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Antimicrobial photodynamic therapy compared to systemic antibiotic therapy in non-surgical treatment of periodontitis: Systematic review and meta-analysis.

Antimicrobial photodynamic therapy compared to systemic antibiotic therapy in non-surgical treatment of periodontitis: Systematic review and meta-analysis.

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ABSTRACT

Background: Periodontitis is one of the most prevalent inflammatory diseases in humans. It is associated with the presence of bacteria and is mediated by the host's immune response This study represents a systematic review and meta-analysis trying to answer the following question: "What is the effect of antimicrobial photodynamic therapy (aPDT) as an adjunct to scaling and root planing (SRP) compared to systemic antibiotic therapy with amoxicillin plus metronidazole (AMX+MTZ) on the non-surgical treatment of periodontitis?". **Methods:** Clinical studies comparing aPDT with systemic use of AMX / MTZ were searched until January of 2020 using the databases: PubMed / MEDLINE, SCOPUS, EMBASE, Cochrane Central, Web of Science and Scielo, as well manual searches in related journals. Periodontal clinical parameters such as probing depth (PD), clinical attachment level (CAL) and bleeding on probing (BOP) were statistically analyzed. **Results:** Five randomized clinical studies (RCTs) were included within the eligibility criteria and served as a basis for qualitative and quantitative analyzes. All the studies reported an improvement in the clinical parameters with both therapies, although in a direct comparison, our analyzes did not find statistical differences that indicate the superiority of one supporting treatment in relation to the other. **Conclusion:** Although the limited number of RCTs and the great heterogeneity between them, it can conclude that aPDT presents similar clinical results compared to antibiotic therapy with AMX+MTZ as adjuvants in the non-surgical treatment of periodontitis.

Key words: Photodynamic Therapy; Periodontitis; Amoxicillin; Metronidazole.

1. INTRODUCTION

Periodontitis is characterized as an inflammatory disease associated with the presence of bacteria and their products, and mediated by the host's immune response, resulting in insertion loss [1]. In the new classification of periodontal diseases, there was a unification of what we previously knew as chronic periodontitis and aggressive periodontitis [2]. These two disease modalities were unified and structured in a single strand, graded progressively in stages and degrees, according to severity or complexity and speed of progression [3]. The positioning articles of the World Periodontics Workshop held in 2017 reached a consensus that: (1) there is not enough pathophysiological evidence to divide these two conditions, or to establish different interventions for their treatment; (2) there is little consistent evidence that these are distinct diseases; (3) the averages of periodontitis progression are consistent in the observed populations; (4) however, there is evidence that specific segments of the population exhibit more rapid severity and progression compared to other individuals of the same age; (5) a classification based only on the severity of the disease becomes a failure in the management of an individualized approach, leaving aside risk factors and the complexity of the therapy in each case [4-6].

Non-surgical mechanical therapy is still the treatment of choice for periodontitis, although in cases where there are periodontal pockets with depths greater than 6 mm surgical therapy, as well as prescription of systemic antibiotics and /or adjunctive therapies are usually indicated [7]. In patients with aggressive periodontitis [8] and also in chronic disease [9,10] (as periodontitis was previously divided [2]), the use of systemic antibiotic therapy combined with conventional mechanical treatment presents better clinical parameters than scaling and root planing as monotherapy [11]. However, the administration of antibiotics in addition to periodontal therapy is often empirically-based by the clinician, and there is a belief that amoxicillin plus metronidazole (AMX+MTZ) is the most potent combination of antibiotics to reduce clinical parameters such as probing depth in medium and deep pockets, bleeding on probing and gain of clinical attachment level [8,9,10,11,12]. A recent systematic review [13] reported that the combination of these antibiotics shows the best results in periodontal clinical tests in the adjunctive treatment of periodontitis, compared to the other antibiotics that were used in periodontal treatment [13].

With the constant growth of bacterial resistance to antibiotics, and the complex structure and organization of bacteria biofilms in the oral cavity [14], it is becoming important to develop new alternatives and clinical approaches to reduce the indiscriminate prescription of antibiotics. Thus, antimicrobial photodynamic therapy (aPDT) has become a promising adjunctive therapy to scaling and root planing (SRP) in the treatment of periodontitis. Experimental studies in animals [12,15] and clinical studies in humans [16,17] have shown significant improvements in periodontal clinical parameters compared conventional mechanical treatment, and some studies

have compared the effects of systemic antibiotic therapy with aPDT in periodontal clinical treatment [18,19,20,21,22].

aPDT basically consists of three components: a light source, a chemical molecule known as a photosensitizer (PS) and the presence of oxygen [14]. After a pre-irradiation period in the tissues, the PS is excited by light (in a length of wave compatible with its absorption spectrum) and reactive oxygen species (ROS) are produced, reacting with bacteria and their by-products. This mechanism can progress in two ways: (1) "type I reactions", by electron transfer, where the PS molecules are excited from their singlet electronic state, to a triplet state (due to a change in the electron spin) being able to interact with biomolecules around it via electron transfer. This process allows the production of reactive oxygen species such as hydroxyl radicals, hydrogen peroxide and superoxide anions; (2) "type 2 reactions" by the transfer of energy, as a result of the change in the state of the PS molecule, energy is transferred directly to the oxygen molecules, being elevated from the ground state (triplet) to the excited state (singlet oxygen), which has highly oxidative properties [23,24].

In this context, aPDT stands out as a local treatment, non-toxic to tissues and that does not lead to the selection of resistant bacteria [23], due to the ability to destroy a lot of molecular targets of less complex microorganisms such as bacteria, viruses and fungi [25]. Therefore, the objective of this study was to conduct a systematic review and meta-analysis trying to investigate if the aPDT as an adjunct to SRP promotes similar clinical benefits when compared to systemic antibiotic therapy using a mixture of AMX+MTZ in non-surgical treatment of periodontitis.

2. MATERIAL AND METHODS

2.1 Registration of the PICO protocol and strategy

This systematic review was structured according to the "Preferred Reporting Items for Systematic Review and Meta-Analysis" guide (PRISMA) [26]. The PICO strategy (patients / intervention / comparison / results) was developed through the following question: “What is the effect of antimicrobial photodynamic therapy (aPDT) as an adjunct to scaling and root planing (SRP) compared to systemic antibiotic therapy with amoxicillin plus metronidazole (AMX+MTZ) on non-surgical treatment of periodontitis?” The criteria considered were (1) population: patients over 20 years of age with aggressive or chronic periodontitis[2]; (2) intervention: patients treated with antimicrobial photodynamic therapy in conjunction with basic periodontal therapy; (3) comparison: patients treated with systemic antibiotic therapy with AMX+MTZ in conjunction with basic periodontal therapy; (4) results: improvements in periodontal clinical parameters such as probing depth (PD), gain of clinical attachment level (CAL), reduction of bleeding at probing (BOP).

2.2 Eligibility Criteria

The eligibility criteria used in this review were: Randomized clinical studies (RCTs) only (1); adult patients over 20 years of age diagnosed with chronic or aggressive periodontitis [2], regardless of gender (2); Studies that had groups with the two treatments proposed in this review, with the control group (systemic antibiotic therapy) being treated with the association of AMX+MTZ and test group being treated with aPDT.; (3) Studies that had clinical parameters containing probing depth (primary result), clinical attachment level, and bleeding on probing (secondary results); (4) Articles in English text.

In-vitro studies (1), in animals (2), only with laser therapy (3), patients without antimicrobial therapy associated to scaling and root planing (4), use of systemic antibiotics other than AMX+MTZ (5), clinical case (6), case series (7), letters to the editor (8), abstracts (9) and opinion articles (10) were not considered for the analysis.

2.3 Search strategy

First, keywords were defined with searches in the MESH descriptors to form the search strategy, free terms were also used, as well as combinations such as "Periodontitis", "Chronic Periodontitis", "Photochemotherapy", "Photodynamic therapy", "aPDT", "anti-bacterial agents", "antibiotic therapy", "amoxicillin", "metronidazole", "dental scaling", "root scaling" were searched together in different formats by two authors (L.F.T and T.E.R) on PubMed / MEDLINE, SCOPUS, EMBASE, Cochrane Central, Web of Science and Scielo, resulting in a search like "[photodynamic [All Fields] AND (" amoxicillin "[MeSH Terms] OR" amoxicillin "[All Fields]) AND (" metronidazole "[MeSH Terms] OR" metronidazole "[All Fields]) AND (" periodontitis "[MeSH Terms] OR" periodontitis "[All Fields])]". A complementary manual search was also accomplished in articles from the last 6 months in the newspapers: Journal of Periodontology, Journal of Clinical Periodontology, Lasers in Medical Science, Lasers in Surgery and Medicine, Journal of Photochemistry and Photobiology B and Photodiagnosis and Photodynamic Therapy. The survey was conducted in January, 2020.

The screening and scanning of the articles were accomplished by two independent authors, a primary reading of the titles and later of the abstracts was accomplished to select eligible articles. If there was an omission of some important information, within the eligibility criteria, or if any doubts regarding the content of the article were created after reading the title, it was chosen to read the abstract, and the same criterion was used in the selection of the articles for complete reading of the text after reading the abstract. Agreement between examiners was assessed using the Kappa test and any discrepancies that occurred were resolved with joint meetings and discussions, in case it was not resolved by common agreement, a third author

(L.H.T), based on the criteria eligibility criteria determined whether or not the study could be included in the systematic review. After that, the complete texts that met the previously determined inclusion and exclusion criteria were identified and included for qualitative and quantitative analyzes.

2.4 Data extraction.

The complete reading of the texts and the extraction of data from the selected articles were accomplish by two independent authors. After reading the full texts, the first author (E.Q.M.S) tabulated the data, and a second author (L.F.T) was responsible for checking them. Any discrepancies were resolved with meetings until an agreement was reached and in cases of doubt a third author (L.H.T.) was consulted to resolve the conflict based on the established criteria. The tabulation of the data involved: authors, country of origin of the research, existence or absence of systemic changes, average age in years of the participants, percentage of female patients, criteria for diagnosing periodontitis, number of patients per group, time of follow-up, main results of each study, as well as the parameters of the laser used, characteristics of the PS and the photodynamic therapy employed, periods of irradiation and pre-irradiation, dosage of antibiotic therapy and numerical data with mean and standard deviation for clinical conditions such as PD, gain of CAL and reduction of BOP.

2.5 Risk of bias

The risk of bias was estimated for each RCT in isolation, based on the "Cochrane Handbook for Systematic Reviews of Interventions" [27]. For each domain a risk judgment was selected according to the classification: 1) low risk of bias (when all criteria were met); 2) undefined risk (when any criterion has insufficient information to generate judgment); 3) high risk of bias (when one or more criteria were not met). The risk of bias was independently conducted by two authors (E.Q.M.S and T.E.R), and in case of doubt, a third author (E.E.) participated to resolve the discrepancies.

2.6 Data synthesis and Meta-analysis

Data that were considered inadequate for quantitative analysis were described qualitatively. Details of the experiments, parameters of the laser used, data from the photosensitizers and experimental periods were extracted and tabulated. The main individual differences in each study, with significant statistical differences found by each author, were also described qualitatively.

The meta-analysis was conducted separately for each primary (PD) and secondary (CAL and BOP) outcome, at 3 and 6 months. The heterogeneity of the data was assessed by the I^2 test and considered heterogeneous with I^2 values greater than 40%. A 95% confidence interval was adopted, forest plots with results of the difference in means between the "baseline" and the postoperative periods were performed, considering statistical differences for a $p<0.05$. The random effect model was chosen. The analysis was performed using the statistical program STATA (version 15, Stata corp LLC, Texas, USA).

3. RESULTS

3.1 Selection of studies

A total of 208 studies were found by searching the Cochrane Central, MEDLINE, PubMed, Embase, Scopus, Web of Science and Scielo databases, and 1 study in the manual search of journals in the last 6 months. After removing duplicates, 170 articles were identified. After reading the title, 150 were excluded for not meeting the eligibility criteria, of the remanning 20 articles selected for reading the abstract, a total of 7 articles were selected for complete reading of the text, of these seven, two were excluded, one because presented only biochemical analyzes and the other because used antibiotic therapy in both test groups. Five studies were included and processed for data extraction for qualitative and quantitative analysis. Figure 1 shows the flowchart for the identification of studies according to PRISMA with the reason for excluding abstracts and full texts found.

3.2 General characteristics of the included studies

Five randomized clinical trials (RCT) were included in this review. The studies were conducted in Saudi Arabia [18] in Brazil [19,20] and in Poland [21,22]. The number of participants varied between 17 and 35 individuals per study, with a minimum age of 26 and a maximum age of 57 years. The percentage of female participants ranged from 29.4% to 65.5%. One study was conducted with smoking patients [19] while in the other four studies, smoking was one of the exclusion criteria. Patients diagnosed with chronic periodontitis were included in two studies [19,20] while the other three studies included patients with aggressive periodontitis [18,21,22].

In all studies, the test group received basic periodontal therapy plus the application of aPDT, while the control group received SRP plus systemic antibiotic therapy with AMX+MTZ. Only one study [19] used an extra control group with SRP without adjuvant therapy. Patient

follow-up in all included studies was between 3 and 6 months postoperatively. One study showed favorable results to aPDT in the analyzed parameters [18], two studies showed equivalent results between the test and control group [19,20] and two studies showed better clinical results in group that used systemic antibiotic therapy [21,22] (Table 1).

3.3 Characteristics of clinical treatments performed

In group test (aPDT) in all studies the light source used was a diode laser, with wavelengths ranging from 660 to 670 nm. An optical fiber coupled to the laser tip and inserted into the bottom of the periodontal pocket was used to reach the root surface in all studies. A total application time of 48 seconds [19,20] to 60 seconds [18,21,22] was used. Although it is still necessary to create protocols for a direct comparison between the parameters of the lasers used between the different studies, the power of the laser ranged from 75mW [18] to 100 mW [19,20]. Two studies [19,20] used a total energy density by application of 160 J / cm^2 and a study [18] used a creep per tooth of 14.94 J / cm^2. Two papers [21,22] did not mention anything about the energy fluence, power or diameter of the fiber used, just citing the commercial name of the optical fiber.

In relation the photosensitizers used all five studies [18-22] described phenothiazine chloride as a photosensitizer. The pre-irradiation time of the photosensitizer ranged from 60 [18-20] to 180 seconds [21,22]. The frequency of aPDT application varied between two to four applications, varying from days to a week between each application in the included studies.

In antibiotic groups the antibiotic therapy with AMX+MTZ was administered 3 times daily for 7 days in all studies. The concentration of AMX was 375 [21,22] or 500 mg [18,19,20] 3 times a day and that of metronidazole was 240 [21,22], 400 [19,20] or 500 mg [18] 3 times a day for 7 days. The clinical measurements at baseline, 3 and 6 months postoperatively are shown in table 2, with mean and standard deviation (SD) in millimeters for PD and CAL; and mean and standard deviation in percentage for BOP.

3.4 Bias analysis

There were no divergencies between the authors in assessing and evaluating the quality of the included studies. One study was classified as having low risk of bias [19], two [18,20] were classified as undefined risk because they have one or more parameters defined as "unclear", and two studies [21,22] showed a high risk of bias, showing two parameters classified as high risk of bias, the summary of the bias classification of studies included in this systematic review are presented in figure 2. All five clinical randomized studies reported that patients were randomly divided between groups, although their method of allocation has not been described in two studies

[21,22]. Another three research groups [18,19,20] reported the distribution of patients with the use of envelopes and an online randomization site, these same authors describe methods of blinding the team with envelopes, involving different members at each stage, until the end of the study, blinding the surgeons who underwent basic periodontal treatment and also the examiners, although some authors [18,20] do not make it clear whether the data were also extracted from a researcher blinded to the treatments. Theodoro et al., 2018 [19] and Theodoro et al., 2017 [20] distributed placebo pills among participants in the aPDT group, which makes difficult to exchange information between them in the waiting room or in relation to the treatment being carried out, which could add another communication bias among the participants in the other studies. At 3 months, no data was lost due to patient abandonment or exclusion, at 6 months two studies [18,19] lost information, the cause of which was duly reported. A bias that we consider serious in relation to the correct use of the antimicrobial photodynamic therapy technique is found in two studies [21,22], since the authors irrigated the gingival sulcus with sterile saline after the pre-irradiation period of the PS, removing the most of it at the site of periodontal pockets before laser irradiation.

3.5 Main results of studies and Meta-Analysis

All studies found that reported periodontal clinical parameters demonstrated that aPDT in addition to conventional mechanical treatment was effective in reducing the probing depth (PD), gain in clinical attachment level (CAL) and in reducing of the degree of bleeding on probing (BOP), being as effective as systemic antibiotic therapy with AMX+MTZ. A study [18] demonstrated favorable statistical differences in the test group for the reduction of deep periodontal pockets, and gain in clinical attachment level at 3 months, a difference that remained at 6 months of follow-up. Theodoro et al., 2017 [20] found a significant difference only in the gain of clinical attachment level in medium pockets in the aPDT group compared to the control group at 90 days postoperatively. In contrast, Arweiler et al., 2013 [22] and 2014 [21] found better results for reducing PD and a smaller number of residual pockets ≥ 7 in the group using systemic antibiotic therapy when compared to the test group at 3 and 6 months respectively.

For the meta-analysis, all studies included were RCTs with a parallel study design made by comparing the systemic use of AMX+MTZ (ANT) and aPDT as adjuvant therapies to SRP, the difference between the means for reducing PD did not show statistical difference at 3 (Fig. 3a) and 6 months (Fig. 3b) between the two groups, as well as for the difference between the means of CAL gain (Fig. 4) and reduction of BOP (Fig. 5).

DISCUSSION

The aim of this systematic review was to evaluate the hypothesis that aPDT as an adjunct to SRP would promote similar clinical results to systemic antibiotic therapy with AMX+MTZ adjunct to SRP in the treatment of periodontitis, within the scope of discussing a new clinical approach, and creating new perspectives to reduce the indiscriminate use of antibiotics, a use that, when erroneous, further increases the potential development of bacterial resistance.

Periodontitis is one of the most common inflammatory diseases in humans [28], and AMX+MTZ is the combination of antibiotics most used as an adjunct treatment in non-surgical periodontal treatment [29,30]. Two reviews similar to this one were published previously, in 2017 [31] and 2019 [32], although they did not include recent studies published in 2018 [19], and approved for publication in 2020, with an online version in 2019 [18], in addition to not focusing on the combination of antibiotics studied in this review, giving a possible bias to the results that could be attributed to the type of antibiotic used instead of analyzing the effectiveness of antibiotic treatment as a better or worse adjunctive therapy than aPDT for periodontitis. Teugheus, et al. [13] in a recent systematic review showed that the association of AMX+MTZ in the adjunctive treatment of periodontitis had the best clinical periodontal improvements when compared to amoxicillin and metronidazole used alone, azithromycin, clarithromycin and moxifloxacin. Due to these findings, it was necessary to compare aPDT with the best systemic antibiotic therapy for non-surgical periodontal treatment.

All five studies [18,19,20,21,22] included in this systematic review showed that aPDT+SRP improved the periodontal clinical parameters in patients with the disease, but when compared to the concomitant use of AMX+MTZ and SRP, no single study showed the best results in all three clinical parameters evaluated (PD, BOP and CAL). Our results, in a direct comparison between the two therapies, found no statistical differences between the treatments in the periods of 3 and 6 months. Only one study [19] compared the two groups analyzed in this systematic review with a control group consisting of SRP only. Although other studies have shown positive results with aPDT [16,17] or AMX+MTZ [13] compared to a SRP group as monotherapy, the lack of a direct comparison in the studies included in this review with the SRP group makes us question the real benefit of both supporting therapies in the studied population. Due to the discrepancy in results between the studies, and methodological biases between them, we cannot conclude that one therapy is better than the other.

Four [19,20,21,22] of the five included studies did not mention any oral hygiene technique or instruction performed prior to the mechanical treatment of periodontitis, which may have added bias to the analyzed results. Oral hygiene instructions are of fundamental importance for any periodontal treatment, influencing the removal of plaque and calculus by the patient,

which can affect bacterial recolonization after treatment and compromise the clinical success of therapy [32].

Regarding the dosage of antibiotic therapy, there are variations in the prescribed doses, but the interval of administration seems to be a consensus among the included studies. In a systematic review conducted by McGowan et al., 2017 [33] the authors concluded that there is no statistical difference between the different doses and duration of treatment with AMX+MTZ used in the adjunctive therapy of periodontitis over a short period. However, in an attempt to decrease antimicrobial resistance, it was suggested that short regimens with higher doses should be recommended, citing as reference the same dosages used by three studies [18,19,20] included in this review.

The number of aPDT applications seems to be an important bias for clinical results, studies with two applications [21,22] resulted in lower clinical benefits than studies with three [19,20] and four [18] applications respectively. There seems to be a tendency that the greater the number of applications, the better the clinical results, although there is insufficient scientific evidence to determine an adequate number of applications. Although all five studies used here started aPDT applications on day 0, consecutively with SRP, there is no information on the presence or absence of bleeding in the periodontal pockets during the application of PS in any of the included studies, which may have influenced contact of PS with tissues, and altered the bactericidal effect of photodynamic therapy at different levels between studies, adding yet another bias to the periodontal clinical results found.

Regarding the aPDT methodological bias, there is no consensus on the parameters of the laser and the photosensitizers used: power density, fluence, energy, pre-irradiation time, irradiation time and the diameter of the optical fiber are not established, and were often inadequately reported [21,22]. There is a need for the scientific community to establish and require minimum parameters of information in order to be able to replicate or compare studies with different models of lasers and different protocols.

In two studies [21,22] periodontal pockets were irrigated with sterile saline prior to the laser application, after the pre-irradiation period, removing most of the PS in contact with the periodontal tissue. This method does not seem to go according to the principles of aPDT [23], since when removing the PS, minimal remaining amounts of it are responsible for producing reactive oxygen species, drastically reducing the antimicrobial effect of the therapy. This important bias may have increased the heterogeneity of the samples for the meta -analysis, since these two articles had clinical results that opposed the other studies [18,19,20].

The main bias and limitation of this systematic review and meta-analysis is perhaps the small number of studies included in the qualitative and quantitative analyzes, as well as the small number of participants (under 20 per subgroup) included in each study. Longer periods of analysis may also bring clarifications about the studied therapies, since all five studies [18,19, 20,21,22]

included presented results of a maximum of 6 months of follow-up. Periodontitis presents different evolutionary patterns depending on systemic factors, related to the host's immune response and local factors inherent to the affected site, such as the presence of specific bacteria, anatomical variations or poor dental positioning. The control of clinical situations like these is not always possible, and if such conditions are not taken into account by researchers, they can lead to errors in the interpretation of the results. We suggest that new RCTs with direct comparisons between SRP+aPDT and antibiotic therapy with SRP+AMX+MTZ be carried out, since a greater number of studies should reduce the heterogeneity of the data, and allow direct comparisons with more homogeneous parameters between the two therapies.

In our inclusion and exclusion criteria, we did not separate studies with aggressive or chronic periodontitis, due to the new classification of periodontal diseases [3] and the consensus that there is not enough scientific evidence to separate their treatments [1]. Since 1999, a substantial amount of information has added new evidence and perspectives regarding environmental and risk factors of periodontitis. In an extensive review by Fine et al., 2018 [34] in an attempt to characterize aggressive periodontitis as an independent condition, the authors did not find sufficient evidence regarding the specificity of the infectious microbiota, the host's immune response, and factors linked to specific genes. With regard to microbiological aspects, in a systematic review, Monbelli et al., [35] concluded that the presence or absence of *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus and Campylobacter rectus* could not discriminate against individuals with aggressive periodontitis or the chronic condition. The analysis of all this evidence led to the 2017 World Workshop, based on the current pathophysiological knowledge of the disease, to divide it into three forms: "Necrotic Periodontitis", "Periodontitis as a manifestation of systemic diseases" and "periodontitis", with this latter being categorized based on a multidimensional staging and grading system, with the characteristic of being able to be adapted and updated as new evidence emerged [36]. Despite this, some bias can be added to the fact that some studies [19,21,22] have dealt with a period of more acute manifestation of the disease. Smoking was considered an important risk factor that affects the speed of disease progression, and we decided not to exclude the study with smokers [19], since it makes a direct comparison between the two groups, not mixing smoking and non-smoking patients, and the limited amount of papers present in the literature.

Thus, our findings for the comparison of SRP+aPDT with the SRP+AMX+ MTZ for the non-surgical treatment of periodontitis are in agreement with the other two [31,32] similar reviews previously published. Although of the new studies added, of narrowing the comparison with only a combination of antibiotics and pointing out new possibilities of bias in the included studies, we cannot conclude that any of the studied therapies present better or worse results for any of the analyzed clinical parameters. With regard to the future of aPDT, we believe that it is a therapy that deserves greater attention from the dental community, despite the need to adapt clinical time

to carry out additional consultations for more than one application. When we think globally, in the scenario of the growing microbial resistance that we find, it seems to be a viable alternative to the systemic use of antibiotics that represents the adjunctive therapy most prescribed by clinicians in the treatment of periodontitis.

CONCLUSION

Although there were a limited number of RCTs within the eligibility criteria, and great heterogeneity between them, we can conclude, to date, that aPDT presents similar clinical results compared to antibiotic therapy with AMX+MTZ as adjuvants in the non-surgical treatment of periodontitis. A local therapy that presents effects similar to those of systemic antibiotic therapy, without its adverse effects, particularly in terms of increased drug resistance, deserves to be further studied and applied. Based on the small amount of scientific evidence available, and the great variability of the aPDT parameters presented, further research, using more controlled clinical parameters, needs to be carried out in order to make it possible to choose one therapy over the other.

Conflict of interest

The authors declare no conflicts of interest.

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Tables Legends

Table 1. General Characteristics of included Studies.

Table 2. Parameters of clinical treatments.

Figures Legends

Fig 1. PRISMA flow diagram.

Fig 2. Cochrane risk of bias for each study (summary).

Fig. 3 – Forest plot comparison between systemic AMX+MTZ and aPDT as an adjunctive therapy for SRP for PD mean reduction at 3 (a) and 6 (b) months.

Fig 4 - Forest plot comparison between systemic AMX+ MTZ and aPDT as an adjunctive therapy for SRP for CAL mean gain at 3 (a) and 6 (b) months.

Fig 5 - Forest plot comparison between systemic AMX+MTZ and aPDT as an adjunctive therapy for SRP for BOP mean reduction at 3 (a) and 6 (b) months.