens
Betsy J et al. 2014[24]	RCT	Diode laser [655nm]	MB	60 Mw 60 s into periodontal pocket	6 months	Significant reduction in PD and gain in CAL
Carvalho VF et al. 2015[25]	RCT	Diode laser [660 nm]	MB	40 Mw 90 s per site in to periodontal pocket	9 months	No significant differences between test and control group.

CAL, clinical attachment level; PD, probing depth; RCT, randomized clinical trial; SRP, scaling and root planing

Table-2: Clinical Studies of The Application of Photodynamic Therapy as an adjunct to SRP in Treatment of Chronic Periodontitis.

if adequate care is not taken. Table 3 elaborates the various risks and precautions associated with photodynamic therapy

Current status of antimicrobial PDT

PDT has the potential to be a popular treatment option in periodontology and implantology due to the comparatively low cost of this therapeutic modality.[4] Antimicrobial PDT ensures minimal systemic side effects due to local administration.[9] Since, the drug is applied in high concentration locally it most likely ensures complete bacterial elimination. On interpreting the data from the various above mentioned clinical studies, it becomes obvious that in patients with chronic periodontitis, aggressive periodontitis and peri-implantitis, the adjunctive use of PDT to scaling and root planing may result in significant bacterial reduction.[4] Also, significant reduction in gingival inflammation and clinical attachment level gains has been reported.

Antimicrobial PDT appears to be promising however its parameters for optimal results is still unclear. There is a wide range of options available for photosensitizers and light source. However, the ideal combination of photosensitizer and light source which ensures complete removal of periodontopathogens clinically is not yet proven. It is still unclear whether the light source or the photosensitizer is more important. The ideal duration of light source and quantity of photosensitizer for significant clinical effectiveness is also still unclear.

The bactericidal effects of PDT on periodontopathogens has already been established. However the effect of this treatment modality on beneficial oral commensals is yet to be understood. Another drawback is that, temporary pigmentation

Risks and precautions associated with photodynamic therapy 9	
Potential risks • Excessive tissue destruction by direct ablation and thermal side effects. • Destruction of the attachment apparatus at the bottom of pockets • Excessive ablation of root surface and gingival tissue within periodontal pockets. • Thermal injury to the root surface, gingival tissue, dentin, pulp and bone tissue.	Precautions before and during Irradiation • Use glasses for eye protection (patient, operator and assistant) • Prevent inadvertent radiation (action in noncontact mode) • Protect the patient's eyes, throat, and oral tissues outside the target site. • Use of wet gauze packs to avoid reflection from shiny metal surfaces. • Ensure adequate high- speed evacuation to capture the laser plume

Table-3: Risks and precautions associated with photodynamic therapy

has been reported with PDT application.[5] Furthermore, it is difficult to clear the photosensitizer dyes from periodontal pockets.[5] The long term impact of photosensitizer dyes on periodontal tissues is still unclear. Therefore future studies are required to make PDT a safe and effective means for treatment of periodontal diseases.

New Frontiers in Oral Antimicrobial Photodynamic Therapy

Since complex oral biofilms have limited susceptibility to antimicrobial photodynamic therapy the development of novel delivery and targeting approaches is essential. Recent innovations in the field of antimicrobial photodynamic therapy have been discussed below.

1. Phototherapy

In the oral black –pigmented species, the application of photosensitizer may not be required because photosensitizer occurs naturally in this species. Studies have shown that visible light ranging from 380 to 520 nm was able to achieve a threefold reduction in the growth of P. gingivalis, P. intermedia, P. nigrescens and P. melangencia in dental plaque samples obtained from human subjects diagnosed with chronic periodontitis.[9] Inactivation of black-pigmented bacteria by visible light has also been reported by other investigators.[11]

2. Antibody-targeted antibacterial approaches using photodynamic therapy

Antibodies conjugated with photosensitizer have been used to target staphylococcus aureus.[11] Selective killing of P. gingivalis was achieved in the presence of streptococcus sanguinis or in human gingival fibroblasts using a murine monoclonal antibody against P. gingivalis lipopolysaccharide conjugated with toluidine blue O.[9]

Recently gold nanoparticles were used as photo-thermal sensitizer which were conjugated to antibodies.[19] During irradiation the energy absorbed by these particles during irradiation was quickly transferred into heat and accompanied bubble-formation phenomena around the clustered nanoparticles, leading to irreparable bacterial damage.[9]

3. Nanoparticle –based antimicrobial photodynamic therapy

To overcome the incomplete penetration of methylene blue in oral biofilms has led to the development of new delivery systems that significantly improve the pharmacological characteristics of methylene blue.

Researchers recently proposed the encapsulation of methylene blue within poly D,L-lactide-co-glycolide [PLGA] nanoparticle [150-200 nm in diameter] that may offer a novel design of nano-platform for enhanced drug delivery and photodestruction of oral biofilm.[15] When the nanoparticles were incubated with cells, they showed a time-depended release of the PS, which then regained its phototoxicity and resulted in a activatable photodynamic therapy-nanoagent.[9] Nanoparticles were not internalized by microorganisms, but they were mainly concentrated on to their cell walls. This may have rendered the cell wall permeability to methylene blue released by the nanoparticles. This intracellular localization and the local surroundings of methylene blue influence the phototoxicity.

Ideal properties of nanoagent as photosensitizer[9]

- A large critical mass for the production of reactive oxygen species that destroy cells.
- It limits the ability to pump the drug molecules back out and reduces the possibility of multiple drug resistance.
- Selectivity of treatment by localized delivery agents, which can be achieved by either passive targeting or by active targeting via the charged surface of nanoparticles.
- The nanoparticles matrix is immunogenic.

CONCLUSION

Antimicrobial photodynamic therapy seems to be a promising tool in the treatment of periodontal disease. The results of a number of in-vitro studies clearly demonstrate the significant bactericidal effect of antimicrobial photodynamic therapy. However, sufficient clinical and microbiological data that support the superior effects of the adjunctive use of photodynamic therapy have not been demonstrated clinically in either periodontal or peri-implant therapies. The discrepancies in the results obtained from previous clinical studies is being speculated to be due to a number of reasons. However recent innovations in photodynamic therapy seem to be promising. Further, randomized long-term clinical trials and meta-analyses are necessary to demonstrate the role of photodynamic therapy in the management of chronic periodontitis.

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