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Evaluation of the Adjuvant Effect of Antimicrobial Photodynamic Therapy in the Treatment of Periodontal Disease: Literature Review

Avaliação do Efeito Adjuvante da Terapia Fotodinâmica Antimicrobiana no Tratamento da Doença Periodontal: Revisão de Literatura

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Abstract

Introduction: Antimicrobial Photodynamic Therapy (aPDT) is a promising approach with several clinical applications, including the treatment of periodontal diseases, by acting as an adjuvant to the conventional treatment of periodontal disease by allowing reduction of periodontopathogens, with no systemic side effects and minimal possibilities of bacterial resistance. Objective: To verify, through the scientific literature, the effectiveness of Antimicrobial Photodynamic Therapy associated with conventional periodontal treatment. Methodology: The literature review was conducted in the MEDLINE databases - PubMed, Scopus and Web of Science. The articles were selected through the analysis of titles and abstracts published in the period from 2007 to 2018. Selected articles were published in their entirety and with free or controlled access, of the type clinical trial on the subject, without restriction of languages. The terms used were: "Periodontal diseases"; "Chronic Periodontitis" and "Photochemotherapy." Results: 84 articles were found, and 20 clinical trials that met the inclusion criteria were analyzed. There were different clinical protocols for the association of aPDT with the conventional treatment of periodontal disease. a number of different clinical outcomes were found for each of the proposed clinical protocols. Conclusion: Considering the clinical trials investigated, conflicting results regarding the efficacy of aPTD as an adjuvant treatment of the conventional treatment of periodontal disease are observed. and lack of standardization of clinical parameters and protocols.

Keywords: Chronic Periodontitis. Periodontal Diseases. Photochemotherapy.

Resumo

A terapia fotodinâmica antimicrobiana (aPDT) é uma abordagem promissora com várias aplicações clínicas, incluindo o tratamento das doenças periodontais, ao atuar como um adjuvante ao tratamento convencional da doença periodontal por permitir redução de periodontopatógenos, com ausência de efeitos sistêmicos colaterais e mínimas possibilidades de resistência bacteriana. O objetivo deste estudo é verificar, por meio da literatura científica, a eficácia da terapia fotodinâmica antimicrobiana associada ao tratamento periodontal convencional. A revisão de literatura foi conduzida nas bases de dados MEDLINE – PubMed, Scopus e Web of Science. Os artigos foram selecionados através da análise de títulos e de resumos publicados no período de 2007 a 2018. Foram selecionados artigos publicados na íntegra e com acesso livre e gratuito, ou controlado, do tipo ensaio clínico sobre o tema, sem restrição de idiomas. *Os termos utilizados foram: Periodontal diseases; Chronic Periodontitis e Photochemotherapy. Foram encontrados 84 artigos, e 20 ensaios clínicos que atenderam os critérios de inclusão, foram analisados. Observou-se diferentes protocolos clínicos para a associação da aPDT com o tratamento convencional da doença periodontal. Também foram encontrados diferentes desfechos clínicos para cada um dos protocolos clínicos propostos. Conclusão: Considerando os ensaios clínicos pesquisados, observa-se resultados conflitantes frente à eficácia da aPDT como tratamento adjuvante do tratamento convencional da doença periodontal. Observa-se, ainda, uma produção literária escassa e a falta de uma padronização dos parâmetros e dos protocolos clínicos.*

Palavras-chaves: *Periodontite Crônica. Doença Periodontal. Fotoquimioterapia.*

Introduction

Periodontal disease is defined as an inflammatory disease of the teeth supporting tissues caused by specific micro-organisms - forming a pathogenic microbiota - resulting in gingival bleeding, loss of periodontal tissue support, manifested through the presence of periodontal pockets, gingival recession or both, clinical insertion loss, alveolar bone loss, this being the latter evaluated radiographically[1,2].

The primary etiological factor of periodontal disease is the dental biofilm, but its interaction with the host - defense mechanisms, genetic and environmental factors - is what will determine the degree and the evolution of the disease[3].

The conventional treatment of periodontal disease consists of reducing pathogenic microbiota through guidance of oral hygiene associated with scaling and crown-root planing. The scraping and crown-root planing performed with hand instruments, and even with the use of ultrasonic devices, can result in significant clinical improvement in the vast majority of cases. In some cases, however, the techniques of manual instrumentation currently available are not sufficient for the complete elimination of microbiota and subgingival calculus[4-6].

The effectiveness of scraping and crown-root planing may decrease with the presence of deep periodontal pockets, the involvement of furcation areas and the presence of anatomical variations - for example of the root curvature, and the ability that some bacteria have to invade adjacent tissues. Thus, the complete removal of bacterial deposits is hardly performed, and the bacterial reservoirs can survive in areas inaccessible mechanically, causing the microbial activity in deep periodontal pockets can persist or return after the mechanical therapy[7-9].

Thus, other therapeutic approaches, such as open field scraping and the use of antibiotics, are used to reduce the therapeutic failure. However, adverse effects are reported with the use of these therapeutic strategies, in a way that the proposed techniques may be associated to undesirable results, such as discomfort and post-operative morbidity or development of bacterial resistance. Based on these facts, alternative methods are being studied with the objective of achieving a more efficient therapy, such as antimicrobial phytochemicals and the use of lasers[10-12].

The association of LASER (In English: *Light Amplification by Stimulated Emission of Radiation - Amplificação da luz por emissão estimulada de radiação*) of low power with photosensitizers - also called Photodynamic Therapy - has been presented as one of the most effective treatments in the reduction of bacterial contamination of periodontal pockets[13], once that proved to be really effective in eliminating pathogens present in periodontal infections, when associated to the scraping and planing of root surfaces[4,8,12,14-18].

The objective of this study was to conduct a review of the scientific literature through a critical analysis about the efficacy of Antimicrobial Photodynamic therapy associated with conventional periodontal treatment.

2 Development

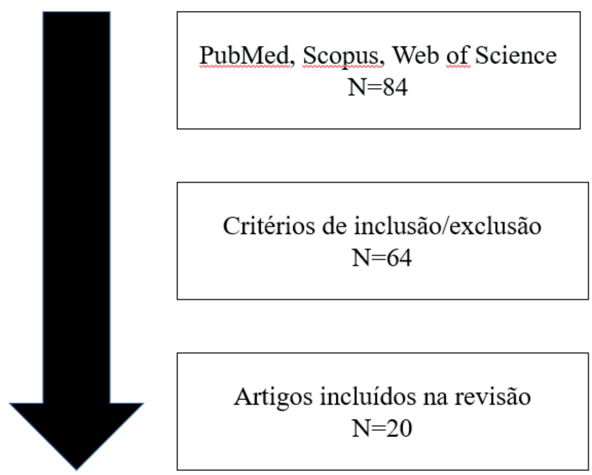
2.1 Methodology

The search for scientific articles was conducted in the databases Pubmed, Scopus and Web of Science, using the following keywords: *periodontal diseases* AND/OR *chronic periodontitis* AND/OR *Photochemotherapy*.

The eligibility criteria were: Articles published in their entirety and with free or controlled access, of the type clinical trial on the subject, without restriction of languages, published between 2007 and 2018 were selected. As exclusion criteria clinical trials were adopted with patients with systemic diseases (diabetes, immunocompromised patients, obese), because such clinical signals can affect the progression of chronic periodontitis and compromise the host response to periodontal therapy; smokers, since studies indicate a dependent relationship between smoking and the increase of residual pockets[11] patients diagnosed with aggressive periodontitis and patients who made use of antibiotic therapy. This cutting-off was necessary since it is intended to evaluate the efficacy of therapy, to begin with, in healthy patients.

84 articles indexed with the selected descriptors were found. After reading the abstracts, 64 articles were excluded because they did not meet the inclusion criteria. Therefore, the revision was attended by 20 studies (Figure 1).

Figure 1- Organogram of the selection process of the studies



Source: The authors.

The selected clinical trials are shown in Table 1, in chronological order, highlighting its main characteristics such as sample used, clinical parameters evaluated, clinical protocol used, and the results obtained.

Table 1 - Main information of trials included in the review

Authors:	Type of Study	n	Average Age	Clinical Protocol	Clinical parameters evaluated	Outcome
Braun et al., [14]	*Split mouth*	20	46.6 ± 6.1	FS: Phenothiazine chloride Laser used: Diode (660 nm) Single Application Follow-up time: 3 months	Bleeding on probing, level of clinical insertion and gingival recession.	RACR combined with aPDT led to significant improvement of clinical parameters investigated
Ruhling et al.[7]	Parallel	60	48 ± 8	FS: ortho-toluidine blue 5% Laser used: Diode (635 nm) Single Application Follow-up time: 3 months	Plaque index, bleeding on probing, level of clinical insertion and bleeding on probing	RACR combined with aPDT led to significant differences among the clinical parameters investigated

Lui, Carbet, Jin[19]	*Split mouth*	24	50	FS: methylene blue 1% Laser used: Diode (940 nm) Single Application Follow-up time: 1 and 3 months	Plaque index, bleeding on probing, depth of probing and gingival recession	RACR combined with aPDT led to significant improvement of clinical parameters investigated, in the short term
Theodoro et al.[6]	*Split mouth*	33	43.12 ± 8.2	FS: Toluidine Blue Laser used: Diode (660 nm) Single Application Follow-up time: 2, 3 and 6 months	Plaque index, bleeding on probing, depth of probing, gingival recession and level of clinical insertion	RACR combined with aPDT led to significant differences among the clinical parameters investigated
Berakdar et al. [16]	*Split mouth*	22	59.3	FS: methylene blue 0.005% Laser used: Diode (670 nm) Single Application Follow-up time: 1, 3 and 6 months	Plaque index, bleeding on probing, depth of probing, and level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated
Campos et al.[11]	*Split mouth*	13	48.15 ± 7.53	FS: methylene blue Laser used: Diode (660 nm) Single Application Follow-up time: 3 months	Plaque index, bleeding on probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, in single root teeth
Alweali, Al-Khateeb; Al-Sadi[8]	*Split mouth*	16	40.9 ± 13.34	FS: Phenothiazine chloride Laser used: Diode (660 nm) Single Application Follow-up time: 1, 3, 6 and 12 months	Plaque index,; depth of probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, for at least one year.
Balata et al.,[17]	*Split mouth*	22	43.18	FS: methylene blue 0.005% Laser used: Diode (660 nm) Single Application Follow-up time: 1, 3 and 6 months	Plaque index, bleeding on probing, gingival recession; depth of probing; level of clinical insertion	RACR combined with aPDT led to significant differences among the clinical parameters investigated
Dilsiz; Canacki, Aydin, [20]	*Split mouth*	24	40.7 ± 7.3	FS: methylene blue 1% Laser used: Diode (660 nm) Two applications Follow-up time: 6 months	Plaque index, bleeding on probing, depth of probing; level of clinical insertion	RACR combined with aPDT led to significant differences among the clinical parameters investigated
Joseph et al.[12]	Parallel	88	39.6 ± 8.7	FS: methylene blue Laser used: Diode (655 nm) Single Application Follow-up time: 1, 3 and 6 months	Plaque index, bleeding on probing, depth of probing; level of clinical insertion; gingival recession	RACR combined with aPDT led to significant improvement of clinical parameters investigated, in the short term
Joseph et al.[21]	Parallel	27	47	FS: Phenothiazine chloride Laser used: Diode (660 nm) Three applications Follow-up time: 3, 6, 9 and 12 months	depth of probing; bleeding on probing; level of clinical insertion	There was no additional improvement in terms of reducing the level of clinical insertion and probing depth, but it resulted in a significant improvement of bleeding on probing.
Pourabbas et al.[22]	*Split mouth*	22	46 ± 8	FS: Toluidine Blue Laser used: (638 nm) Single Application Follow-up time: 3 months	Plaque index,;depth of probing; level of clinical insertion;gingival recession	RACR combined with aPDT led to significant differences among the clinical parameters investigated
Carvalho et al.[23]	Parallel	34	48.2 ± 9.5	FS: methylene blue 0.01% Laser used: Diode (660 nm) Single Application Follow-up time: 3, 6 and 12 months	Plaque index, bleeding on probing, depth of probing; level of clinical insertion	RACR combined with aPDT led to significant differences among the clinical parameters investigated
Correa et al.[24]	*Split mouth*	15	48.1 ± 7.5	FS: methylene blue Laser used: Diode (660 nm) Single Application Follow-up time: 3 months	Plaque index, bleeding on probing, depth of probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, in the short term
Birang et al.[25]	*Split mouth*	20	37.2 ± 8.6	FS: Malachite green Laser used: Diode (810 nm) Two applications Follow-up time: 3 months	Plaque index,;depth of probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, in the short term

Monzavi et al.[26]	Parallel	50	49.6 ± 8.5	FS: Green Indocyanine Laser used: Diode (810 nm) Three applications Follow-up time: 1 and 3 months	Plaque index, depth on probing; bleeding on probing; level of clinical insertion	There was no additional improvement in terms of reducing the level of clinical insertion and plaque index, but it resulted in a significant improvement of depth probing.
Pulikkotil et al.[27]	*Split mouth*	20	45.2 ± 6.7	FS: methylene blue Laser used: LED 628 Hz Single Application Follow-up time: 7 days, 1 and 3 months	Plaque index, bleeding on probing, depth of probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, after 1 and 3 months.
Ahad et al.[18]	*Split mouth*	30	38.67 ± 10.52	FS: Phenothiazine chloride Laser used: Diode (660 nm) Single Application Follow-up time: 1 and 3 months	Plaque index; index of modified sulcular bleeding; depth on probing; clinical level of insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated
Theodoro et al.[9]	Parallel	34	43.12 ± 8.2	FS: methylene blue Laser used: Diode (660 nm) Single Application Follow-up time: 2, 3 and 6 months	Bleeding on probing; depth on probing; level of clinical insertion	RACR combined with aPDT led to significant improvement of clinical parameters investigated, when compared to the use of amoxicillin and metronidazole, as adjuvant.
Segarra-Vidal et al.[28]	Parallel	60	55 ± 2	FS: methylene blue 0.005% Laser used: Diode (670 nm) Three applications Follow-up time: 5, 13 and 25 weeks	Plaque index; probing depth; gingival recession, clinical level of insertion; bleeding on probing	RACR combined with aPDT led to significant differences among the clinical parameters investigated

FS: photosensitizer
RACR: Scaling and crown-root planing
aPDT: Antimicrobial Photodynamic Therapy
NM: nanometers
Source: Research Data.

The association of Laser (*light amplification by stimulated emission of radiation - Amplificação da luz por emissão estimulada de radiação*) of low power with photosensitizers - called Antimicrobial Photodynamic Therapy (aPDT - *Antimicrobial Photodynamic Therapy*) - is presented as one of the most effective treatments in the reduction of bacterial contamination of periodontal pockets.

The antimicrobial Photodynamic Therapy (aPDT - in English: *Antimicrobial photodynamic therapy*) is a new treatment modality that has been developing rapidly in various medical specialties since the decade of 1960 and was defined as "the inactivation of cells, micro-organisms or molecules induced by light ". The action of aPDT was observed for the first time in 1900 by Oscar Raab who described that a protozoan could be killed in the presence of acridine orange associated to a source of visible light. It was, therefore, a modality phototherapy unit where three factors act simultaneously: The photosensitizer (or dye), a source of light and oxygen[29-31].

Photosensitizers are dyes composed of molecules able to absorb light energy and use it to promote chemical reactions in cells and tissues when exposed to light. To have the desired effect, the color of the dye used in photodynamic therapy must be compatible with the wavelength of light emitted and must have a minimum toxicity and high capacity of absorption[31].

There are several photosensitizers available to aPDT, but the disinfection related to periodontopathogens usually indicates the use of phenothiazinic photosensitizers, as toluidine blue and methylene blue. Nevertheless, other photosensitizers have been tested in vitro studies , such as: the green malachite, rose bengal, phthalocyanine, porphyries, the photo diazine and erythrosine. The interaction between the photosensitizer and micro-organisms occurs in a few minutes and this period (time of incubation or pre-irradiation) must be complied with before the phototherapy[13,31].

In order to occur the photochemical and photophysical reactions that cause cell death, after phototherapy, at an appropriate wavelength, the molecule of the photosensitizer must absorb a photon of light, and undergo a transition from its fundamental state, low energy level, for a singlet state of higher energy. At this moment, there may be loss of energy through processes of fluorescence of singlet state to the fundamental state and/or the process of intersystem crossing occur, leading the molecule to the triplet state. In the triplet state, the energy can be dissipated by the process of phosphorescence , returning the molecule to its fundamental state and/or transfer energy to other molecules of the medium [29,30].

The positive effects of aPDT in periodontal biofilm were tested *in vitro* and its cytotoxic action against many periodontal pathogens, including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis* and *Fusobacterium nucleatum,* was demonstrated[29.32].

Andersen et al.[4] developed the first study that sought to assess the effectiveness of aPDT to conventional periodontal treatment. The sample consisted of 33 individuals diagnosed with periodontal disease, which were randomly divided into three groups: Group 1 - aPDT; Group 2 - RACR (scaling and crown-root planing); and Group 3 - aPDT + RACR. The clinical parameters assessed were: bleeding on probing, the depth of the periodontal pocket and level of clinical insertion. The photosensitizer used was 0.005% methylene blue and the laser was the diode (Periowave ™), with a wavelength of 670 nm and a maximum power of 150 mW. The results showed that the association between aPDT and RACR produces more effective results, for the clinical parameters assessed, than the conventional treatment.

The effectiveness of the periodontal treatment is observed , ideally, through the following clinical parameters: Plaque index, bleeding on probing, depth of probing; level of clinical insertion; gingival recession[6].

The plaque Index refers to the presence of microbial biofilms on dental surfaces. The bleeding on probing index consists of the occurrence of gingival bleeding observed in up to 10 seconds after the removal of the probe from the furrow. The probing depth, in turn, is determined by the distance between the gingival margin and the bottom of the furrow or periodontal pocket. The level of clinical insertion is determined from the distance between the cement-enamel junction (JCE) and the bottom of the furrow or the periodontal pocket. The gingival recession corresponds to the insertion loss, resulting in a lower position of the free gingival margin, in any part of the exposed root surface.

In search of effective results, the clinical research makes use of various types of clinical protocols that accumulate successes and failures before the aPDT while treatment of conventional therapy for episodes of periodontal disease.

The 20 trials included in this review of the literature were published between the years of 2008 and 2018 and comprised a total of 640 healthy patients diagnosed with chronic periodontitis. The mean age among the participants ranged from 37.2 ± 8.6[25] to 59.3 years[16]. The size of the sample ranged from 13[11] to 88 individuals[12] included in the searches.

In terms of the design of the study, 13 are the type split mouth[8,9,11,14,16-20,22,24,25,31] and 7 were conducted by parallel type[6,7,12,21,23,26,28]. The positive results for the association were found in 9 studies of the type split mouth and in 2 studies of parallel type. The studies of the type split mouth have a lower standard of error when compared to the type parallel. The statistical efficiency increases when the patient serves as his or her own control, reducing the number of patients necessary for the study. The main disadvantage of this type of study is the risk of systemic intervention, making the treatment interfere in the outcome of the control group, known as "*carry-across*"[33] effect.

In relation to the type of photosensitizer used in the aPDT, it was observed the use of methylene blue (at concentrations of 0.005%, 0.01% and 1%), the phenothiazine chloride, blue toluidine, green malachite and green indocyanine. The effect dyes are the most commonly used in dentistry, being the methylene blue the most well-known. It is also important to know the concentration used by the photosensitizer. In that regard, specifically, the use of methylene blue in periodontics methylene blue must be chosen in the concentration of 0.01%, since the concentration of 0.005% is indicated in cases where there is no exudate, blood, gingival fluid, saliva or any other type of diluent or protein content[34].

The diode laser was used in different wave lengths, ranging from 635 nm[7] to 810 nm[25,26] and one of the studies used LED[31]. In 11 studies, the wavelength used was 660 nm[6,8,9,11,14,17,18,20,21,23,24]. It is considered that the best source of radiation is that, at a lower cost, provides the greatest amount of light possible in maximum absorption of photosensitizer without significant thermal effects.

In relation to the number of sessions, 15 studies have made a single application of aPDT[6-9,11,12,14,16-19,22-24,31] and 5[20,21,25,26,28] used multiple sessions. It was observed that the application of the aPDT more than once did not result in significant improvements to the therapy.

The duration of the studies follow-up varied considerably, ranging from 7 days [27] up to 1 year[8,21,23]. Regarding the type of outcome observed, it was observed that, in 11 trials, the association between the aPDT and conventional periodontal treatment showed significant improvements of the clinical parameters evaluated. In one study, such improvements were observed only for the index of bleeding on probing and, in another, only for the depth of probing. In 7 trials it was not possible to observe significant improvements of clinical parameters observed. In general, it can be observed an additional benefit of association between aPDT and the conventional treatment, in short-term studies, according to the results of clinical trials with follow-up of up to 3 months. In studies with follow-up time exceeding 6 months[8,21,23] controversial results were found. It is believed that the success of the periodontal treatment reflects the control of oral hygiene of participants included, highlighting the importance of support periodontal therapy. Thus, regular oral hygiene instructions must be provided to patients with periodontal treatment in order to strengthen the clinical improvements reached[35].

The clinical protocols used underwent an intense variety of methodologies, in what refers to the type of *laser*, the frequency of application, the type of the photosensitizer and its concentration, causing the results found to be understood in the light of the heterogeneity that characterize them. This fact is justified by the lack of a protocol considered as ideal for use of aPDT in dental practice.

3 Conclusion

The trials that assessed the efficacy of aPDT as adjuvant treatment to conventional treatment of periodontal disease are still limited and there is not a standardization of parameters and clinical protocols, making conflicting results to be found and it is not possible to a direct comparison between the protocols applied and the results obtained. Thus, the results obtained in this literature review motivate the search for the standardization of a clinical protocol, in order to promote greater benefits to patients affected by periodontal disease.

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