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Light in the Horizon: A Perspective on Photodynamic Therapy

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Review

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ABSTRACT

Dental treatment, in general, has been associated with fear and anxiety. The prospect of undergoing a painful experience compels many prospective patients to postpone his/her dental appointment. A previous occurrence of the distressful event has often left patients traumatized. Repeated visits for follow-up treatments also serve as a deterrent for seeking dental consultation. Alternative methods need exploration to mitigate such inconveniences.

Photodynamic therapy is emerging as an extension of dental therapeutic options with the benefits of improved treatment outcomes and patient acceptability. The present narrative review explores its applications in general dentistry and highlights its potential in the periodontal discipline.

Being minimally invasive, it offers promise in pain-free management of dental conditions, particularly infections. It has relevance in managing oral mucosal lesions, periodontitis, and dental caries. Current evidence suggests photodynamic therapy as an adjuvant to contemporary measures of dental rehabilitation.

Key words: Dental Caries, Lasers, Mouth Mucosa, Photodynamic Therapy, Periodontitis.

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Introduction

Periodontal disease is a chronic ailment affecting the tissues investing and supporting the dentition, leading to its progressive loss, with possible loss of teeth, related functions, and disfigurement. The disease is often attributed to the persistence of a sub-gingival biofilm on the tooth surfaces, harbouring numerous bacterial colonies, some commensal, some pathogenic and others opportunistic. This disruption of the local homeostatic balance unzips the tooth-soft tissue attachment creating a morbid pocket environment, favouring the colonization of several pathogenic bacterial species, most notably, *Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia* and *Tannerella forsythia*.[1] Consequently, features of periodontal breakdown ensue, such as gingival bleeding, exudation, loss of clinical attachment, root exposure, abscess formation and, in extreme cases, tooth exfoliation.

Periodontal treatment involves supra and subgingival tooth debridement, chemical lavage/irrigation solutions, and antimicrobial mouth rinses. Often, adjunctive systemically or locally delivered antimicrobials are also provided. Alternatively, resective or regenerative periodontal therapy focuses on altering the affected bone morphology and eliminating niches of microbial repopulation through surgical means, wherever warranted. Therefore, reducing the levels of these pathogenic bacteria is critical to improving periodontal health with these conventional strategies. However, uneven tooth morphology in furcation areas or root concavities often limits effective instrumentation. Likewise, the possibility of rising antibiotic resistance hinders widespread and frequent use of anti-infective therapy.

A low-intensity laser-based photodynamic treatment (PDT) is currently advocated for different therapeutic procedures in dentistry and medicine. This treatment modality directs light of a specific wavelength to the site of concern, where a previously applied photosensitizing agent is applied. Light activation of this agent generates free radicals and singlet oxygen, which would interact with bacteria and intracellular molecules that uptake the photosensitizer in surrounding tissues, obliterating them. Singlet oxygen produced in PDT appears to significantly induce tissue damage, with a 100 nm diffusion distance and half-life <0.04 µs.[2] Therefore, only cells in the vicinity are affected, without harming distant cells, suggesting the localized effect of PDT.

The concept of 'Photodynamic therapy' has evolved, spanning applications across various fields of dentistry, and aptly termed 'photo-activated disinfection.' Other synonymous terms include photodynamic disinfection, photodynamic antimicrobial chemotherapy (PACT) and light-activated disinfection (LAD).[3]

PDT detects premalignant oral lesions finding a place in treating oral cancer, and bacterial and fungal infections.[4] Other indications include actinic keratosis, severe lip

dysplasia due to nicotine abuse, psoriasis, Bowen's disease, Paget's disease, Kaposi's sarcoma, HIV-associated molluscum contagiosum and basal cell carcinoma.[5] PDT benefits cutaneous vascular malformations and patchy alopecia areata with excellent cosmetic results. It is proposed as an antimicrobial intervention for periodontitis due to its effects on microbial flora. The review examines photodynamic therapy, a new dimension in managing dental maladies. Further, the role of this emerging alternate therapy in periodontal treatment is discussed.

Principles of functioning of PDT

PDT involves photosensitizers triggered by a source of light.

Photosensitizer

The photosensitizer can be a dye or chemical that absorbs specific wavelengths of light energy and passes it on to nearby molecules. Hematoporphyrin derivatives have been the first generation of photosensitizers. Porphyrin-based dyes (like Photofrin) have a characteristic tetrapyrrole ring structure, termed porphyrin. Others include chlorophyll-based photosensitizers, such as chlorins and bacteriochlorins, having reduced double bonds, while dyes like phthalocyanines and naphthalocyanines have an extended ring structure. A Soret band around 400 nm and 500 – 600 nm characterizes these photosensitizers.[6]

Subsequent second-generation photosensitizers or benzoporphyrin derivatives (with absorption at 650 to 800 nm) have good tissue penetration.[7] Examples include 5-aminolevulinic acid and Focsan. However, caution must be exercised during use as even minimal lighting can lead to severe skin photosensitivity and pain during therapy.

Methyl aminolevulinate (Metvix) 5-aminolevulinic acid (ALA or Levulan) and Porfimer sodium (Photofrin) are Food and Drug Administration (FDA) approved photosensitizers.

Modifying the existing dyes by conjugating proteins, receptors or antibodies with radioactive tags or nanoparticles allowed the evolution of a successive generation of photosensitizers with the advantage of fluorescence, which helps in the detection of malignancy due to uptake by affected cells.[8]

Acridine orange, proflavine, riboflavin, fluorescein and erythrosine are another group of tricyclic dye photosensitizers. Another distinct variety is Psoralen and its derivatives (xanthotoxin, bergaptene) belonging to the furocoumarin group.[9]

Periodontal therapy employs phenothiazinium dyes (toluidine blue, methylene blue) to lower bacterial and fungal species. Curcumin is another agent used for PDT in dentistry.[10] Erythrosine and malachite green, used to disclose dental plaque, are photosensitizers.

Other photosensitizers with potential include chloro-aluminium phthalocyanine (AlClPc), methyl aminolevulinate, and poly-L-lysine-chlorine conjugates.[11, 12] Other photosensitizing agents used in periodontal therapy are phenothiazinium chloride and indocyanine green. Antimicrobials like tetracyclines show a photosensitizer effect by producing singlet oxygen.

Methylene blue, with an absorption peak at 670 nm (dark red), has effective light penetration, permitting access to deeper infection sites. Apart from its routine use as a marker dye, it has a role in detecting premalignant lesions. Therapeutically, it is safe for local application, as evident in PDT of bladder and oesophageal cancers. Anti-infective uses were demonstrated against *H. pylori* in the rat gastric mucosa and *Aggregatibacter actinomycetemcomitans* in dental biofilms.[13]

While light activation is unnecessary for Toluidine blue (Tolonium chloride or TBO), effective bacteria elimination occurs with concomitant exposure to a 630 nm laser. Hence, toluidine blue and methylene blue are appropriate for endodontic infections with diverse bacteria.[10]

The FDA has also permitted the use of the anionic, hydrophilic, and lipophilic 'indocyanine green' (ICG). ICG can be used in subgingival regions with anaerobic conditions, particularly in reducing *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans,* leaving less than 10% viable bacteria. With absorption around 800-810 nm, it is similar to Diode laser wavelengths, suggesting the combination to be synergistic in reducing periodontal pocket bacteria.[14] While visible light sources activate toluidine blue, methylene blue and malachite green, indocyanine green activates with near-infrared light.

Specific oral, black-pigmented bacteria have natural photosensitizers (protoporphyrin IX), making them amenable to PDT. Light in the range of 380 to 520 nm wavelength diminished *P. gingivalis P.intermedia, P. nigrescens,* and *P. melaninogenica* growth by almost three times within dental plaque.[15] Visible light used as PDT may have similar effects.[16]

Another photosensitizer proposed is curcumin, which has antimicrobial properties and is hydrophobic. It can absorb blue light and produce reactive oxygen species. It has peak absorption at 430 nm. Further, when exposed to blue light, riboflavin, a vitamin B2 supplement, is also considered a biocompatible photosensitizer, which does not discolour the teeth like toluidine blue.[17]

Light Source

PDT uses either noncoherent or coherent laser light as a source of activation.[18] Noncoherent light sources include lamps with a tungsten filament, sodium pump, quartz halogen, and metal halide, providing diverse wavelength spectra. However, neither the dose of light delivered can be controlled nor the associated thermal effects are lessened. Recent LED light sources are attractive as they can be custom-assembled to produce light of desired wavelengths.

Laser light, in contrast, is a coherent source of energy of a specific wavelength only delivered to target sites over optic fibre cables and through lenses customized to achieve homogenous illumination. For PDT, laser light wavelengths of 633 nm (Helium-neon), 630–690/ 830/ 906 nm (gallium-aluminium-arsenide), and 488–514 nm (argon) are often employed.[19] Diode lasers offer advantages in ease of use and portability and are therefore preferred.

Certain factors affect the effectiveness of PDT after the photosensitizer has been applied and light directed at the treatment site. Fluence (radiant energy), light wavelength (long/short) and the availability of oxygen, the molar extinction coefficient of the photosensitizer,

photosensitizer concentration, type, location of the photosensitizer and incubation time are some of these determinants.[20] Long wavelengths of light have a deeper penetration. The presence of adequate amounts of dye ensures effective antibacterial action. Red light (630-700 nm) is adequate for most photosensitizers, achieving a light penetration depth of 0.5 – 1.5cm. This distance defines the therapeutic effect, usually via cell death resulting from autophagy, apoptosis, or cellular necrosis.

General applications of PDT

PDT initially found scope in treating viral lesions like herpes keratitis and genital herpes (PDT using methylene blue/neutral red), although recurrence could not be prevented. It is also used to manage HPV-related lesions like epidermodysplasia verruciformis, papillomatosis and warts. Hematoporphyrin ester activated by a 630 nm laser improved cervical intraepithelial neoplasia and eradicated HPV.[21]

Skin lesions have been the primary focus of PDT, with a substantial role in treating lesions such as wrinkles, rosacea, hidradenitis suppurativa, actinic keratosis, non-melanoma skin cancer, and psoriasis. In actinic keratosis, a 20% topical solution of Aminolevulinic (Levulan ®, DUSA Pharmaceuticals, Inc., Wilmington, MA 01887, USA) is applied for 14–18 hours, followed by blue light illumination (417–432 nm) of the target lesions. Acne, leishmaniasis and fungal skin infections have also been treated with ALA–PDT. Indocyanine green dye and chlorophyll are other photosensitizers used for acne.[22, 23] Rosacea, erythrasma, tinea pedis, tinea cruris, toenail onychomycosis, Malassezia folliculitis, and Pityriasis versicolor have all shown improvement with PDT.[24]

Ophthalmologic conditions requiring PDT include macular degeneration and pathologic myopia. Verteporfin (trade name Visudyne®, CHEPLAPHARM Arzneimittel GmbH, Ziegelhof 23-24, 17489 Greifswald, Germany) has been reported as the accompanying photosensitizer administered intravenously.

Porfimer sodium, a hematoporphyrin derivative, is commonly used in oncology to treat lung cancer (non-small cell) and oesophageal pre-cancer and cancer. Another potent photosensitizer is temoporfin (brand name Foscan® (biolitec Pharma Ltd., Otto-Schott-Str. 15, 07745 Jena, Germany), which is required in small doses (0.1 mg/kg body weight) with low doses of light energy (10 J/cm^2). These photosensitizers selectively accumulate in tumour regions, allowing cell and tumour apoptosis during PDT. Gross oedema and erythema are the first clinical signs of PDT response.[25]

Deep tissue abscesses are polymicrobial infections where prolonged antibiotic use may result in the development of resistance. Hence, photodynamic therapy can be an option as it is effective against many microorganisms.

Acinetobacter baumannii infections and *Pseudomonas aeruginosa* are important pathogens posing a life-threatening risk in burn patients. Photodynamic therapy can be effective against these bacteria with fewer side effects without posing a risk of drug resistance.[26]

Diagnosis and treatment of dental disease

i. Oral premalignant lesions

PDT causes superficial necrosis of the oral mucosa, with minimal scarring and no toxicity, when using 5-ALA for treating oral leukoplakia. Maloth *et al.* (2016) compared PDT outcomes in oral leukoplakia and lichen planus lesions. They used blue light LED (420 nm) with 5-ALA to provide around 500 mW/cm^2 intensity to a spot size of 1 cm^2 for 10 mins over lesions and surrounding tissue. In cases of oral leukoplakia, 16.6% showed complete response, with 66.6% showing partial response. Similarly, in oral lichen planus cases, 80 % of cases showed partial response. Therefore, PDT promises to be an option for premalignant lesions.[27]

ii. Oral candidiasis

In a study by Scwingel (2005) on HIV-infected patients, PDT for ten seconds [660 nm, 30 mW power, 7.5 J/cm^2 fluence, in contact mode] eradicated 100% of candidiasis colonies with no recurrence when observed for a month. The comparator, Fluconazole, could not prevent the recurrence of candidiasis.[28] Fungal infections in the oral cavity requiring PDT use toluidine blue, porphyrins, and methylene blue as photosensitizers and 455 nm–660 nm diode lasers.[29]

Carmello *et al.* (2016) found PDT with red LED light at 660 nm and photodithazine® as effective as nystatin treatment for treating oral candidiasis in a study on female mice.[30] Using 660 nm red light with InGaAIP laser inactivated oral Candida from those with children and without almost comparably, with methylene blue photosensitizer.[31]

iii. Restorative dentistry

Antibiofilm effect:

Bacterial elimination within carious lesions can be achieved non-invasively with PDT. In an animal study, samples of *S. mutans* were observed at various intervals before and after photosensitization with methylene blue (100 µM for 5 min). Bacterial counts were notably lower than in controls treated without PDT.[32]

Photodynamic treatment with erythrosine resulted in bacterial cell death in *S. mutans* biofilms *in vitro*.[33] Similarly, red light and Toluidine blue significantly reduced cariogenic bacteria within dentine caries.[34]

Nassaj *et al.* (2020) suggested using PDT with indocyanine green to manage micro-leakage in composite restorations. It could disinfect cavities within enamel and cementum by decreasing the microbial load and preventing secondary caries.[35]

Endodontics:

Photodynamic treatment synergizes with the antimicrobial intra-canal cleaning and shaping in conventional endodontics to kill microorganisms in root canals, which is particularly relevant in single-session endodontic therapy. There are reports of toluidine blue with red light and urea peroxide for sterilization of root canals of deciduous teeth. The instrumentation alone reduced viable bacteria by 82.59%, while using PDT resulted in a 98.37% decrease in bacterial load.[36] Bonsor *et al.* (2006) found PDT to be as efficacious as the combination of NaOCl and citric acid irrigation after root canal

biomechanical preparation.[37] Similarly, Borba *et al.,* (2017) observed that LED with erythrosine eliminated almost all planktonic forms of *Enterococcus faecalis*.[38]

Contradictory reports state no significant additional effect of PDT on chemo-mechanical preparation in reducing bacterial counts due to low oxygen concentration within the root canal irregularities, dentinal tubules, or bacterial biofilms on the canal walls. Complete photosensitizer permeation into the root canals is uncertain and may diminish the outcome of root canal treatment. Some reports suggest that 17% EDTA irrigation before PDT overcomes this limitation.[39]

Factors considered critical for intra-canal microbial killing using PDT include the energy and time of irradiation. Pourhajibagher & Bahador (2018) utilized a 635 nm wavelength laser for 60 s at a power of 220 mW to obtain a significantly diminished microbial count.[40] Therefore, sufficient time for photosensitizer uptake by the microorganism is necessary to achieve either cell wall damage or nucleic acid breaks.[41]

Periapical surgery:

PDT had shown accelerated healing of periradicular lesions in the maxillary incisors when PDT was used along with methylene blue. It is opined that red laser light enhances bone repair.[42]

Peri-apical cysts:

Conventional root canal therapy is ineffective in managing periapical cysts. Hasna *et al.* (2019) report on administering root canals with methylene blue for 5 min and irradiation with a 660 nm red laser at 100 mW/cm^2 for 2 minutes, allowing approximately 120.0 J/cm^2 of energy density into each canal. Subsequently, Ca $(OH)_2$ paste is placed into the root canals with laser radiation repeated twice weekly for 45 days. They suggested that this combination strategy caused remission of clinical signs and symptoms, with evidence of bone repair, thus averting the need for surgical therapy.[43] Similarly, the strategy may effectively manage alveolar osteitis and pain related to the extraction.

iv. Pediatric Dentistry

Conservation of deciduous teeth with pulpal involvement is challenging. In this context, antimicrobial photodynamic therapy promises to eliminate persistent microorganisms following chemo-mechanical preparation.

Methylene blue with papain has been used to treat deep caries in a primary tooth, along with caries excavation, and 660 nm red laser PDT with 30 J of energy and 100 mW power for 5 mins before restoring it with glass ionomer. Using the photosensitizer prevented pulp exposure and preserved tooth structure.[44]

Pourhajibagher & Bahador (2018) noted decreased microbial counts within infected root canals of primary teeth when PDT was used with toluidine blue.[45] Barbosa *et al.* (2014) suggested the use of methylene blue for root canal decontamination (50 μg/mL for 3–5 minutes; energy density 40 J/cm^2), with the benefit of reduced treatment time in children using lasers.[46]

Anand *et al.* (2020) observed that PDT for pulp therapy in deciduous molars obtained similar results to sodium hypochlorite and clotrimazole disinfection, with comparable postoperative *C. albicans* colony-forming units.[47]

v. Oral surgery

Camilo-Silva *et al.* (2021) report PDT used for treating alveolar osteitis. Curettage of the alveolus was done under local anaesthesia. Next, methylene blue photosensitizer was syringed into the alveolus for 5 mins. Then, laser light of 660 nm was irradiated with a 321 J/cm^2 dose for 90 seconds (100 mW power, radiance energy 9 J, spot area 0.028 cm^2) and repeated after seven days. Closure of the alveolus with no inflammation was noted within fifteen days.[48]

Sarkarat *et al*. (2019) demonstrated that PDT assisted subsidence of symptoms related to bisphosphonate-related osteonecrosis of jaws (BRONJ). Twenty rats received zoledronic acid for five weeks and then underwent extraction. The PDT-treated group showed decreased bone exposure and clinical inflammation, and a higher percentage of healthy bone with neovascularization histologically compared to controls.[49]

Almeida *et al.* (2021) used adjunctive PDT in the management of bilateral medication-related osteonecrosis of the jaw (MRONJ) in the tuberosity of a breast cancer patient on zoledronic acid. The laser device (gaAIAs and InGaAIP) used continuous wave mode with 100 mW power settings and 0.03 cm^2 spot size. The injury site received a red wavelength (660 nm), emitted for 90 seconds, providing 9 J of energy, with a methylene blue gel photosensitizer. About twelve PDT sessions, with 48-hour intervals, facilitated reducing the symptoms and resolution of the lesion.[50]

vi. Periodontal therapy

PDT has relevance in managing periodontal disease, particularly in the initial phase and during recall maintenance. A decreased oxygen tension and pH alteration during inflammatory soft tissue changes allow the flourishing of anaerobic bacteria within the periodontal pocket. Photodynamic treatment improves tissue vascularity and oxygen perfusion to enable the resolution of inflammatory changes. Furthermore, it is effective as adjunctive antimicrobial therapy or Photodynamic antimicrobial chemotherapy (PACT). Using photosensitizers reduces and allows the localization of action within disease sites. Low levels of laser energy enable hemostasis, minimizing perceived pain and enhancing healing.

PDT and periodontal clinical parameters

PDT preserves cementum by reducing the need for aggressive root planing, thus enhancing tissue attachment to root surfaces and deterring hypersensitivity.[51] The antibacterial effects of PDT have a bearing on those who are immunosuppressed or show antibiotic resistance.

Braun *et al.* (2008) observed toluidine blue with PDT (670 nm laser, 100 mW/cm^2) to significantly improve the outcome of subgingival debridement.[52] A considerable diminishing of gingival bleeding after probing has also been noted in periodontal sites treated with PDT versus scaling and root planing (SRP).[53] Photodynamic therapy concomitant to SRP resulted in reduced probing depths and

better attachment gain up to twelve months compared to conventional nonsurgical treatment in another study.[54]

Clinical parameters such as the plaque index, gingival index, probing pocket depth, and clinical attachment loss were noted to improve with PDT. Similarly, microbiologic parameters were better in the group treated with scaling and root planing compared with SRP alone, with a single session of PDT in a study by Raj *et al* (2016).[55]

Malgikar *et al.* (2016) treated chronic periodontitis with a 980 nm Diode laser, methylene blue photosensitizer, and LLT. They observed reduced gingival bleeding and pocket depths with improved clinical attachment in the SRP, PDT, and low-level laser treatment groups compared to SRP and PDT combined and SRP alone.[56]

Martins *et al.* 2017 noted significant pocket depth reduction and greater elimination of the red complex periodontal pathogens with a single application of Diode laser and phenothiazine at three months post-surgery.[57]

Shignapurkar *et al.* (2017) used an 810 nm laser with indocyanine green as a photosensitizer. The combination significantly improved probing depth and relative attachment levels at three months compared to scaling and root planing alone.[58]

Similarly, Sethi *et al.* (2019) showed a reduction in clinical parameters in thirty subjects treated with scaling and root planing along with PDT compared with SRP as a monotherapy, when indocyanine green was used as the photosensitizer along with 810 nm Diode laser. They also observed a reduction of bacterial colonies within the pockets.[59]

Sgolastra *et al*., however, in a meta-analysis, suggest only short-term benefits occur, like reduced pocket depths and gain in clinical attachment with PDT when used in addition to conventional periodontal treatment.[60] A systematic review by Chambrone *et al.* (2018) suggests PDT provides a significant reduction in probing depth and attachment loss unlike conventional periodontitis and peri-implantitis treatment protocols.[61] Meimandi *et al.*[62] (2017) surmised from a review that multiple sessions of PDT would be more beneficial than a single PDT session. In the meta-analysis by Azaripour *et al.*[63] (2018), PDT adjunctive to scaling/root planing results in 0.21 mm probing depth reduction and 0.36 mm gain in attachment by three months itself unlike that achieved conventionally by around six months.

Yet contrasting reports suggest beneficial effects in terms of bleeding on probing only with no changes in the probing depth or attachment levels when photodynamic therapy is used as an adjunct to scaling and root planing.[64] Azarpazhooh *et al.*[65] (2010), in their systemic review, opined no superiority of PDT alone to the nonsurgical phase of periodontal therapy.

When smokers with chronic periodontitis received phase 1 periodontal debridement with or without a single session of antimicrobial photodynamic therapy (phenothiazine photosensitizer), the observed clinical probing depth and attachment improvement seen within the groups did not extrapolate to between-group comparisons. A slight benefit was perceived with suppression of GCF IL-1beta and IL-8 in the PDT group.[66]

Therefore, antimicrobial PDT shows clinical benefits in the short term. Presently, there needs to be more consistency in the results of long-term evaluations. Nevertheless, PDT may be an option for those who do not prefer extended periodontal surgical procedures.

PDT and periodontal microbes

Periodontal pathogens within a biofilm are vulnerable to PDT with photosensitizers like methylene blue, indocyanine-green, phthalocyanine, safranine O, toluidine blue and hematoporphyrin.[67] Laser wavelengths ranging from 380 nm-520 nm can inhibit the growth of dental plaque bacteria by almost threefold, including *Porphyromonas gingivalis*, *P. intermedia*, *Prevotella melaninogenica* and *P. nigrescens.* While PDT killed 63% of bacteria in planktonic conditions, this effect reduced the plaque biofilm to 31%, attributed to the protective phenotype observed with tooth attachment.[16]

Dental plaque biofilm treated with photosensitizer and PDT are relatively thin and less dense, with fewer channels. Such biofilms showed bacterial membrane damage and cytoplasmic vacuoles after PDT.[68]

Light wavelength and energy density can influence the extent of bactericidal activity. Diode lasers at 665 nm and 830 nm using methylene blue photosensitizer carrying an energy density of 21.2 J/cm^2 almost eliminated black-pigmented bacteria (*P. gingivalis* and *P. intermedia*) and *S. sanguis,* and 95% of *A. actinomycetemcomitans* and *F. nucleatum.*[69]

Pinheiro *et al.* 2009 observed that 81.24% of bacteria within periodontal pockets reduce after scaling compared to 95.90% with adjunctive photodynamic therapy (Diode laser energy of 4 J/cm^2 for 3 mins). Therefore, photodynamic therapy proved effective clinically in affecting viable bacterial counts.[70] However, another study showed that treatment with PDT resulted in 80.11% and 91.37% bacterial count reduction after one month and three months.[52]

A systematic review by Akram *et al.* (2016) evaluated seventeen clinical studies with wavelengths ranging from 470 – 810 nm. Follow-up visits in these studies showed reduced microbial counts with PDT.[71]

Another study compared antimicrobial PDT and locally placed minocycline microspheres in deep periodontal pockets. Although clinical and microbiological parameters improved from the pretreatment status, no additional influence of either PDT or minocycline was apparent compared to SRP alone.[72] Furthermore, photosensitizer application may not be required in all instances, as several oral bacteria naturally possess photosensitizer.[16]

PDT and periodontal structure

A 70 ^{0}C increase in the temperature of periodontal tissues defines the threshold limit to avoid periodontal tissue damage.[73] Further, the light dosage intended for bacterial killing does not induce host cell photo-cytotoxicity as the dose falls below the toxicity of fibroblasts and keratinocyte cells.[74]

Qiao *et al*. (2014) showed PDT (Diode 675 nm, Pmax = 280 mW) produced no cytotoxicity on the human periodontal ligament and gingival fibroblast cells. It was observed to stimulate fibroblast proliferation, attachment, and collagen synthesis. Similarly, stimulative action on alkaline phosphatase activity of periodontal ligament cells was noted.[75]

Interestingly, Kashef *et al.* (2012) observed that exposure to a Diode laser (660 nm, 35 mW, 163.8 J/cm^2) and methylene blue reduced human fibroblast mitochondrial activity by 27%, while the absence of photosensitizer showed no significant cytotoxicity. Similarly, a 630 nm Diode laser exposure (46.8 J/cm^2 for 24 h) with toluidine blue photosensitizer resulted in the inactivation of 39.6% of the fibroblasts, unlike PDT without toluidine blue.[74] However, curcumin as a photosensitizer showed no cytotoxicity or inhibition of fibroblast viability during PDT.[76]

Red light (665 nm, 20 or 40 mW/cm^2, five minutes duration) with methylene blue photosensitizer showed moderate effects on osteoclasts, and no apoptosis was evident at 24 hours in a study by Xu *et al.*[77] (2009).

PDT, combined with low-level laser therapy (LLLT), manifested less bone loss in experimentally induced furcations compared to only LLLT or methylene blue photosensitizer in a study on rat models by de Almeida *et al.* 2008.[78] Hence PDT application can promote the healing of tissues following treatment.

PDT and Aggressive Periodontitis

Chatzopoulos *et al*.[79] (2016) opine that for effectively treating aggressive periodontitis, repeat sessions of PDT application along with nonsurgical treatment would be necessary. A study comparing clinical outcomes of PDT (690 nm laser, phenothiazine photosensitizer) vs SRP in ten aggressive periodontitis cases inferred similar efficacy of the two treatment modalities.[80]

PDT and Peri-implantitis

Peri-implantitis management warrants decontaminating the dental implant surface, often with mechanical methods or antimicrobial irrigation using chlorhexidine or hydrogen peroxide. PDT can also be combined with surgical exposure of the implant site to decontaminate the implant surface.[81]

Laser treatment of implant surfaces increases the temperature of the implant surface, regardless of whether photosensitizer is used or not. Nevertheless, this raised temperature is less than 4.3 ^{0}C. Therefore, tissues surrounding the implant are relatively safe during peri-implantitis treatment.[82]

According to Shibli *et al.* (2003), PDT reduced *Streptococcus beta hemolyticus, Fusobacterium* and *Prevotella* counts in most peri-implantitis samples. Azulene is an effective photosensitizer for microbial inhibition at peri-implantitis sites, with no staining of the adjacent soft tissues and implant surfaces.[83]

PDT with CO_2 laser around 'ailing' implants is reported as being more effective than conventional methods. Using 810 or 980 nm Diode laser wavelengths to decontaminate implant surfaces was effective, without any dramatic temperature increase.[84]

Pourhajibagher *et al.* (2020) found a reduction in bacterial counts by using 'photo-sonodynamic antimicrobial chemotherapy' (810 nm Diode laser) using an indocyanine-green photosensitizer with a nanoparticulate form of chitosan.[85]

According to a systematic review, adjunctive antimicrobial photodynamic therapy has benefits in reducing pocket depth and clinical bleeding on probing akin to established peri-implant treatment.[86]

PDT & healing of periodontal tissues

In an animal study, less alveolar bone loss with reduced cytokine production was evident with Toluidine-blue mediated-PDT [650 nm Diode] for four weeks.[87] PDT also tended to improve bleeding on probing with treatment. Further, enhanced gene expression of fibroblast growth factor (FGF2), receptor activator of nuclear factor-kappa B (RANK), and osteoprotegerin (OPG), was observed in biopsy samples, thus mitigating osteoclastogenesis and promoting periodontal repair.[88]

Procedure

Phase 1 debridement usually precedes photodynamic therapy. The periodontal pocket is flushed with a photosensitizer, allowing pigment uptake for one minute before laser radiation. This is followed by navigation of the laser tip into the pocket with exposure to an appropriate laser wavelength. The laser fibre is moved laterally within the pocket and drawn coronally upwards and out of the gingiva.

Similarly, for disinfection of root canals, after biomechanical preparation, photosensitizer irrigation allows contact with the bacterial biofilm. The laser tip is then introduced into the canal and irradiated for 30 seconds.

PDT guidelines have been given for oral mucosal application, such as in leukoplakia. PDT is advised to be carried out in a dark room or a strict light-proof environment. The site to be treated must be isolated from saliva. A cotton swab soaked with the photosensitizer solution is gently placed over the lesion. A starch film is placed over the cotton swab to improve the adhesion of the photosensitizer to the oral mucosa. Finally, the site is layered with a cling film and gauze to protect the photosensitizer from saliva and incubated for 2-3 hours.

After removing the swab, the site is tested by UV light (wavelength, 370–470 nm). The patient then rinses off the excess photosensitizer. Local anesthesia (2% lidocaine or 4% primacaine) is administered. The patient, clinician and assistant should wear safety goggles before laser irradiation. Laser power settings may be performed according to the literature. A power of 100 mW/cm^2 is recommended at 630 nm for 3 mins followed by 3 mins of rest. The laser beam is directed perpendicular to the surface of the lesion with an optimal distance between the end of the optical fibre and the surface of the lesion. Lasing can be repeated once in 2-3 weeks. Exposure of the treated site to light should be avoided for the next 48 hours. Irritable foods may be avoided during this period. Topical

0.01% dexamethasone paste and 0.1% chlorhexidine mouth rinse can be prescribed to reduce associated inflammation. The lesion should be treated once every 2–3 weeks, depending on the healing of the lesion.[89]

Advantages of PDT

As PDT is delivered to the target area through fiberoptic cables, where it provides concentrated light energy, it is safe for the healthy tissues nearby. Further, it does not require local anaesthesia. Unlike the usual antimicrobial regimen, the procedure eliminates bacteria quickly, with no added systemic toxicity. It is of particular benefit in areas difficult – to – access with mechanical instrumentation around the teeth, dental implants, and pockets like furcations and root concavities. There is no risk of bacteremia as well. The effects of nonsurgical therapy are hastened while precluding the need for root planing. It is a valuable tool during the maintenance recall phase, as biofilm removal in deep pockets can be achieved non-intrusively. It is a safer approach for systemically compromised patients and the geriatric population.

The Limitations of PDT

PDT may sometimes induce side effects like erythema, burns, oedema, and desquamation. Further, laser-induced tissue damage or nerve stimulation can result in pain. Rare instances of urticaria, contact dermatitis, erosive pustular dermatosis, and squamous cell carcinoma have been observed during skin lesion treatment. Some reports also suggest that PDT causes DNA alterations. Photophobia, scars, allergic reactions, sensitivity to sun exposure and hyperpigmentation/hypopigmentation are other unwanted effects of PDT. Thermal injury due to increased temperature changes within tissues can cause irreversible damage to the gingival tissues, root surface [with attachment loss], dentin, pulp, and bone. The type of bacterial species present, the dosage of photosensitizer and laser light parameters such as depth of penetration may impact the effectiveness of PDT. [90]

Methylene blue can stain the teeth. Extending the irradiation time beyond five minutes allows deep penetration of the photosensitizer almost to the enamel–dentine interface.[91] Often irrigants, bleaching agents (2.5% NaOCl), solvents, photosensitizer efflux pump inhibitors, chitosan nanoparticles and ultrasonics have been used to remove this discolouration.[92] Methylene blue, a non-porphyrin dye, has inherent cytotoxicity by methylation and localizes intracellularly in the cytoplasm targeting the nucleus and mitochondria, promoting apoptosis. When used for clinical indications other than PDT, it has been shown to lead to blue-green discoloration of urine. It is advised to use caution when using methylene blue along with serotonergic drugs and in those with renal failure. It is known to cause central nervous system-related symptoms like dizziness and headaches. It is contraindicated in those with hypersensitivity to it, those with glucose-6-phosphate dehydrogenase deficiency and in pregnant women.[93]

Most photosensitizer dyes are also insoluble, hydrophobic and aggregate at sites increasing the chances of complications. [94] Photosensitizers like Photofrin® can accumulate not solely at target sites but in other distant organs, such as the liver, kidney, and spleen. Further, it persists in the skin for prolonged periods and may cause severe photosensitization reactions in patients long after treatment ceases. It has also been reported that it competes with melanin for light absorption, and its effectiveness in treating malignant conditions like melanoma is doubtful.

Nausea, exanthema, urtication, and itchiness have been reported with Indocyanine green.[95] Anaphylaxis and cross-reaction in patients with iodine sensitivity have also been reported.[96] Ocular complications have been noticed with PDT in patients undergoing multiple sessions of verteporfin. Risks are decreased with reduced dose/fluence settings. [97]

Hence, attention to laser parameters and selecting an appropriate photosensitizer can avoid these side effects. Operators should also exercise caution with PDT due to the risk of non-ionizing radiation from the light source causing eye and skin hazards. Blue light wavelengths can induce retinal damage (photoretinitis). Therefore, eye protection for patients, operators and assistants is mandatory. Reflection from metal surfaces can be avoided by covering them with wet gauze or use of tape. Additionally, high-speed evacuation to capture the laser plume is necessary. Habits like smoking and alcohol intake are also discouraged during PDT.

Advances in PDT

Conjugation of photosensitizers in PDT with antibodies against specific bacteria is an area of thrust.[98] Another variation of PDT employs polymeric or gold nanoparticles incorporated into the photosensitizer to allow bacterial cell wall disruption and thereby destruction of the oral biofilm.[99] Ultrasound activation of microbubbles through a sonosensitizer combined with molecular oxygen is another strategy that leads to the formation of pores in cells along with free oxygen radicals, causing cell death.[100] Similarly, the biofilm within the root canals has been treated with photosensitizer-containing oxidizers.[101] Another modification of PDT is the use of “photo-brushing" for plaque control.

Commercial kits

Various commercial kits are available for photodynamic treatment. 'Periowave' (Periowave Dental Technologies Inc., 888-1100 Melville Street, Vancouver, British Columbia V6E 4A6, Canada) with methylene blue has been advocated for treating periodontitis. Phenothiazine chloride is the photosensitizer in the Helbo® (Photodynamic Systems GmbH & Co. KG, Grieskirchen, Austria) system. Similarly, PAD™ uses toluidine blue.[16]

Conclusion

Photodynamic therapy offers a substitute for conventional antimicrobial treatment mitigating the development of resistance, especially while treating infectious diseases like periodontitis. The diverse applications of PDT, with the possibility of pain-free management, lend credence to this mode of treatment. The growing popularity of dental lasers has ensured that photodynamic treatment has a place in mainstream dental management.

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There are no potential conflicts of interest to declare.

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