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Applications Of Photodynamic Therapy In Periodontal Diseases

Shashank Deshpande[1], Anup Cholepatil[2], Ganesh Nandnavare[3]
[1]*(Department Of Periodontology And Implantology, Csmss Dental College & Hospital, India)*
[2]*(Department Of Periodontology And Implantology, Csmss Dental College & Hospital, India)*
[3]*(Department Of Periodontology And Implantology, Csmss Dental College & Hospital, India)*

Abstract:
Background: *According to A. Marcacci et al (1888), when many reports emerged on light absorbing properties and of fluorescence of various dyes, it became clear that dye excitation by light exerts destructive action in biological systems. This so-called photodynamic action was described as a process in which light, after being absorbed by dyes sensitizes organisms for visible light inducing cell damage. The supra- and subgingival plaque biofilm on tooth surfaces should easily be accessible for flushing with the dye and for activating them by light. Thus, periodontal diseases are promising applications of Photodynamic Therapy.*
Introduction: *Chronic periodontitis is the most common periodontal disease which is related to the chronic accumulation of bacterial plaque. Since mechanical methods are not sufficient in the treatment of this disease, administration of local/systemic antibiotic is recommended following mechanical debridement. However, side effects of antibiotics such as microbial resistance and patient allergy led to development of alternative methods. One of these suggested methods is the antimicrobial photodynamic therapy (aPDT). PDT is a local noninvasive treatment modality without the side effects caused by antibiotics.*
Objectives: *In this review, the mechanism of action of PDT and its application in the treatment of various periodontal conditions along with its future trends are discussed.*
Conclusion: *Even though PDT is still in experimental stages of development and testing, the method may be an adjunct to conventional antibacterial measures in periodontology and Implant related perspectives.*
Keywords: *Chronic periodontitis; Laser; Photodynamic therapy; Non-surgical periodontal therapy; Scaling and root planing.*

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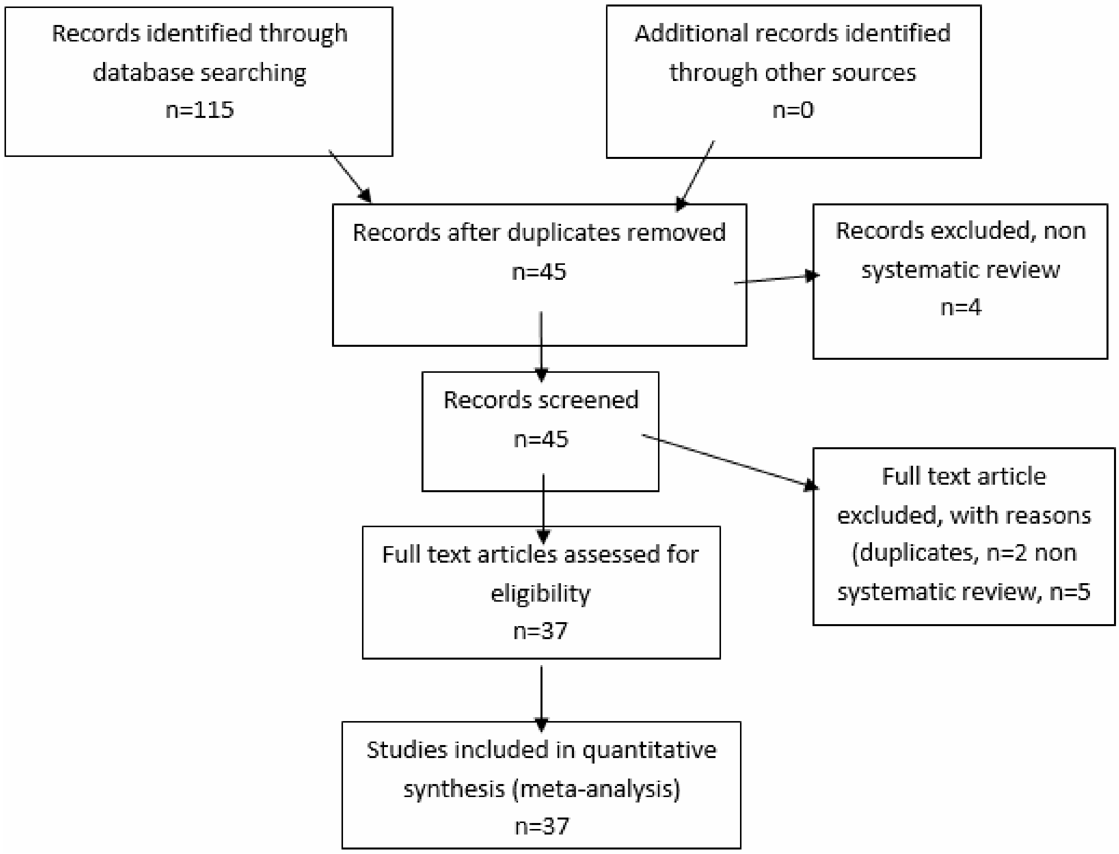
I. Introduction

Chronic periodontitis is one of the most common periodontal diseases and bacterial biofilm is its etiologic factor.[1] Of the most important pathogens causing periodontal disease, complex microorganisms such as *Aggregatibacter Actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Treponema denticola*, *Tannerella forsythia* bacteria can be noted.[2] At first, exclusively ultraviolet radiation was applied for therapeutic purposes, e.g., for the treatment of skin tuberculosis or rickets.[3] When reports emerged on light absorbing properties and of fluorescence of various dyes, it became clear that dye excitation by light exerts destructive action in biological systems. This so-called photodynamic action was described as a process in which light, after being absorbed by dyes sensitizes organisms for visible light inducing cell damage.[4] Raab studied this reaction showing the killing of protozoa in the presence of acridine when irradiated with light in the visible range of the spectrum. [5]

Due to the fact that the main goal of periodontal treatments is to reduce microbial agents, common treatments such as the mechanical debridement (the use of ultrasonic equipment and manually) as well as the use of topical or systemic antibiotics are considered as the main therapeutic measures in the treatment of chronic periodontitis.[6] Although the use of antibiotics can reduce the periodontal pathogens, their frequent use can cause bacterial resistance. Also, causing allergy in patients and the inability to make proper concentration of drug in the periodontal pockets are other disadvantages of using antibiotics.[7] Due to the complex anatomy of the furcation area, the pockets depth, and the penetration of microorganisms into tissues, it is difficult to have an appropriate access to clean up. Therefore, for the reasons outlined, efforts to find adjunctive treatment have increased. One of these treatments is photodynamic therapy (PDT).[8] This method was first used in 1990 for the treatment of cancer. It was determined that its use stimulates autophagy (a method of cell catabolism, which leads to the destruction of abnormal cells) in resistant cancer cells or precancerous cells. In this method, wavelengths between 650-900 nm which are within the visible red light and near infrared, and have great influence on biological tissue are used.[9]

METHOD

Prisma 2009 Flow Diagram



II. Material And Methods

Mechanism Of PDT

According to Allison et al, PDT involves the use of 3 components: (1) Light, (2) Oxygen free radicals, and (3) Photosensitizer.[10] When the photosensitizer is stimulated by an appropriate light wavelength (wavelengths between 650-900 nm which are within the visible red light and near infrared), it provides free radicals of oxygen that causes tissue damage.[11] The cytotoxic products have a short half-life (about 0.04 µs) and limited radius effect (0.20 µm). In other words, they are limited to the infected area, where the photosensitizer is accumulated. Thus, PDT is a topical method that does not affect other host tissues.[12]

The basic photobiological principles apply for the mechanism of light therapy:

(i) The Grotthus–Draper law. The light used must be of an appropriate wavelength because only absorbed light can trigger a photochemical reaction.

(ii) The Stark–Einstein law. Each molecule involved in a light-induced reaction absorbs one quantum of the light emitted.

(iii) Bunsen–Roscoe law. The photochemical effect is a function of the product of the intensity of the light and the duration of the treatment (the exposure or light dose).[13]

By irradiation with light in the visible range of the spectrum the dye (photosensitizer) will be excited to its triplet state, the energy of which is transferred to molecular oxygen. The product formed is the very reactive singlet oxygen capable of reacting with biological systems and destroying them.[14]

Since the 1890s, scientists used the staining properties of dyes to develop the idea of selective toxicity. Well established photosensitizers such as methylene blue were reported to be antibacterial, antiviral, and antiprotozoal since the Second World War.[15]

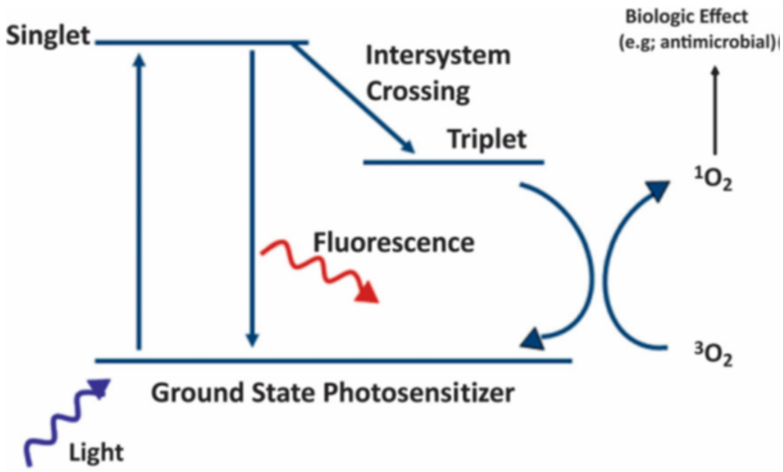


Fig 1. Principals of PDT.
(Courtesy of Dr. Brian Wilson, Princess Margaret Hospital, Toronto, ON).

The basic phenomenon (Fig. 1) requires that the photosensitizer within affected areas of the periodontium (i.e., within periodontal pockets) be light activated or excited from its so-called ground or singlet state (which is a single peak if analyzed spectrophotometrically) into either a doublet or triplet state. This leads to the transfer of energy (electrons) that precipitates the formation of singlet oxygen species, which are cytotoxic, thereby mediating bacterial kill.[16] Typically, the light must be of a specific wavelength as described by others, but even broad-spectrum light can activate photosensitizers such as toluidine blue. Because high-power lasers may induce trauma to surrounding tissues through thermal injury, low power light with a photosensitizer is an attractive alternative therapy. Microorganisms that are killed by singlet oxygen include viruses, bacteria, protozoa, and fungi. The practical exploitations of these antimicrobial effects are the use of PDT in virostatic applications[17] in dermatological Settings[18] and for decontamination of blood products.[19]

Application Of Pdt As An Adjunct To Non-Surgical Periodontal Therapy

Andersen et al in 2007, 23 patients with chronic periodontitis were randomly divided into 3 groups: group 1- treatment with PDT, group 2- treatment with SRP and PDT (laser diodes) and group 3- treatment with SRP alone (control group). The results of the study showed that the addition of PDT to SRP statistically significantly improved the clinical attachment level (CAL) and the depth of probing pocket (PPD).[20]

Braun et al in 2008, the main purpose was to compare clinical outcomes of doing SRP with or without PDT. In this study, 20 patients with chronic periodontitis were randomly divided into 2 groups by using the split-mouth method. All patients were under SRP. In a quadrant, PDT was performed by means of laser diode 660 nm and photosensitizer phenothiazine chloride.

At the beginning of the study, 1 week and 3 months after treatment, the gingival crevicular fluid (GCF), PPD, bleeding on probing (BOP) and gingival recession (GR) were measured. In all cases except for GR, better results were obtained in the group treated with PDT; however, there was no difference in the recession in the 2 groups.[21]

Christodoulides et al, 24 patients with chronic periodontitis were randomly divided into 2 groups: 1-treatment with SRP, 2-treatment with SRP and PDT (diode laser 670 nm and power of 75 mW) and no statistically significant difference was seen between the 2 groups, and only BOP showed significant improvements in the group treated with SRP and PDT, compared to the one treated with SRP alone.[22]

2009 by Chondros et al, 24 patients with chronic periodontitis were divided into 2 groups: group 1-treatment by SRP and group 2- treatment with SRP and PDT (670 nm, 75 mW laser diode and photosensitizer phenothiazine chloride for 60 seconds), respectively. Both groups were assessed at 2 time periods of 3 and 6 months. No significant differences in terms of PPD, CAL, and the amount of plaque were seen, but the BOP was significantly reduced in the group of treatment by SRP and PDT.[23]

2009, Polansky et al, treated 58 patients with chronic periodontitis in 2 treatment groups: 1-treatment with SRP and 2- treatment with SRP and PDT (laser diode 680 and 75 mW), and no difference in the amount of CAL, BOP, and PPD were seen between the 2 groups. Based on the results obtained, the use of PDT once, did not have significant clinical effect compared to SRP treatment alone.[24]

Ruhling et al on 25 patients using 636 nm diode laser photo synthesizer phenothiazine chloride, similar results were obtained.[25]

Lui et al in 2011 in a clinical trial investigated 24 patients with chronic periodontitis. The patients were randomly divided into 2 groups: group 1- under SRP treatment and group 2-under SRP and PDT treatment (diode laser 940 nm for 3 days). A month later, BOP and GCF had a greater reduction in the first group, but after 3 months no difference between the 2 groups was seen. Also, the amount of IL-1β had dropped more in the second group than the control group in a week; therefore, the researchers concluded that the use of PDT with SRP is more effective in improving patients' periodontal health in short term.[26]

2011, Aykol et al divided 24 patients with chronic periodontitis into two groups during a clinical trial. Group 1 was treated with SRP, and group 2 was treated with SRP and PDT (diode laser 808 nm, power of 0.25 W) on the first, second and seventh day of treatment. Then all the patients were divided into 2 groups of smokers and non-smokers. The group treated with SRP and PDT for both smokers and non-smokers showed better results in terms of improved clinical parameters.[27]

2011, Cappuyns et al randomly assigned 32 patients with a history of non-surgical chronic periodontitis treatment into 3 groups in a clinical trial: (1) treatment with SRP, (2) treatment with diode laser 810 nm, and (3) treatment with PDT, diode laser 660 nm and photosensitizer phenothiazine chloride. All of the 3 groups showed an improvement in GR, BOP and PPD clinical parameters and there was not any difference between them.[28]

2012, Noro Filho et al investigated 12 patients with HIV and chronic periodontitis treatment history in a clinical trial by split-mouth method. They have randomly divided them into 2 groups: (1) treatment with SRP and (2) treatment with SRP and PDT (diode laser 660 nm, and photosensitizer methylene blue). Six months later they have observed improvements in PPD and CAL clinical parameters in the second group.[29]

2012, Berakdar et al randomly assigned 22 patients with chronic periodontitis with at least 4 teeth in each quadrant with residual pockets over 5 mm into 2 groups: (1) treatment with SRP and (2) treatment with SRP and PDT (laser 670 nm, 150 mW and photo sensitizer 0.005% methylene blue. They have observed PD, CAL and BOP improvement in both groups but the amount of PD improvement was significant in the second group.[30]

2012, Giannelli et al compared the clinical outcomes of chronic periodontitis treatment with SRP and SRP combined with PDT and photo-ablation with diode laser. They have perused 26 patients. The results of the study showed that treatment of chronic periodontitis with photo-ablation along several PDT sessions is more effective in improving patients' periodontal health condition compared to SRP alone.[31]

2013, during a clinical trial, Balata et al have divided 22 patients presenting chronic periodontitis with depth of 5-7 mm pockets in each quadrant into 2 groups, using split mouth method. Group 1 was treated with SRP. Group 2 was treated with SRP and PDT (laser 660 nm, 100 W and photo sensitizer methylene blue 0.005%). They have checked BOP, CAL and PD clinical parameters before the treatments as well as 1 month, 3 months and 6 months after the treatment. In each group no statistically significant difference was observed clinically after the treatment.[32]

2013, Souza et al studied the impacts of microbial PDT on the level of transforming growth factor (TGF) β1 in GCF on patients. In that study they chose 50 patients with bilateral grade III furcation involvement in mandibular molars. Each pair of molar teeth was randomly divided into experimental group and control group. They have applied SRP into control group and SRP accompanied with PDT applied into the experimental group. Forty-five days later, the control group had received flap surgery and SRP, and the experiment group had received flap surgery, SRP and PDT. They have checked GCF collected by ELISA method by the amount of TGF β1 at baseline, 45 days after the initial treatment and 21 days after the surgical treatment. The experiment group compared to the control group at 45 days after the initial treatment and 21 days after the surgical treatment has shown statistically significant differences.[33]

2014, Pourabbas et al carried out a clinical trial for 3 months on 22 patients affected with chronic periodontitis, which has shown that adding one extra therapy session with toluidine blue and concentrated light of 638 nm does not add any extra improvement on clinical indicators. Although that would causes reducing the rate of tumor necrosis factor alpha (TNF-α) in gingival sulcus fluid, flashing concentrated light only once along scaling may impact the ability to show the effects of treatment with PDT, and makes it impossible to interpret the results.[34]

2014, Kolbe et al randomly assigned 22 patients with chronic periodontitis during a clinical trial by split mouth method. They have divided the patients into 3 groups based on the random points they have been selected before: (1) Treatment with SRP, (2) Treatment with SRP and photosensitizer, and (3) Treatment with SRP and PDT. Patients were checked at baseline, 3 months and 6 months after it was done. The results of the study showed that each group resulted in improvement of clinical conditions but only in the third group, an increasing of IL-4 perception and reduction of IL-6, IL-8 and IL-1β were reported.[35]

Although the use of laser in many studies showed similar results to SRP, but we cannot disregard the shorter treatment time, more rapid onset of action, reduced need for anesthesia and the absence of bacterial resistance occurrence when using laser. It seems that the most useful effect in using laser is in the maintenance phase because usually at this time retreatment is limited to residual deep pockets and is localized. Using laser prevents removing extra dental tissues. Also this method prevents tooth sensitivity. In addition, there is no need of using antibiotics after surgery due to the use of laser with its anti-bacterial effect. Since the use of PDT reduces bacteremia, it may be recommended for patients who are at risks of endocarditis. The use of PDT as an adjunct therapy in non-surgical treatments is economical in comparison to periodontal surgeries. In addition, due to its focal effect, using systematic antibiotics is unnecessary. Also high concentrated photosensitizer at the site of infection plays an important role in reducing the bacteria without adverse effects on host cells.[36]

2021 Shevchenko V. K et al. The aim of the study was to study the effect of red and orange spectra of incoherent radiation of the device «UFL-122» in the complex treatment of patients with generalized periodontitis with morphological and radiological confirmation of clinical results. We performed clinical, laboratory diagnosis and comprehensive treatment of 52 patients with generalized periodontitis aged 35 to 61 years. Additionally, light therapy was used with the device «UFL-122», mode «R» with a base wavelength of 600-670 nm. (luminous flux density 560 mW/cm2) and «O» with a base wavelength of 570-780 nm. (luminous flux density 1300 mW/cm2). The combined use of red and orange spectra of light in the complex therapy of 52 patients with generalized periodontitis received positive treatment results in 94% of patients.[37]

2021 Pragna et al. A split mouth design was used in A total of 20 patients (as per the criteria laid down for selection), 3quadrents were selected in each patient and divided in to three groups. Group A: Received Photodynamic Therapy by means of 0.5% indocyanine green and irradiated by Laser after scaling and root planing. Group B: Received scaling and root planing. Group C: Received laser therapy. The clinical readings and the microbial analysis were done at base line, 1 month and 3 months from the 1st visit. Among the SRP+PDT and SRP groups SRP+PDT group showed slightly higher reduction in the mean values than SRP group. The microbiological parameters showed higher reduction in their mean values in PDT+SRP group when compared to the other two groups.

III. Conclusion

If PDT application has an adjunctive benefit besides mechanical treatment at sites with difficult access (e.g., furcations, deep invaginations, concavities). Necessity for flap operations may be reduced, patient comfort may increase and treatment time decrease.

_ If PDT removes the biofilm in residual deep pockets during maintenance, no more root substance is removed by mechanical retreatment. Thus the patient may experience less dentine hypersensitivity.

_ If PDT may decrease the risk of bacteremia which routinely occurs after periodontal treatment procedures and, on the other hand, unequivocal evidence is presented showing an periodontal risk of systemic diseases such as cardiovascular diseases and diabetes,

_ If the resistance against antibiotics may become worse, PDT may be a valuable alternative for most indications in which hitherto antibiotic drugs were administered.

_ If the number of immunosuppressed patients bring new challenges for treatment strategies.

The concept of PDT is plausible and could foster new therapy concepts for periodontal disease. The available knowledge should enable and encourage steps forward into more clinical oriented research and development.

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