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Applications and Efficacy of Photodynamic Therapy in Periodontics: A Review Study

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Authors' contributions

This work was carried out in collaboration between both authors. Author MT designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author RT managed the literature searches, analyses of the studies gathered in literature review. Author MT read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: Periodontitis is a common cause of tooth loss in adults and is an anaerobic bacterial infection. Enzymes, endotoxins and other cytotoxic bacterial products result in tissue destruction and initiation of chronic inflammation. Mechanical debridement by scaling and root planing (SRP) is the most effective treatment for this condition. Local delivery of antibiotics is an effective alternative treatment with less systemic side effects. Photodynamic therapy (PDT) is a technique of local delivery of antimicrobial agents. This study reviews the applications and efficacy of PDT for treatment of chronic and aggressive periodontitis.
Place and Duration of Study: Sample: Department of periodontics, Shahid Beheshti University of Medical Sciences, Dental School, between June 2015 and April 2015.
Methodology: A search was carried out in PubMed and Google Scholar using the keywords "photodynamic therapy" AND "chronic periodontitis" (MeSH), "photodynamic therapy" AND "aggressive periodontitis" and "photodynamic therapy" AND "periodontal treatment" (MeSH). English articles published from 2000 to 2015 were searched and a total of 32 papers including 8 articles on aggressive periodontitis and 24 on chronic periodontitis were found.
Conclusion: PDT is a minimally invasive treatment for periodontal disease. Methodological

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limitations of studies in this regard prevent a conclusion being drawn regarding the optimal efficacy of PDT as an adjunct for treatment of periodontitis.

Keywords: Photodynamic therapy; chronic periodontitis; aggressive periodontitis; periodontal therapy.

ABBREVIATIONS

GCF : Gingival crevicular fluid
Aa : Actinobacillus actinomycetem comitans
Tf : Tannerella forsythia
Td : Treponema denticola
KTP : Potassium titanyl phosphate
Pg : Porphyromonas gingivalis
BOP : Bleeding on probing
Fn : Fusobacterium nucleatum
CAL : Clinical attachment level
APCs : Antigen Presenting Cells

1. INTRODUCTION

Periodontitis is a common cause of tooth loss in adults [1] and is an anaerobic bacterial infection [2]. Enzymes, endotoxins and other cytotoxic bacterial products result in tissue destruction and initiation of chronic inflammation [3]. Mechanical debridement by SRP is the most effective treatment for this condition. Surgery is also indicated in many cases. Systemic antimicrobial therapy may effectively decrease the risk of tooth loss and the need for surgery [4]. PDT is an acceptable alternative for local delivery of antibiotics with lower risk of systemic side effects [5]. PDT is a method for local delivery of antimicrobial agents [6]. Since 1890, scientists have benefitted from the staining properties of dyes for selective toxicity [7,8]. A combination of light and dye has long been used for destruction of microbial strains in labs [7,8]. Photosensitizers such as methylene blue have been known as antibacterial, antiviral and antiprotozoal agents since the World War II [8] Raab was the first to show the destruction of Paramecium Caudatum by irradiation of visible light in presence of Acridine Orange. Combination of these two non-toxic elements (light and dye) in an oxygenated environment results in destruction of microorganisms [5]. In 1904, Jodlbaner and Van Tappeiner used the term “photodynamic” to describe oxygen-dependent chemical reactions induced by photosensitizers for inactivation of bacteria [6].

PDT requires three components of light, photosensitizer and oxygen. Irradiation of a photosensitizer with light at a specific wavelength converts it from a low-energy state to a high-energy state. Following irradiation of fluorescent light, photosensitizers may return to their initial state or a higher energy state (triplet state). The dye in triplet state reacts with endogenous oxygen to produce singlet oxygen or other free radicals and eventually causes selective and quick destruction of the target tissue. The photosensitizers in triplet state react with biomolecules via two mechanisms: Type I reaction includes direct electron/hydrogen transfer from the photosensitizers and production of ions and free radicals by electron/hydrogen removal from the molecules of materials. Type II reaction generates singlet oxygen (electronically excited). These two reactions indicate cellular mechanisms depending on the oxygen pressure and concentration of photosensitizers [8] (Fig. 1).

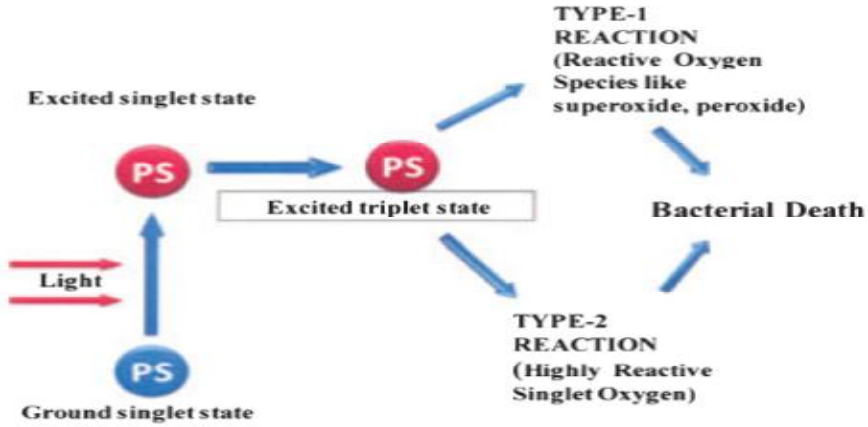

Fig. 1. Mechanism of action of PDT

A suitable photosensitizer must have specific chemical, photo-physical and biological properties. For treatment of periodontal infections, photosensitizers must adhere to bacteria and dental plaque with no adverse esthetic consequences such as gingival staining [8].

Types of photosensitizers include [9]:

1a. Dyes such as toluidine blue and Acridine Orange
1b. Phthalocyanines such as phthalocyanine aluminum disulfonate and cationic zinc phthalocyanine
2. Chlorines such as poly lysine and poly-ethyleneimine
3. Porphyrins such as hematoporphyrin HCl and photofrin
4. Xanthenes such as erythrosine
5. Photo Terpenessuch as esolene

2. REVIEW OF THE LITERATURE

A search was carried out in PubMed and Google Scholar using the key words “photodynamic therapy” AND “aggressive periodontitis”, “photodynamic therapy” AND “periodontal treatment” (MeSH), “photodynamic therapy” AND “chronic periodontitis” (MeSH) and “photodynamic therapy” AND “aggressive periodontitis”. Articles published in English from 2000 to 2015 were searched.

3. RESULTS

Table 1 presents the list of articles using PDT as part of non-surgical treatment of chronic periodontitis. Table 2 presents the list of articles that reported using PDT for treatment of aggressive periodontitis.

Table 1. Studies that used PDT for treatment of chronic periodontitis

Author	Study design	Publication date	Study objectives	Results
Pour Abbas [10]	Split mouth clinical trial	2014	Comparison of clinical parameters and cytokine profile (IL-1β, TNFα, MMP8, MMP9) in GCF of moderate to severe periodontitis patients after SRP+PDT and SRP alone	PDT had no superior efficacy to SRP after 3 months
Betsy [11]	Clinical trial	2014	Assessment of the effect of PDT as an adjunct for treatment of chronic periodontitis	PDT in short-term showed superior efficacy to SRP
Petelin [12]	Clinical trial	2014	Comparison of the effects of ultrasonic SRP in conjunction with multi-step PDT, ultrasonic SRP alone and manual SRP on subgingival pathogens in chronic periodontitis patients	PDT caused a greater reduction in Aa, Tf and Td compared to mechanical debridement alone
Queiroz [13]	Split mouth clinical trial	2014	Assessment of the microbiological effects of PDT as an adjunct for non-surgical periodontal therapy in smoker patients with chronic periodontitis	Neither PDT associated with SRP nor SRP alone decreasedthe microbial count in smokers.
Balata [14]	Split mouth clinical trial	2014	Assessment of the efficacy of PDT as an adjunct in treatment of chronic severe periodontitis	PDT had no superior efficacy to SRP after 6 months

Alwaeli [15]	Split mouth clinical trial	2013	Assessment of the long-term clinical efficacy of PDT associated with SRP in treatment of chronic periodontitis	PDT as an adjunct was suggested to be a novel approach for treatment of periodontitis
Quirozac [16]	Split mouth clinical trial	2013	Assessment of the efficacy of PDT as an adjunct to SRP in smokers with chronic periodontitis	PDT had no superior clinical efficacy to SRP but decreased inflammatory markers(IL-1β, MMP8)
Luchesi [17]	Clinical trial	2013	Assessment of the effect of PDT as an adjunct in treatment of CL II furcation involvement	PDT had no superior efficacy to SRP but decreased the levels of cytokines(IL-1β,IL-4,IL-8,IL-10,IL-6,GM-CSF,INF γ) and pathogens
Dilsiz [18]	Split mouth clinical trial	2012	Clinical assessment and comparison of the efficacy of KTP laser and PDT for treatment of chronic periodontitis	KTP plus SRP showed superior clinical results in deep pockets
Theodoro [19]	Split mouth clinical trial	2012	Assessment of the long-term clinical and microbiological effects of PDT in conjunction with non-surgical periodontal therapy for treatment of chronic periodontitis	PDT decreased some key pathogens but had no significant effect.
Berakdar [20]	Clinical trial	2012	Assessment of the efficacy of PDT in conjunction with SRP in chronic periodontitis patients	PDT in conjunction with SRP was more effective than PDT alone
Cappuyns [21]	Split mouth clinical trial	2012	Comparison of the efficacy of PDT with diode laser plus SRP in management of residual pockets in chronic periodontitis	PDT plus SRP caused a greater reduction in Td, Tf and Pg counts
Alzahrani [22]	Split mouth clinical trial	2011	Comparison of the efficacy of PDT as an adjunct with SRP for treatment of chronic periodontitis in smokers	PDT may be beneficial for treatment of chronic periodontitis in smoker patients
Ge [23]	Clinical trial	2011	Assessment of the clinical effects of PDT plus SRP for treatment of chronic periodontitis	PDT was more effective than SRP alone for treatment of pockets deeper than 5mm and reduction of BOP
Metteaux [24]	Clinical trial	2011	Assessment of the efficacy of PDT as an adjunct for treatment of chronic periodontitis	PDT had significant clinical and antibacterial effects comparable to those reported in the literature

Seguiers [25]	Clinical trial	2010	Assessment of the effect of PDT on inflammatory infiltrate and collagen network in patients with severe periodontitis	PDT affected gingival inflammation and depending on the type of delivery system caused a significant reduction in APCs
Sigusch [26]	Clinical trial	2010	Assessment of the clinical and microbiological effects of PDT on patients with chronic periodontitis due to Fn	PDT decreased the inflammatory signs and symptoms and was successful in treatment of Fn infection
Polansky [27]	Clinical trial	2009	Assessment of the microbiological and clinical efficacy of PDT in treatment of chronic periodontitis	Single session application of PDT had no superior efficacy to SRP
Alzahrani [28]	Clinical trial	2009	Assessment of the effect of PDT on periodontal status and blood sugar of diabetic patients with chronic periodontitis	PDT had no superior efficacy to conventional treatment in diabetic patients
Fontana [29]	Clinical trial	2009	Assessment of the efficacy of PDT for decreasing the biofilm bacterial count compared to the planktonic state	Biofilm was less susceptible to PDT compared to the planktonic state.
Ge [30]	Clinical trial	2008	Assessment of the efficacy of PDT with diode laser for treatment of chronic periodontitis	The results of PDT+SRP lasted for a longer period of time
Braun [31]	Split mouth clinical trial	2008	Assessment of the efficacy of PDT as an adjunct in treatment of chronic periodontitis	The results of mechanical debridement improved when combined with PDT.
Christodoulides [32]	Clinical trial	2008	Assessment of the clinical and microbiological effects of PDT as an adjunct in non-surgical treatment of chronic periodontitis	PDT showed no superior results in terms of pocket depth reduction and CAL gain but decreased BOP more significantly
Ameida [33]	Animal experiment	2007	Radiographic and histological assessment of the effects of PDT on progression of chronic periodontitis in rats	PDT transiently decreased periodontal tissue destruction

3.1 PDT for Treatment of Chronic Periodontitis

A total of 24 articles were found in this regard out of which 10 had a split mouth design (This design is characterised by subdividing the mouth of the subjects into homogeneous within-patient experimental units such as quadrants, sextants, contralateral or ipsilateral quadrants or sextants or a symmetrical combination of these). and only one study was an experimental animal study [33]. The focus of most studies was on clinical and microbiological changes and only a small number of studies had evaluated the levels of different inflammatory cytokines [10,16,30]. Of inflammatory biomarkers, (GCF had been more commonly evaluated than RANKL, TNFα, IL-1B, MMP8 and MMP9. Of these studies, only one

study failed to show the superior efficacy of PDT in decreasing the level of biomarkers [10]. Microbiological studies yielded controversial results. Some did not find a significant difference between PDT and conventional mechanical debridement in decreasing periodontopathogenic strains [13,27,32]; but some others [12,17,21, 24,26] showed a greater reduction in the red complex (Pg, Td and Tf), Aa and Fn in PDT group. Three studies investigated the effects of PDT on smokers with chronic periodontitis [13,16,22] and reportedno extra clinical [16,22] or microbiological [13] effects attributed to PDT in comparison with SRP alone. A noteworthy point is the multi-step protocol of PDT (2 or 3 steps) [12,13,30]. The multi-step protocol in all cases showed superior biological and microbial effects compared to SRP. Only one study evaluated the efficacy of PDT in diabetic patients [28]. Alzahrani in 2009 showed the superior efficacy of PDT compared to non-surgical conventional periodontal treatment in diabetic patients [28].

Table 2. Studies on the applications of PDT for treatment of aggressive periodontitis

Author	Type of study	Publication date	Study objectives	Results
Moreira [34]	Split mouth clinical trial	2014	Assessment of the efficacy of multi-step PDT as an adjunct to SRP for treatment of aggressive periodontitis	PDT enhanced the clinical, microbiological and immunological outcomes
Arweiler [35]	Clinical trial	2014	Assessment of the outcome of non-surgical periodontal therapy with PDT and antibiotic therapy in patients with aggressive periodontitis	Antibiotic therapy showed superior efficacy in terms of pocket depth reduction in comparison with PDT
Moreira [34]	Clinical trial	2014	Assessment of the efficacy of multi-step PDT as an adjunct in patients with aggressive periodontitis	Four sessions of PDT in conjunction with SRP enhanced clinical, immunological and microbiological outcomes
Chitsazi [36]	Split mouth clinical trial	2014	Assessment of the efficacy of PDT in treatment of aggressive periodontitis	The results showed no extra benefit for PDT in comparison with SRP
Arweiler [37]	Clinical trial	2013	Assessment of the efficacy of short-term non-surgical periodontal therapy, systemic antibiotic therapy and PDT in patients with aggressive periodontitis	Systemic administration of antibiotics was more effective in decreasing pocket depth than PDT
Novacs [38]	Split mouth clinical trial	2012	Assessment of the microbial profile following PDT in patients with aggressive periodontitis	PDT+SRP may be efficient for treatment of aggressive periodontitis
Deoliviera [39]	Clinical trial	2009	Assessment of the level of cytokines in GCF of patients with aggressive periodontitis following PDT plus SRP	SRP and PDT had similar effects on TNFα and RANKL in aggressive periodontitis
Deoliviera [40]	Clinical trial	2007	Assessment of the efficacy of PDT for non-surgical treatment of periodontitis in comparison with SRP	PDT and SRP showed similar efficacy.

Another noteworthy point was the comparison of two drug delivery systems in PDT, which was done in only one study [25]. Seguiers in 2010 compared two delivery systems of liposome and nano-emulsion and concluded that antigen-presenting cells decreased in use of both systems [25]. However, macrophages decreased in the liposome group while Langerhans cells decreased in the nano-emulsion group. In general, results on the efficacy of PDT are controversial. Some studies failed to show the superiority of PDT to conventional SRP in clinical, microbiological or immunological aspects [10,13,14,16,17,19,20,27,28,32].

3.2 Pdt for Treatment of Aggressive Periodontitis

A total of 8 articles were found in this regard out of which 4 had a split mouth design. Of the mentioned articles, 3 studies failed to show the superior efficacy of PDT to SRP alone [37,40,41]. Two studies evaluated systemic administration of antibiotics and PDT as adjuncts to non-surgical periodontal therapy [35,38]. Both studies showed that systemic administration of antibiotics was more effective in decreasing the pocket depth than PDT. The four-step PDT was only evaluated in one study and was shown to enhance the treatment outcome [34]. In 4 studies, microbiological parameters were evaluated in addition to clinical parameters [34,36,38]. The majority of these studies indicated a reduction in red and orange complexes and only one study reported a reduction in Aa [39].

4. DISCUSSION

Based on Tables 1 and 2, it is concluded that most previous studies have evaluated the efficacy of PDT for treatment of chronic periodontitis and only a few studies evaluated aggressive periodontitis. The results on the adjunct role of PDT are controversial and this controversy is more significant when it comes to the treatment of aggressive periodontitis [36,39,40]. In general, studies on the efficacy of PDT have high heterogeneity and small sample size. For instance, type of photosensitizers, wavelengths, maximum laser power and duration of irradiation are variable in different studies. The duration of assessment has also been variable from 1 to 12 months. Most previous studies have evaluated the variables for a maximum of 6 months and only two studies evaluated them for 12 months [12,16]. Randomized double blind clinical trials with a proper design and long-term follow ups are required to obtain more reliable results. Also, measurement methods must be standardized and important clinical parameters must be analyzed. Periodontal clinical parameters such as clinical attachment loss, probing depth, gingival recession, total plaque index and total bleeding index, biological variables such as inflammatory cytokines and microbial changes as well as patient-related factors such as patient expectations and perspectives, pain, discomfort and halitosis must also be analyzed and reported.

Considering the fact that neither the patient nor the clinician can be blinded to the treatment plan, the examiners must be necessarily calibrated and blinded (for example they must be blinded to the type of treatment performed) in order for bias-free assessment of clinical outcome.

Using the mean value of probing depth may not be appropriate for evaluation of the treatment results due to the high variability among different examiners and patients and also the remaining inflammation. Thus, analysis must be done using frequency distributions. Similarly, use of mean values for reporting the changes in indexes used for assessment of the severity of periodontal disease is inappropriate and is not recommended. The information obtained from these indexes should not be reported as mean values; instead, they must be analyzed using frequency distributions. This trend along with the patient-related factors is necessary for determining the efficacy and safety of PDT [41].

5. CONCLUSION

PDT is a less invasive new strategy in periodontal therapy, which is still under investigation. Advances in development of new photosensitizers, more efficient photo-transfer systems and further clinical trials are required to determine and confirm optimal therapeutic parameters in PDT. Methodological limitations of studies in this regard prevent a conclusion being drawn regarding the superior efficacy of PDT as an adjunct for treatment of periodontitis. However, this does not refute the optimal efficacy of PDT; but rather indicates the lack of adequate information on the efficacy of this treatment modality.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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