USE OF PHOTODYNAMIC THERAPY IN PERIODONTAL DISEASE: INTEGRATIVE REVIEW

USO DA TERAPIA FOTODINÂMICA NA DOENÇA PERIODONTAL: REVISÃO INTEGRATIVA

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RESUMO

Objetivo: O objetivo do presente estudo é avaliar o uso da TFD no tratamento periodontal como um adjunto na redução da disbiose bacteriana, bem como seus benefícios na redução dos sinais clínicos da periodontite. Material e Métodos: trata-se de revisão integrativa da literatura realizada na base de dados Pubmed. Adotou-se como critério de inclusão artigos em inglês e português, disponíveis na integra, no período de 2016 a 2021.Resultados: Após a leitura do título e resumo foram incluídos 19 artigos que relataram a relação entre o uso da TFD no tratamento periodontal. Conclusão:Estudos comprovaram que a aplicação e os efeitos da TFD como terapia complementar aos tratamentos convencionais são altamente positivos por ser indolor, pouco invasivo e com resultados satisfatórios contra agentes patogênicos.

Palavras-chave: Periodontia. Terapia fotodinâmica. Doenças Periodontais

ABSTRACT

Objetive: The aim of this study is to evaluate the use of PDT in periodontal treatment as an adjunct in reducing bacterial dysbiosis, as well as its benefits in reducing clinical signs of periodontitis.Material and Methods:This is an integrative review of the literature performed in the Pubmed database. Articles in English and Portuguese, available in the world from 2016 to 2021, were adopted as inclusion criteria.Results: After reading the title and abstract, 19 articles were included that reported the relationship between the use of PDT in periodontal treatment. Conclusion: Studies have proven that the application and effects of PDT as complementary therapy to conventional treatments are highly positive because they are painless, noninvasive, and with satisfactory results against pathogens.

Keywords: Periodontics. Laser Therapy. Periodontal Diseases.

INTRODUCTION

Periodontal disease is a pathology of inflammatory and infectious character, which affects the supporting and protective tissues of the teeth, and occurs due to an interaction between bacterial dysbiosis and the immunoinflammatory response of the host[1].

The classic approach for periodontal treatment is mainly due to the management of conventional non-surgical therapy, through root debridement, which acts in the elimination of microorganisms located in periodontal pockets and lithiasis. This can be performed by means of manual instrumentation, with curettes and/or use of ultrasonic and sonic devices, which were developed to potentiate the action of manual periodontal instruments[2,3]. However, the anatomical complexity of the roots of the teeth, the presence of extensive probing depth and gum areas hinder effectively cleaning this region, in view of this, adjuvant procedures were developed, such as the use of antimicrobials and photodynamic therapy (PDT)[4].

In periodontics, antibiotic prescription especially for individuals with more severe periodontitis (stage III and IV) is a common practice (CIEPLIK *et al.*, 2018), but the side effects resulting from this drug, associated with the increasing number of resistant microorganisms should not be neglected[5,4]. Therefore, PDT presents itself as a promising strategy as an auxiliary therapy in the treatment of periodontal disease[6].

The use of phototherapy directed to the treatment of periodontal diseases began to be used at the end of the 20th century. This noninvasive and painless therapeutic modality consists of the combination of a light source (low-power laser) and a photosensitizer that has the function of causing cellular necrosis and consequently the death of periodontal pathogens[7,8]. PDT is a procedure that consists of the application of a photosensitizing agent easily absorbable by microorganisms, which is activated by light at specific wavelengths, through low-power lasers (LBP), that, when into contact with oxygen (O2), generates O2 Singleto, which is an electronically excited species of the O2 molecule, highly reactive, and free radicals, which are selectively toxic to pathogenic periodontal microorganisms[7]. . These cytotoxic substances can damage the plasma membranes and deoxyribonucleic acid (DNA) of microorganisms, resulting in cell death, by damaging multiple cellular mechanisms, such as lipid peroxidation, inactivation of the membrane transport system and inhibition of enzymatic activities of the plasma membrane[8].

PDT has minimal side and systemic effects, and is unlikely to cause bacterial resistance, is also a painless procedure, being able to be used in areas of difficult access, thus reducing the number of periodontal surgeries, treatment time and bacteremias[9]. Therefore, the aim of this study is to evaluate the use of PDT in periodontal treatment as an adjunct in reducing bacterial dysbiosis, as well as its benefits in reducing the clinical signs of periodontitis.

METHODOLOGY

This is an integrative review of the literature on the use of photodynamic therapy in the treatment of periodontal disease. The searches were performed at the PubMed database. In the search, journals in Portuguese and English were selected. When in Portuguese, the descriptors "*terapia fotodinâmica*", "*laserterapia*" and "*periodontia*", and when in English "photodynamic therapy", "laser therapy", "periodontics" were used. For the combinations, the Boolean operator "AND" was used. Articles that presented relevance to the theme on the use of photodynamic therapy in the treatment of periodontal disease, fully available, in the period from 2016 to 2021 were included. Articles not fully available, letter-type to the reader and all gray literature were excluded.

DEVOLOPMENT

PERIODONTAL DISEASE

Periodontitis is an inflammatory and multifactorial disease associated with a dysbiotic biofilm that promotes degradation and, consequently, the loss of the periodontum of insertion and protection of teeth. The prevalence of Periodontal Disease is high and is one of the major responsible for tooth loss in the world, directly affecting the quality of life of the individual [10].

The essential responsible factor of the pathology is the combination of Gram-negative anaerobic bacteria within the periodontal pouch, with this, the nutrition of the gingival epithelium is compromised and the cells of the junctional epithelium proliferate and migrate in the apical sense, leading to the main characteristic of the formation of periodontal pockets[11].

Because of this destruction, caused by microorganisms, occurs the release of critical inflammatory cells, such as macrophages and innate immune cells, which play an important role during the development of the disease. These cells exert a defensive function and maintain periodontal tissue homeostasis, however, they can also interact with local tissue cells, including gingival epithelials, fibroblasts, endothelials and osteoblasts, and secrete IL-1, IL-6, TNF-α, PGE2 and other cytokines, resulting in loss of insertion (JIANG, et al., 2019). The main determinant for the individual's predisposition to this disease is related to the host's inflammatory immune response to the biogingival biofilm[12].

PERIODONTAL TREATMENT

Traditional therapy for the treatment of periodontitis aims to interrupt the inflammatory process by eliminating etiological factors on the root surface, through non-surgical mechanical instrumentation that is considered the gold standard of cause-related therapy in sick individuals[8]. Subgingival debridement can be performed by manual and/or motorized instruments (ultrasonic or sonic) and promotes an improvement in the clinical parameters of periodontal disease (reduction of probing depth, bleeding and gain of clinical insertion) [13].

However, studies show that mechanical instrumentation has impaired access in deeper periodontal pockets and areas of gum, which promotes a less favorable response to conventional treatment, since residues of subgingival stones and bacterial deposits may remain on the root surface corroborating the recolonization of these microorganisms[2].

Therefore, the use of complementary therapy to traditional therapy is necessary, among which the use of antimicrobials and PDT stands out[13]. Anselmo *et al.*, (2020) points out that the patient's collaboration is extremely valuable in maintaining periodontal health[11].

Antibiotic therapy has systemic action, enabling the reach of the entire oral and periodontal region. Nevertheless, medically may cause undesirable effects such as gastrointestinal disorders, bacterial resistance besides having to rely on the collaboration of the patient in the use of the drug[8]. Setiawatie *et al.*, (2018) adds that the drug has low effiacy in areas of vertical bone loss[14].

Local antimicrobial therapy is also used in a complementary way to root debridement, there are several means used among them belets and local applications. It is noteworthy that local use may be limited due to the depth of penetration of the drug in the deepest area of the pocket[14].

Due to these factors, the use of PDT has been increasingly investigated as an adjunct to approaches to isolated non-surgical mechanical instrumentation[15,16,13].

PHOTODYNAMIC THERAPY

The term "photodynamic therapy" was first introduced by John Toth in 1981, who noted the "photodynamic chemical effect". However, PDT has been used in the medical field for over a century, in which it originated accidentally in the early 20th century, when Oskar Raab and Hermann von Tappeiner "noticed that Paramecium spp. protozoa stained with acridine orange died after exposure to bright light"[16]. Several studies have demonstrated the beneficial effects of PDT on periodontal therapy when associated with a specific photosensitizer.[17,18].

The PDT has the concept of being dose-dependent because it is based on three components to be effective: photosensitizers (PS), light and oxygen, in which none of them can be excluded. Its mechanism of action consists in selective absorption of PS by bacteria and when activated by an appropriate wavelength in the presence of oxygen is taken to an excited state called triplet state[3]. At this moment the electrons are transferred from a low level to a higher energy level, and may occur in two ways, being in the type 1 reaction, which consists of transferring directly to the neighboring molecule or cell membrane to form a radical anion that reacts with oxygen to produce free radicals; or in the type 2 reaction transferring its energy directly to molecular oxygen giving rise to singlet oxygen[19].Both products of the reactions are extremely cytotoxic to microorganisms[20].

Ahad et al., (2016) demonstrated that PDT not only kills microbial cells within the biofilm, but also targets the extracellular matrix. Selectivity is due to the specific binding to unsaturated fatty acids present in the bacterial cell membrane, which are susceptible to free radical damage because it does not have an enzymatic defense, causing disruption of the cytoplasmic membrane and DNA[8].

PSs considered ideal, need to have non-toxic chemical purity (neutral pH), absorb light at the red band wavelengths of the visible spectrum, be quickly eliminated from normal tissue, have low cost and easy access, besides being able to generate a large number of cytotoxic products[19] .

The PS most commonly used in PDT include blue-methylene and blue toluidine both proved efficient due to their flat tricyclic molecules that have a quaternary nitrogen atom and present effective phototoxicity against various microorganisms[11].However, Wadhawa *et al.*, (2021) stated that these PS present some disadvantages such as accidental dental staining, limitations to determine the concentration and absorption capacity of the photosensitizer, as well as wavelength, and exposure time, which interferes in the range of photochemical effects and consequent microbial death[20].

In relation to the laser, the Diode with a wavelength of 660–680 nm is the most commonly tested combination[1]. Chambrone *et al.*, (2017) add that in the last decade, low-intensity diode lasers in conjunction with PS, i.e., PDT, have been used to reduce or eliminate periodontopathogenic bacteria as an adjunct to mechanical debridement in patients with periodontitis[16].

In addition to its antimicrobial effect, PDT has the ability to photobiomodulation, which corroborates the tissue recovery process [12]. According to Mallineni, *et al.*, (2020), the facilitating action in the healing of periodontal pockets is associated with the improvement in collagen synthesis provided by the use of low-power laser thus providing locations for new fixation of connective tissue[18].

Use of PDT in the periodontal treatment

The potential applications of infrared laser for the treatment of periodontitis and peri-implantitis, was evidenced by the American Academy of Periodontics (AAP), where lasers have been shown to promote the healing and regeneration of periodontal pockets, through debridement and decontamination of infected tissues, modulating or activating cellular metabolism in adjacent tissues[6].

Al-Ahmad, *et al.*, (2016), collected subgingival biofilm samples in patients with chronic periodontitis, found that the adjunct use of PDT associated with root scraping and straightening (RSS) has antimicrobial effects and favorable tissue healing. Similar results were observed in the in vitro study conducted by Jiang, *et al.*, (2019), which proved that the combination of PDT with RSS promotes a reduction in bone absorption levels and tissue inflammation and the decrease in gingival crevicular fluid resulting from increased levels of anti-inflammatory factors (IL-4 and IL-10) and decreasing inflammatory factors (IL-1 β, IL-6 and TNF-α), relieving not only the clinical effects of periodontitis through its antimicrobial effect, but also inhibitory the progression of periodontitis by inducing apoptosis of superinfiltrated macrophages[6]. Mistry, *et al.*, (2016) add as a result of their study a significant decrease in the level of IL-17 in GCF in patients with chronic periodontitis in both treatment modalities[12].

According to Ahad, *et al.*, (2016), the adjunct use of PDT in periodontal therapy promotes antimicrobial effects, a significant reduction in bleeding rates, however, their research demonstrated that the reduction of the depth of the pocket and in the gain of clinical insertion seems to be limited in patients with ≥ 6 mm probing depth and probing bleeding in at least 2 different quadrants. However, Shingnapurkar, *et al.*, (2016) and Wadhwa, *et al.*, (2021), showed that there is a reduction in probing depth and gain in the level of insertion with the adjunct use of PDT to RSS, at the end of 3 and 6 months. Gandhi, *et al.*, (2019), add that in addition to the improvement in all aforementioned clinical parameters, there is a reduction in the number of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*[22].

The effects of PDT have also been researched in the treatment of perimplantitis. Birang, *et al.*, (2017) found that there was no additional benefit with the use of PDT in the treatment of this pathology, however, PDT has short-term benefits for the treatment of primary peri-implantitis[17].

Case-control studies conducted by Bundidpun, *et al.*, (2018) showed a significant greater reduction in bleeding and gingival inflammation in patients in the test group when compared to patients who were part of the control group[20,23]. These improvements in clinical and microbiological parameters were also observed by Mallineni, *et al.*, (2020), who, in their study, used PDT with diode laser in a single session, associated with RSS in patients with chronic periodontitis[18]. According to Lin *et al.*, (2021), it is important that these treatments be done together, since PDT as monotherapy do not present statistically significant results regarding the depth of probing of clinical insertion leve[24].

Chambrone, *et al.*, (2017) also agree with the aforementioned assumption, although there is a need for further studies to deliberate the efficacy of PDT and its long-term effects[16]. The systematic reviews of Salvi *et al.*, (2019) and Dalvi *et al.*, (2021) show that PDT is more effective when associated with RSS, but the improvement in clinical parameters is debatable due to the fact that the use protocol is still considered heterogeneous, which limits the evidence about this therapy[22,23,21,13].

In contrast to the various benefits presented, the study by ANSELMO *et al.*, (2020) selected patients with chronic periodontal disease, and submitted the group to the RSS associated with PDT, using methylene blue as PS, however it was observed that it presents limitations regarding its concentration, which causes the formation of dimmer, due to its high aggregation capacity. Thus, it was observed that in contact with papain gel, which has antimicrobial activities, there is a reduction in this property of PS[11].

In vitro studies were conducted comparing PDT with drugs such as Cieplik, *et al.*, (2018), in which there was experimentation with three periodontal pathogens to investigate its antimicrobial efficacy and compared with chlorhexidine and metronidazole, which proved that PDT is as effective as antimicrobials, and does not damage cytoplasmic membranes[5]. Regarding Doxycycline, Setiawatie, *et al.*, (2018) showed that the results were better when a drug was associated with PDT than as monotherapy[14].

Studies by Rad, *et al.*, (2019) evaluated the virulence of strains of the bacterium *A. actinomycetemcomitans* treated with the combinations PDT + nanoparticles of chitosan, which generated a significant reduction in the expression of the bacteria colonization gene and biofilm formation, while PDT + chitosan nanoparticles + indocyanin green, was not able to reduce the expression of this gene[24]. In contrast, Pourhajibagher, *et al.*, (2021), when evaluating the same bacterium chose to make simultaneous use of PDT with curcumin photosensitizer and sonodynamic antimicrobial chemotherapy (ultrasonic waves), obtaining as a result the ability to reduce the expression of virulence genes and decrease the severity of periodontal disease affected by the bacteria mentioned in the present study[19].

RESULTS

Articles that addressed the use of photodynamic therapy in the treatment of periodontal disease and for the recovery of a larger number of articles were included, the inclusion and exclusion criteria were not applied at first, totaling 397 journals. All publications were analyzed, then applying the predefined criteria. All the studies then chosen were evaluated by reading the title, abstract and then selected for full reading.

The search resulted in 397 articles, of which 378 did not meet the inclusion criteria: 150 were outside the inclusion period, 22 clinical case reports, 40 literature narrative reviews, 102 were excluded by title, and 64 were excluded by their abstract, totaling 19 articles included in the study (Flowchart 1).

YEAR	AUTHOR	SAMPLE	RESULTS
2016	**Ahad, *et al.*** [8]	Case-control: One group underwent only RSS and another group underwent PDT+RSS using phenothiazine chloride as a photosensitizer. Patients with periodontal pockets ≥ 6 mm in depth and bleeding on probing in at least 2 different quadrants.	The association of PDT+ RSS showed antimicrobial effects, significantly reduced bleeding rates, but reduced pocket depth and limited clinical attachment gain.
2016	**Al-Ahmad, *et al.*** [6]	Use of PDT in bacterial strain suspensions and collected subgingival biofilm samples in patients with chronic periodontitis.	High antimicrobial effects on subgingival biofilm associated with more favorable tissue healing effects.
2016	**Mistry, *et al.*** [12]	Diode laser PDT + RSS in patients with chronic periodontitis	Significant decrease in the level of IL-17 in the GCF in patients with chronic periodontitis.
2016	**Shingnapurkar *et al.*** [1]	Diode laser PDT + RSS in patients with chronic periodontitis	Probing depth reduction and insertion level gain with use adjunct to RSS.
2017	**Birang, *et al.*** [17]	Control case: Patients with peri-implantitis, divided into a control and test group (PDT), followed for 3 months	There were no significant differences between groups. Although PDT has short-term benefits for treating primary peri-implantitis

2017	**Chambrone, *et al.*** [16]	Meta-analysis of randomized clinical trials of RSS and PDT with patients over 18 years of age with chronic periodontitis	PDT shows improvement in clinical attachment level and probing depth. However, standardization in the protocol for the use of PDT is necessary.
2018	**Bundidpun, *et al.*** [20]	Control case: Patients with moderate to severe chronic periodontitis, with PS ≥ 4 mm treated with subgingival ultrasonic piezoelectric device alone in the control group and auxiliary treatment with PDT in the test group.	The association of PDT with RSS with ultrasound leads to a significantly greater reduction in gingival bleeding and gingival inflammation.
2018	**Cieplik, *et al.*** [5]	In vitro study with three periodontal pathogens to investigate the antimicrobial efficacy of PDT compared to chlorhexidine and metronidazole	PDT in conjunction with a phenalenone derivative (SAPYR) is as effective as chlorhexidine, in addition to not damaging the cytoplasmic membranes.
2018	**Setiawatie, *et al.*** [14]	In vitro study with a sample of *A. actinomycetemcomitans* strain divided into 4 groups: A – Treated with PDT; B – Treated with 0.1% doxycycline and PDT; C – Only with dioxycycline; D - Control group	When exposed to laser for 120s, group A and B did not show significant differences. However, for 30s, the most used time in clinical treatment, the combination of doxycycline and PDT showed better results in antibacterial activity
2019	**Gandhi, *et al.*** [22]	Control case: Patients with periodontitis, with a 5mm bag in each upper quadrant. Each quadrant was divided into a control group (RSS in 2 quadrants), test group 1 (RSS + PDT) and test group 2 (RSS + low power laser)	Both test groups showed significant reductions in gingival index, probing depth, level of clinical attachment and in the number of *P. gingivalis*, and A. *actinomycetemcomitans*.
2019	**Jiang, *et al.*** [3]	Control case: Patients with periodontitis, with a 5mm bag in each upper quadrant. Each quadrant was divided into a control group (RSS in 2 quadrants), test group 1 (RSS + PDT) and test group 2 (RSS + low power laser)	PDT + RSS - decrease in bone absorption levels and tissue inflammation.
2019	**Rad, *et al.*** [24]	Control case: Patients with periodontitis, with a 5mm bag in each upper quadrant. Each quadrant was divided into a control group (RSS in 2	PDT + chitosan nanoparticles - significant reduction in gene expression for bacterial colonization and biofilm formation

		quadrants), test group 1 (RSS + PDT) and test group 2 (RSS + low power laser)	
2019	**Salvi, *et al.*[13]**	Systematic review and meta-analysis	It was found that there is a high variability of clinical results within a period of 6 months, a low number of controlled studies and heterogeneity of studies limit the evidence on PDT
2020	**Anselmo, *et al.*[11]**	Control case: Patients with periodontitis in control group (RSS alone) and test group (RSS+TFD). They will use methylene blue, as a photosensitizer, associated with papain gel due to its bactericidal action.	PDT with methylene blue photosensitizer has concentration limitations due to dimmer formation. Papain gel will be used to decrease FS aggregation.
2020	**Mallineni, *et al.*[18]**	Control case: Individuals with chronic periodontitis were randomly treated with RSS, followed by a single session of PDT (test) or RSS (control) alone	PDT + RSS - significant improvement in clinical and microbiological parameters
2021	**Dalvi, *et al.*[21]**	Systematic review and meta-analysis	PDT is more effective when performed in conjunction with RSS, but the improvement in results is debatable. In addition to the protocol of use still being considered inconsistent and inconclusive
2021	**Lin, *et al.*[23]**	Systematic review and meta-analysis	No statistically significant differences were identified in PDT in probing depth and clinical attachment level
2021	**Pourhajibagher, *et al.*[19]**	Analysis of the virulence of the *A. actinomycetemcomitans* bacteria with the simultaneous use of PDT with curcumin photosensitizer and sonodynamic antimicrobial chemotherapy (ultrasonic waves)	PDT together with antimicrobial chemotherapy is able to reduce the expression of virulence genes and reduce the severity of periodontal disease affected by the bacteria mentioned in the study
2021	**Wadhwa, et al.[7]**	Case control: Patients with generalized chronic periodontitis treated with RSS. In some experimental sites (specific periodontal pockets), in addition to RSS, PDT was applied, using indocyanine green as a photosensitizer.	PDT + RSS - Significant improvement in gingival bleeding index, probing depth and attachment level relative to the end of 3 and 6 months of therapy.

Chart 1 – Characteristics of the articles included in the Integrative Review

Conclusion

PDT does not replace conventional periodontal treatments of root debridement, however several studies have shown that its use as an adjuvant is effective in non-surgical therapy, due to its efficacy against oral infections and its ability to reduce inflammation. Its painless and little invasive characteristic, with minimal adverse effects and no risk of microbial resistance, makes PDT an alternative to the use of antibiotic therapy. In addition, it is a simple and low-cost technique, being able to eliminate periodontal pathogens and reach restricted access sites such as gums and deep periodontal pockets.

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