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REVIEW ARTICLE

Assessing the effectiveness of antimicrobial photodynamic therapy as an adjunct for pain reduction in herpes labialis: a comprehensive systematic review

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Abstract:

Introduction: Herpes labialis, caused by the herpes simplex virus (HSV), leads to painful lesions around the lips. Current treatments primarily consist of topic antiviral agents, which often fail to provide immediate pain relief. Antimicrobial photodynamic therapy (aPDT) has emerged as a potential adjunctive treatment, but its effectiveness in reducing pain associated with herpes labialis remains unclear. **Objective:** This study aimed to evaluate the effectiveness of aPDT as an adjunctive treatment for reducing pain in herpes labialis. **Methods:** A systematic review was conducted following PRISMA guidelines and registered in the PROSPERO database (CRD42023474979). The review addressed the PICO question: Is aPDT effective in reducing pain compared to topic antiviral treatment alone? Electronic searches were conducted in PubMed/MEDLINE, Cochrane Library, and Web of Science for studies published until October 2024. Eligible studies were randomized controlled trials (RCTs) published in English that compared aPDT with antiviral agents. **Results:** Of the 184 articles identified, two studies involving 120 patients were selected for qualitative analysis. The findings indicated that aPDT, when used alongside topic antivirals, effectively reduced pain symptoms in herpes labialis compared to antiviral treatment alone. However, due to the limited number of studies and variability in outcome measures, the evidence remains preliminary. **Conclusion:** Based on this review, the use of aPDT as an adjunct to topical antiviral treatment appears to reduce pain symptoms associated with herpes labialis lesions compared to antiviral treatment alone. However, due to the limited number of randomized clinical trials and variability in the results, further research is necessary to establish standardized guidelines for its use.

Keywords: Herpes labialis; Photochemotherapy; Herpes simplex; Systematic review.

INTRODUCTION

Herpes labialis is a highly prevalent condition and one of the most common viral infections worldwide[1]. In 2016, the global prevalence of HSV infections was estimated to be around 200 million cases[2]. Herpes labialis commonly occurs as a result of a viral infection caused by the herpes simplex virus type 1 (HSV-1), which remains latent in the fifth cranial nerve, trigeminal nerve[3]. This infection is characterized by recurrent outbreaks, alternating between latent and active phases[4]. Recurrences are often triggered by various psychosocial factors, such as stress, ultraviolet radiation, and nutritional or immunological deficiencies[5]. Clinically, the lesions appear as vesicles that rupture forming ulcers in the lip region after the prodromal period with numbness and tingling[6]. The diagnosis of herpetic infection can generally be defined based on the patient's medical history and clinical characteristics[7]. Herpes symptoms involve mainly pain and discomfort in the region of the lesion,

Statement of Clinical Significance
Antimicrobial photodynamic therapy combined with topical antivirals may enhance pain relief in herpes labialis more than antivirals alone. It shows promise as a clinical adjunct, though more research is needed to confirm effectiveness and define protocols.

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in addition to the aesthetic factor that can compromise patients' self-esteem[8].

Despite the high prevalence of herpes labialis, treatment options have remained largely unchanged in recent years[9]. Researchers have highlighted the lack of clear guidelines recommending effective treatments for the condition[9]. Currently, conventional treatment for herpes labialis involves antiviral medications to slow the progression of lesions and alleviate pain symptoms[10]. Classic lesions are preceded by the prodrome period, but others appear without this period, making them more difficult to treat[11]. Among antiviral drugs, acyclovir is the most used for treatment[12]. Acyclovir penetrates affected cells and prevents viral replication, interrupting the DNA polymerase of the herpes virus[13]. Although oral or topic treatment with antiviral agents can reduce HSV-1 replication, the main benefits of these therapies are limited to reductions in healing time, reducing lesion size and associated pain[14]. These antiviral drugs do not reduce the viral load[15]. The emergence of resistant strains and drug toxicity are some of the challenges with this type of treatment[16]. The literature demonstrates a greater likelihood of resistance to acyclovir and its analogues in immunocompromised patients, but immunocompetent patients can also be affected[17]. In a recent study, researchers were looking for alternative treatments rather than to standard treatment with acyclovir[18].

Photobiomodulation therapy (PMBT) as an adjuvant therapy to antivirals in the treatment of herpes labialis was reported in the literature[19-21]. This therapy promotes modulation of the inflammatory response, through increased angiogenesis, proliferation, migration, differentiation and cellular activity, essential events to promote tissue repair and symptom relief[22]. Antimicrobial photodynamic therapy (aPDT) emerges as a promising alternative for the adjuvant treatment of herpes labialis[23]. aPDT consists of a treatment using a photoantimicrobial agent, called photosensitizer, it is associated with light at a wavelength resonant with the absorption spectrum of the photosensitizer[24]. The therapy relies on the photoantimicrobial's ability to penetrate the pathogen's cell, absorb light, and transfer energy to molecular oxygen, generating free radicals and reactive oxygen species—such as singlet oxygen — with cytotoxic effects against microorganisms[25]. The pre-irradiation time, dosage and physical-chemical structure of photosensitizers are necessary to ensure biodistribution and tissue penetration of pathogens, in addition to their effectiveness in producing reactive oxygen species[26]. The cytotoxic action occurs through various molecular targets, such as proteins, lipids, and nucleic acids, which are more vulnerable in simpler microorganisms like viruses[27]. Thus, aPDT could serve as an alternative treatment for herpes labialis, potentially reducing its symptoms; however, its effectiveness remains unclear.

Systematic reviews on this topic have been published; however, none have included randomized controlled clinical trials due to the limited availability of studies designed[28-30]. Therefore, the aim of this article was to systematically review the literature to evaluate whether aPDT, as an adjunct to topic antiviral therapy, is effective in reducing pain associated with herpes labialis, compared to conventional treatment with topic acyclovir alone. Lastly, the guiding question of this review was "Is photodynamic therapy as adjuvant therapy effective in reducing pain of herpes labialis when compared to the use of only topical antivirals?"

MATERIALS AND METHODS

Eligibility criteria

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42023474979. The selection of studies was based on the PICO strategy:

- Population: Immunocompetent patients with herpes labialis
- Intervention: Application aPDT
- Comparison: Topical antiviral drugs
- Outcome: Pain reduction

The inclusion criteria were: randomized controlled clinical trials, studies published in English, and studies comparing the use of antiviral medications with aPDT. Studies that did not assess pain both before and after treatment were excluded. Additionally, articles in languages other than English and those in which the full text could not be accessed were also excluded.

To assess inter-examiner agreement in the study selection process across each database, a Kappa test was performed. The agreement was interpreted as follows: 0 = no agreement, <0.8=moderate agreement, and ≥0.8=almost perfect agreement, with scores 0 (no agreement), <0.8 (moderate agreement) and ≥0.8 (almost perfect agreement).

Information sources

A comprehensive electronic search was conducted in the following databases: PubMed/MEDLINE, Cochrane Library, and Web of Science for studies published up to October 2024. The search strategy included a combination of free-text keywords and Medical Subject Headings (MeSH terms) related to herpes labialis, photodynamic therapy, and antiviral agents. No filters were applied regarding publication date, and only studies published in English were considered.

In addition to database searching, the reference lists of all included studies were manually screened to identify other potentially relevant articles that may not have been captured in the initial electronic search.

Search strategy

The search strategy included a combination of free-text keywords and Medical Subject Headings (MeSH terms) related to the condition, intervention, and comparison. The following terms were used:

- Keywords: herpes labialis, herpes simplex, low-level light therapy, laser therapy, lasers, photodynamic therapies, photochemotherapy, antiviral drugs, antiviral agents.
- MeSH Terms: "Herpes Labialis", "Herpes Simplex", "Low-Level Light Therapy", "Laser Therapy", "Photochemotherapy", "Antiviral Agents".

These terms were combined using Boolean operators as follows: (herpes labialis OR herpes simplex) AND (low-level light therapy OR laser therapy OR lasers OR photodynamic therapies OR photochemotherapy) AND (antiviral drugs OR antiviral agents).

Selection process

The selection process was carried out independently by two reviewers (A.P.S. and G.M.S.) in two stages. In the first stage, the titles and abstracts of all retrieved records were screened for relevance. In the second stage, full-text articles of potentially eligible studies were assessed to confirm their eligibility based on the predefined inclusion and exclusion criteria.

Discrepancies between reviewers at any stage of the selection process were resolved through discussion. If no consensus was reached, a third reviewer (L.H.T.) was consulted to make the final decision.

To evaluate the level of agreement between the reviewers, the Kappa coefficient was calculated for each database. The results were interpreted as follows: 0 = no agreement, <0.8=moderate agreement, and ≥0.8=almost perfect agreement.

Data items and collection process

The collected data were added to a spreadsheet table (Excel; Microsoft Corp): author/year/country, type of study, number of patients, type of antiviral medication, type of laser, type of photosensitizer, pre-irradiation time, irradiation, wavelength, power/density, application/exposure time, total energy, treatment time, outcomes evaluation method and study results.

Risk of bias

The risk of bias of the studies included in this review was assessed by the risk of bias tool for randomized clinical trials (RoB 2.0; Cochrane)[31]. The risk of bias for each domain was classified as low, some concerns, or high. The overall risk of bias was determined by combining the risk levels for each domain. If all domains were assessed as having a low risk of bias, the overall risk was considered low. If at least one domain was rated as having a moderate risk, the overall risk was classified as moderate. An overall serious risk of bias was applied when at least one domain was deemed to have a serious risk. Finally, an overall critical risk of bias was assigned when at least one domain was judged to have a critical risk of bias[31].

Effect measures

The primary outcome considered in this systematic review was pain reduction following treatment. To assess this outcome, studies were required to perform pain evaluations before and after the application of both interventions: aPDT and topical antiviral drugs.

The effect measure used to compare groups across studies was the mean difference or standardized mean difference in pain scores, depending on the scale used in each study. When available, 95% confidence intervals were extracted or calculated to assess the precision of the effect estimates. Studies that did not include a quantitative assessment of pain were excluded from this review.

Synthesis of results

Due to the expected heterogeneity in methodologies (e.g., type of laser used, photosensitizer, treatment protocols, and outcome measures), a qualitative synthesis of the findings was primarily conducted. The main characteristics and results of each included study were organized in a comparative table summarizing relevant variables such as patient population, type of intervention, comparator, treatment parameters, and reported outcomes.

RESULTS

Study selection

The inter-rater agreement (Kappa) for article selection was high across all databases: 0.88 for PubMed/MEDLINE, 0.95 for Cochrane, and 0.90 for Web of Science. A total of 184 references were identified: 132 in PubMed/MEDLINE, 10 in the Cochrane Library, and 42 in Web of Science. After removing 73 duplicate articles, titles and abstracts of the remaining studies were screened, and 8 articles were selected for full-text review.

Following the application of eligibility criteria, 5 articles were excluded because they used other types of laser therapy rather than aPDT, and 1 study was excluded for being a clinical protocol without results. Ultimately, 2 randomized controlled clinical trials (32,33) to be included in this systematic review. The search strategy is detailed in Figure 1.

Study characteristics

The qualitative and quantitative data from the included studies are summarized in Tables 1 to 4[32,33]. A total of 120 participants clinically diagnosed with herpes labialis were included across both studies. Regarding the interventions:

- Antiviral therapy: Both studies used topical Acyclovir 5% (Zovirax®).
- aPDT: Methylene blue was used as the photosensitizer at a concentration of 0.005%, and both studies applied a diode laser at 660 nm.
- Application protocol: aPDT was administered once at the beginning of treatment. The topical antiviral protocol ranged from 4 to 5 times per day.

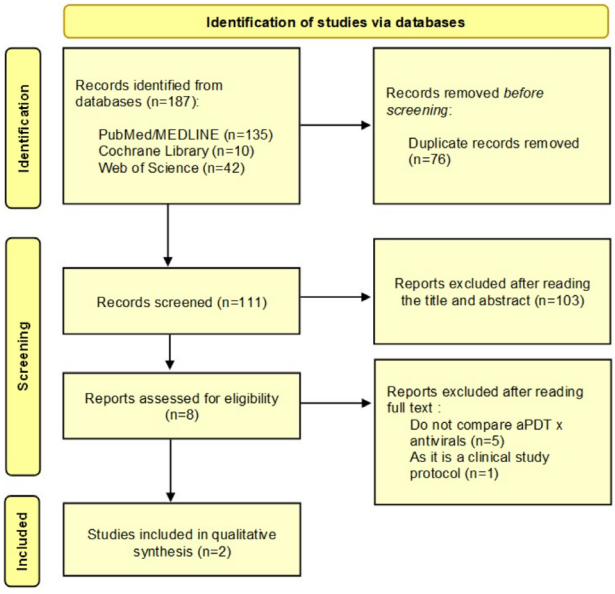

Figure 1. Flow diagram of study selection.

Risk of bias

The 2 articles selected were randomized controlled clinical trials and were evaluated using the RoB 2.0 tool from Cochrane. One study was determined to be low in risk of bias (32) and the other to be of concern in risk of bias (33) (Figure 2)[32,33].

Results of individual studies

The individual outcomes of each study are presented in Table 5[32,33]. Both studies evaluated pain reduction as the primary outcome of interest; however, differences in how the results were grouped and the time points used for analysis hindered direct numerical comparisons between them.

Results of syntheses

A meta-analysis was not feasible due to the heterogeneity in data presentation and differences in analysis timeframes between the studies. Therefore, the results were synthesized qualitatively. Both studies showed that aPDT was effective in reducing pain in patients with herpes labialis when compared to topical antiviral therapy, suggesting that aPDT may serve as a promising alternative or adjunctive treatment.

DISCUSSION

The findings indicated that aPDT, when combined with topical antivirals, was more effective in reducing pain symptoms in herpes labialis than the use of antivirals alone. Herpes labialis is an infection with mild to severe clinical manifestations in patients. The signs and symptoms of herpes labialis range from single or multiple vesicles, fever, lymphadenopathy and mainly pain[8]. The use of an effective treatment to promote adequate control of the signs and especially the symptoms of cold sores is necessary, since the disease can only be cured with the chemotaxis of specific antibodies to the site of the viral infection[34]. In cases where the herpes labialis infection is identified in the initial or prodromal period, the use of systemic or topic antivirals was proved to be more efficient[35]. In addition to the possible development of resistance to antivirals, there may be rupture of the vesicles and the appearance of ulcerations associated with viral secretion and local inflammation, complicating

Table 1. Qualitative characteristics of the included studies.

Reference	Type of study	Sample size	Groups
Ajmal[32]	RCT	45 patients	G1 – topic antiviral; G2 – aPDT; and G3 – topic antiviral+aPDT as an adjunct.
Ramalho et al.[33]	RCT	75 patients	G1 – aPDT; G2 – topic antiviral; and G3 – topic antiviral+aPDT as an adjunct.

RCT randomized clinical trial; aPDT: antimicrobial photodynamic therapy.

Table 2. Topic antiviral protocol of included studies.

Reference	Antiviral protocol	
	Medicine	Treatment period
Ajmal[32]	Topic acyclovir (5%, Zovirax®, Glaxo Ltd, Saudi Arabia).	4x a day, for 7 days.
Ramalho et al.[33]	Topic acyclovir (5%, Zovirax®, Glaxo Smith Kline Brasil Ltda, Rio de Janeiro (RJ), Brazil.	5x a day, at 4-hour intervals, eliminating application at night.

Table 3. Antimicrobial photodynamic therapy protocol of included studies.

Reference	aPDT protocol			
	Type of laser	Photosensitizer	Pre-irradiation time (min)	Treatment period
Ajmal[32]	Diode laser (HELBO® TheraLite – Bredent Medical, Senden, Bavaria, Germany).	Methylene blue 0.005%.	-	1x. A single application before starting study protocols.
Ramalho et al.[33]	Low power laser (MMOPTICS®, São Carlos (SP), Brazil).	Methylene blue 0.005% (Chimiolux®, DMC Importação e Exportação de Equipamentos Ltda, São Carlos (SP), Brazil).	5 min.	1x. A single application before starting study protocols.

aPDT: antimicrobial photodynamic therapy; min: minute.

Table 4. Parameters of the lasers used in the included studies.

Reference	Optical fiber diameter (μm)	Wavelength (nm)	Energy (J)	Power (mW)	Energy density (J/cm²)	Laser movement during application	Duration of laser application (s)	Distance from irradiation points (cm)
Ajmal[32]	0.028 cm^2 -	660nm _	4.5J	150 mW	300 J/cm^2	perpendicular to the lesion	30 s	1 cm
Ramalho et al.[33]	-	660nm _	4.8J	40 mW	120 J/cm^2	perpendicular to the lesion	120 s	1 cm

the mechanism of action of antivirals[36]. New alternatives for treating cold sores should be researched, since topic drugs have a short period of action and do not influence the repair time or the recurrence phase of ulcers[36]. Furthermore, systemic antivirals are associated with cases of hepatotoxicity due to excessive activation of cytochrome P450 (36). HSV-1 is characterized by the lifelong presence of the virus in the sensory neurons of the trigeminal nerve; the virus remains in latency until the host undergoes a period of immunosuppression[37]. After the lesion reappears and symptoms appear, the most widely used treatment is the topic or systemic antiviral acyclovir[14,38]. However, in some cases of immunosuppressed patients or with exacerbated local inflammation in the ulcerated area, treatment with antivirals alone may not be effective[38]. To this end, the use of treatment methods for viral inactivation, such as aPDT, has been studied[22]. This treatment might have the advantage of having a synergistic effect with the antiviral, mainly reducing pain discomfort as presented in the first study included in this review[32]. Furthermore, an advantage of this treatment is the fact that it has no side effects and restrictions on use for the patient, in addition to being a painless treatment, restricted to the site of application, non-invasive, low cost and with a low risk of viral resistance.

aPDT is a therapy associated with the use of light source and photosensitizers with powerful antimicrobial action, notable for its antiviral action[39]. One possible explanation for the pain reduction observed in the first study included in this review could be

Table 5. Quantitative characteristics of the studies analyzed.

Reference	Method	aPDT	Topic Antiviral+aPDT	Conclusion
Ajmal[32]	McGill Pain Questionnaire (MPQ)	Initial: 3.5±1.9 Immediate: 3.4±1.8 15d: 3.0±1.9 28d: 2.8±1.2 90d: 0.5±0.2 180d: 0±0	Initial: 3.2±1.8 Immediate: 3.1±1.6 15d: 1.3±0.7 28d: 1.1±0.4 90d: 0±0 180d: 0±0	G3 reported a statistically significant reduction in pain scores compared to G2 and G1, respectively ($p<0.05$). Scores decreased significantly after 15 days of follow-up and this was significantly reduced further after 28 days of follow-up up to 180 days ($p<0.05$).
	Visual analogue scale (VSA)	Initial: 68±37.3 Immediate: 65±32.3 15d: 58±13.2 28d: 19±5.6 90d: 17.8±6.7 180d: 15.5±4.4	Initial: 75±46.6 Immediate: 68±25.4 15d: 43±22.6 28d: 7.2±3.2 90d: 3.0±2.4 180d: 1.9±2.5	
Ramalho et al.[33]	Scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe)	1d:1.0 2d: 1. 0 3d: 1. 0 4d: 0.5 5d: 0.0 6d: 0.0 7d: 0.0	1d: 0.0 2d: 0.0 3d: 0.0 4d: 0.0 5d: 0.5 6d: 0.5 7d: 0.5	No significant difference in pain reduction over time was observed between treatments at any of the time points observed.

aPDT: antimicrobial photodynamic therapy; d: day.

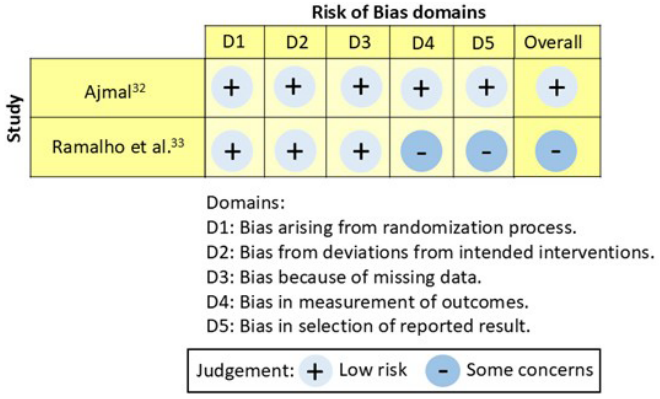

Figure 2. Risk of bias assessment based on the Cochrane risk of bias tool for randomized controlled trials (RoB 2.0).

the activation of photosensitizer molecules by exposed photons. This interaction may facilitate the healing process by promoting tissue repair in the superficial layers damaged by the viral infection[40]. This point should be highlighted, as adjuvant aPDT therapy can also favor subjects with delayed scar repair, such as transplant recipients, diabetics and cancer patients with recurrent cold sores. Despite this, it is worth highlighting the use of aPDT through the photosensitizer and its antimicrobial effect and not just PBMT using a low-power laser for the treatment of the herpes virus[41]. *In vitro* studies indicated the effectiveness of aPDT treatment using diode lasers with 810 and 940 nm and indocyanine photosensitizer in significantly reducing the viral load of HSV-1, but there was no reduction in viral load with isolated PBMT application[41].

Mutation of the HSV-1 virus is a major factor contributing to the ineffectiveness of antiviral therapy with acyclovir, with estimates suggesting that up to 95% of patients may develop resistance to the drug[42]. As a result, the pain and symptoms are likely to recur, complicating effective management of herpes labialis. On the other hand, the use of aPDT is considered a safe and effective therapy for treating resistant microorganisms, including in the management of herpes labialis[43]. This review indicated possible promising results for adjuvant therapy for the treatment of herpes labialis. However, further studies are still essential to define a treatment protocol, as well as the low-power laser parameters, photosensitizer concentration, pre — irradiation time and application frequency. Additionally, one of the key findings in the studies reviewed is the significant pain reduction achieved with adjuvant aPDT therapy. This reduction in pain may decrease the reliance on analgesic medications, potentially lowering the risk of associated side effects and the induction of cytochrome P450 enzymes[44].

The correct pre-irradiation time is a determining factor for the biodistribution of the photosensitizer deep into the tissues and, mainly, into the viral cells[45]. Currently, studies aim to establish an adequate pre-irradiation time protocol in several other oral pathologies[46]. Importantly, in the included articles we found methodological

divergence in relation to this important dependent factor for the success of aPDT. In the methodology proposed by Ajmal et al., the pre -irradiation time of the photosensitizer was not reported[32]. While in the study published by Ramalho et al., the pre-irradiation time used was 5 min[33]. Paradoxically, a significant reduction in pain measurement was found in the study of Ajmal et al.[32]. These findings can be partially explained by the times evaluated by that study[32], and partially by the pre-irradiation time used by Ramalho et al.[32,33]. Regarding the pain assessment period, Ajmal et al. took measurements after 15, 28 and 180 days of treatment[32]. However, the manifestation of clinical signs and painful symptoms of herpes labialis ends within 10 days, in cases where there is no recurrence in immunocompetent patients[47]. Regarding the pre-irradiation time, the literature does not present *in vitro* results on the influence of the pre-irradiation time on the HSV-1 virus. For the reduction of biofilms formed by *Streptococcus mutans* bacteria or *Candida fungi albicans*, variations in pre-irradiation times did not result in a statistically significant difference[45,48].

It is important to highlight the similarities and differences between the two included studies to better understand the role of aPDT in the treatment of herpes labialis. Both studies by Ajmal et al. and Ramalho et al. investigated the efficacy of aPDT combined with topical acyclovir. First, Ajmal et al.[32] focused on adolescent patients, dividing 45 participants into three groups: antiviral alone, aPDT alone, and a combination of both. Their findings indicated that the combined treatment significantly reduced pain and pro-inflammatory biomarkers compared to the other groups. In contrast, Ramalho et al.[33] included 75 patients, also divided into three groups, and observed no significant differences in healing time and pain among the treatments, although aPDT alone showed better outcomes in reducing edema and tingling on the first day. The main difference between the two studies lies in their conclusions: Ajmal et al.[32] reported enhanced outcomes with the combined therapy, while Ramalho et al.[33] found limited benefits, noting improvements only in the early stages. These discrepancies may result from variations in patient demographics, methodology, or evaluation criteria.

In addition to the randomized controlled trials included in this review, observational studies have explored the application of aPDT in treating herpes labialis. For instance, a previous case series where the combination of aPDT and PBMT led to improved modulation of the inflammatory process, pain relief, and accelerated tissue repair in patients with herpes simplex labialis[49]. Similarly, another authors reported positive outcomes using aPDT in a patient with recurrent herpes simplex virus infection and chronic graft-versus-host disease, demonstrating its potential clinical benefits[50]. Although these studies are limited by their design and sample size, their findings consistently report pain relief, faster healing, and reduced recurrence. These preliminary outcomes also offer valuable insights into the real-world application of aPDT and highlight the need for future randomized controlled trials to confirm efficacy, optimize treatment protocols, and evaluate long-term outcomes in a more systematic and controlled manner.

One of the main limitations of this review lies in the constraints related to data analysis. The included studies presented considerable heterogeneity in terms of study design, sample size, evaluation methods, timing of outcome assessments, and reported results. These differences limited the possibility of conducting a meta-analysis, as pooling the data would compromise the validity and accuracy of the findings. Additionally, many studies lacked standardized measures for key outcomes such as pain intensity and healing time, which further hindered direct comparisons. The small number of available randomized controlled trials on the topic also restricted the overall strength of the evidence. As a result, the conclusions of this review are based on a narrative synthesis, which, while informative, may be subject to interpretation bias. Future research using standardized protocols and outcome measures is essential to allow for more robust and quantitative analyses.

Finally, the studies included in this systematic review displayed methodological bias, primarily due to the lack of consensus on key parameters such as optical fiber diameter, wavelength, energy, power, energy density, laser application duration, distance from irradiation points, and pre-irradiation time. These variables are not yet standardized in the literature, and no established clinical protocol exists to guide their use. Consequently, these factors represent important areas for further research. Another limitation of this review is the inclusion of only two studies, underscoring the need for more clinical trials with standardized methodologies to enable robust meta-analysis[51].

CONCLUSION

Based on the available evidence, aPDT, when used as an adjunct to topical antiviral treatment, shows potential in reducing pain symptoms associated with herpes labialis lesions. However, due to the small number

of studies and the variability in methodologies and outcomes, these findings should be interpreted with caution. More robust and standardized randomized clinical trials are necessary to confirm the effectiveness of aPDT and to support the development of clinical guidelines for its use in managing herpes labialis.

AUTHORS' CONTRIBUTIONS

APS: Conceptualization, Data curation, Methodology, Writing – original draft. GMS: Data curation, Methodology, Writing – original draft. WGA: Project administration, Supervision. VGG: Supervision, Writing – review & editing. LHT: Formal analysis, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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