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ORIGINAL ARTICLE

Effectiveness of Laser Therapy for Treatment of Herpes Labialis: A Systematic Review

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ABSTRACT

Objective: This systematic review aimed to determine the effectiveness of laser therapy as a treatment for herpes labialis. This review seeks to answer our research question: What is the effectiveness of laser therapy compared to Acyclovir for treating patients with HSV-1? We consider it important to find new alternatives to treating HSV-1 with the most minor adverse effects, so this question has been posed.

Methods: The Cochrane, Lilacs, Ovid, Embase, Google Scholar, ClinicalTrials.gov, and Open Gray databases were searched for literature and gray literature. Clinical trials were retrieved and manually checked for inclusion. We carried out data extraction and the evaluation of the methodological quality of the included articles. An assessment of the certainty of the evidence was also performed.

Results: The mean healing time in the placebo and acyclovir groups was longer, with healing in the laser therapy groups being faster. Otherwise, one study reported that individuals under acyclovir presented a higher recurrence risk than those submitted to laser therapy. One study reported a significantly smaller lesion size in the laser therapy group than in the acyclovir group. The certainty of the evidence was very low for the outcomes. No side effects have been reported with laser therapy.

Conclusions: Laser therapy reported better results in the disappearance of symptoms and signs than conventional treatment. Although, we should cautiously interpret the findings due to the certainty of the evidence being very low for the outcomes.

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Efectividad de la terapia láser para el tratamiento del herpes labial: revisión sistemática

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RESUMEN

Objetivo: esta revisión sistemática tuvo como objetivo determinar la efectividad de la terapia con láser como tratamiento para el herpes labial. Este objetivo pretende responder a nuestra pregunta de investigación: ¿Cuál es la efectividad de la terapia láser en comparación con Aciclovir para el tratamiento de pacientes con HSV-1? Consideramos importante encontrar nuevas alternativas al tratamiento del HSV-1 con menor cantidad de efectos adversos.

Métodos: se realizaron búsquedas de literatura y literatura gris en las bases de datos Cochrane, Lilacs, Ovid, Embase, Google Scholar, ClinicalTrials.gov y Open Gray. Se recuperaron los ensayos clínicos y se verificaron manualmente para su inclusión. Se realizó la extracción de datos y la evaluación de la calidad metodológica de los artículos incluidos. También se realizó una evaluación de la certeza de la evidencia.

Resultados: la media del tiempo de curación en los grupos de placebo y Aciclovir fue mayor, es decir, la curación en los grupos de terapia láser fue más rápida. Sin embargo, un estudio reportó que los pacientes que usaban Aciclovir tenían mayor riesgo de recurrencia que los de terapia láser. Otro estudio reportó un tamaño de lesión significativamente menor en el grupo de terapia láser comparado con el de Aciclovir. La certeza de la evidencia fue demasiado baja para los resultados. No se reportaron efectos secundarios en la terapia con láser.

Conclusiones: el uso de la terapia láser reportó mejores resultados en la desaparición de signos y síntomas en comparación con el Aciclovir. Debemos interpretar los hallazgos con cautela debido a que la certeza de la evidencia es muy baja para los resultados.

INTRODUCTION

Herpes labialis is an extremely contagious disease caused by herpes simplex virus type 1 (HSV-1). This disease is highly prevalent worldwide, especially in Latin America and the Caribbean. Therefore, it has become a global public health problem that has generated a growing international interest and effort led by the World Health Organization (WHO) to develop a vaccine that controls the transmission of HSV-1 (1,2).

HSV-1 presents initial episodes presenting as asymptomatic or symptomatic small blisters or sores on the skin surrounding the site of infection. The virus can spread to sensory nerve cells, which remain dormant until reactivation occurs and lasts a lifetime (3–6). Most primary infections are brought on by close contact with an infected person's lesions and direct exposure to bodily fluids like saliva or exudate from developing lesions. Additionally, the infection can spread through kissing or sharing towels or utensils. Typically, the initial infection appears 2 to 20 days after exposure and can spread to the face in its most aggressive form (6–8). On the other hand, genital herpes is caused by herpes simplex virus type 2 (HSV-2), primarily through sexual transmission, although cases of newborns infected by the mother during childbirth have been reported (6). Herpes labialis is usually acquired in childhood and is commonly asymptomatic, so most infected people do not know they have the virus (9). It can be caused by stimuli such as exposure to sunlight, psychological stress, fever, menstruation, surgical resection (8,10–12), and suppression of the immune system (13–15). HSV-1 can cause severe symptoms and complications such as encephalitis or keratitis in patients with suppresed immune systems (6). While the illness is typically transmitted during active replication, it can sometimes spread when no symptoms are present. The recurrences can be frequent and vary from person to person (3). Symptoms of cold sores include clustered blisters or painful sores in the mouth and surrounding tissue. Before the appearance of such ulcers, infected people usually have tingling, itching, or burning sensations in the affected area (5,6,16).

The WHO estimated in 2016 (last available estimates) that 3.7 billion people under 50 years old (67%) globally have herpes simplex virus type 1 (HSV-1) infection, the main cause of oral herpes, and another 417 million people from 15 to 49 years old (11%) have HSV-2. The estimated prevalence of HSV-1 was highest in Africa (87%) and lowest in the Americas (40 - 50%) (6). In the United States, a report made in 2015-2016 by the National Survey of Health and Nutrition Examination (NHANES) indicated that the estimated prevalence rate of HSV-1 in people aged 14 to 49 years is 47.8%, with a slight predominance in women with 50.9% compared to 45.2% in men (17). Epidemiological studies in Asia show generally high rates for adults (75%), especially those from low socioeconomic backgrounds, and children (50%) (3).

HSV-1 is a concern for healthcare workers, especially in dentistry, due to the high probability of infection through direct contact with secretions of the oral cavity (17). The patient may suffer a viral spread that evolves into herpetic gingivostomatitis (HGS) or herpetic stomatitis due to traumatic events or dental procedures (4). Both pathologies are very common in both children and adults (18) and produce similar clinical manifestations. Herpetic Stomatitis symptoms vary according to their severity. The disease can manifest in mild, moderate, and severe forms, with symptoms ranging from a slight rise in body temperature up to 37-37.5 °C, minor signs of catarrhal inflammation of the mucous membrane of the nasal cavity and upper respiratory tract, to loss of appetite, signs of an acute respiratory infection, or even apathy, adynamia, headache, musculoskeletal hyperesthesia, arthralgia, and fever up to 39-40 °C (19). Moreover, HGS can be divided into primary (acute HGS) and secondary (recurrent herpes simplex infection). HGS represents the main pattern of primary infection of herpes simplex viruses. Over 90% of HGS cases are due to HSV-1 and occasionally HSV-2. Mild primary HGS usually resolves in 5 to 7 days, but severe cases can last two weeks. Secondary

HGS usually affects the keratinized mucosa attached to bone (attached gingiva and hard palate) (20,21). HGS typically involves kids who have never been exposed to the virus before. While it may occasionally be asymptomatic, most cases present with a prodrome of fever, painful, ulcerative lesions of the gingiva and mucosa, and frequently yellow, perioral, vesicular lesions, anorexia, and irritability. Malaise, sluggishness, and cervical or submandibular lymphadenopathy are all associated symptoms (22).

Although the use of acyclovir provides symptomatic relief in herpetic stomatitis and HGS, it has limitations such as short average life, limited efficacy in the frequency of recurrences, an increased risk of nephrotoxicity on systemic administration, and the risk of new drug-resistant strains of HSV (23).

Acyclovir is an antiviral agent that integrates into viral DNA to stop further synthesis. Once it has been transformed into acyclovir triphosphate by viral and cellular enzymes, it prevents DNA synthesis and viral reproduction. Acyclovir is a synthetic purine nucleoside analog that exhibits an inhibitory effect against the varicella-zoster virus as well as herpes simplex virus types 1 and 2 (24). This medicament has been the most common treatment for HSV-1 for years, considered the gold standard therapy for different herpes virus presentations. Acyclovir can be used during an outbreak of cold sores, but it has shown better results when treatment begins early in the onset of the virus (16,25–28). Acyclovir is generally well-tolerated but may cause important side effects. Topical therapy is associated with burning or stinging on the application zone and mild erythema or drying of the skin in some patient groups (29). On the other hand, systemic therapy can cause adverse effects such as headaches, nausea, vomiting, diarrhea (30), phlebitis at the infusion site, nausea, vomiting, transaminitis, and rash (including Steven-Johnson syndrome). When used orally, patients may also develop headaches, diarrhea, nausea, and vomiting (24). Resistance to acyclovir in herpes simplex virus treatment is unusual and does not seem to be due to long-term chronic therapy (26,31). However, immunocompromised patients with advanced HSV infections have been reported to present strains resistant to acyclovir (24,32), resulting in difficult-to-control mucocutaneous diseases that require prolonged treatment with the possibility of acute kidney injury (24,33) and hemodialysis after kidney injury (25).

Some research suggests that laser therapy, specifically low-level light therapy treats herpes (16,23) with no reported side effects while demonstrating greater efficacy in the disappearance of signs and symptoms than conventional treatment (16). Laser therapy is an increasing technology used to control pain and inflammation, promote healing, prevent tissue necrosis, and recover function and aesthetics (34,35). Some studies have shown that this therapy may be useful in pain relief for treating diseases such as rheumatoid arthritis (36), osteoarthritis (37), tendinopathies (38,39), acute and chronic neck pain (40), chronic joint disorders (41), among others. Laser therapy consists of a light amplified by stimulated emission of radiation (34). Although Low-Level Laser Therapy is the most prominent (LLLT), we also find high-intensity laser therapy (HILT) in sports medicine or kinesiology (42,43). LLLT uses either coherent light sources (lasers) or non-coherent light sources consisting of filtered lamps or light emitting diodes (LEDs), and sometimes a combination of both (34). LLLT generates a wavelength between 650 and 950nm (44), while the HILT wavelength can reach 1300nm (42). The physical properties produce biological effects on tissues, such as analgesia. In the same way, it promotes anti-inflammatory wound regeneration processes, and the stem cells are activated to facilitate higher repair and healing of tissues, encouraging epithelialization (34,45). The application of low lasers is less invasive. It offers an almost total absence of side effects, promoting research and numerous tests in dermatology (34). Despite what has been previously described, there is heterogeneity in the information, and we cannot consider this therapy over Acyclovir. To fill this

gap, we decided to select laser therapy as an intervention to research and propose this study that aims to determine the effectiveness of laser therapy compared with Placebo/Acyclovir for treating patients with Herpes Labialis.

METHODS

This study was performed according to the Cochrane recommendations. The Preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement has been followed (46). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with registration number CRD42020167004. Inclusion criteria involve clinical trials without any restrictions on language or date of publication. Also, we considered studies with the following inclusion criteria according to the PICO strategy: participants 18 years old or older since in most of the world, the legal adult age is 18 (47), and individuals who were undergoing laser therapy for HSV-1 or cold sores; whereas exclusion criteria involved articles in which participants underwent laser therapy to treat herpes labialis for other reasons.

We evaluated studies in which the effectiveness of laser therapy for the treatment of HSV-1 was assessed, and the following comparisons were made in the selected studies: 1) Laser therapy compared with Placebo and 2) Laser therapy compared with Acyclovir. We excluded studies in which the effectiveness of laser therapy was not described. The primary outcomes were the effectiveness in treating HSV-1 using the measurement of the recurrence, the mean healing time in days, and lesion size.

We searched the following electronic databases: MEDLINE through Ovid, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS (Latin American and Caribbean Health Sciences Literature). We searched grey literature in OpenGrey, Google Scholar, and Clinicaltrials.gov. We scoured clinical trial protocols to identify potential unpublished studies. The Ovid search strategy (April 13, 2022) is in Supplementary Table 1. We screened the reference list of the included articles to identify references that might have been missed during the searches in the electronic databases. We contacted some of the authors to recover lost information.

We exported the references retrieved in the Endnote software (Clarivate Analytics, Philadelphia, USA). We removed duplicates after identifying them. To select the studies, two researchers blindly and independently assessed the titles/abstracts of the references retrieved to determine the possible usefulness of the articles. Then, we evaluated the complete texts. References with full texts that met the eligibility criteria were included. We reported the search results in the final systematic review and presented them in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Figure 1) (46). Discrepancies between the review authors during the study selection were solved with the opinion of a third researcher. Two researchers obtained and verified the extracted data twice to improve accuracy. Relevant data were collected using a standardized data collection format. It contains the authors and publication date of the study, country, participants, characteristics of the participants, outcomes evaluated, comparisons of the effectiveness of the laser therapy, and adverse effects.

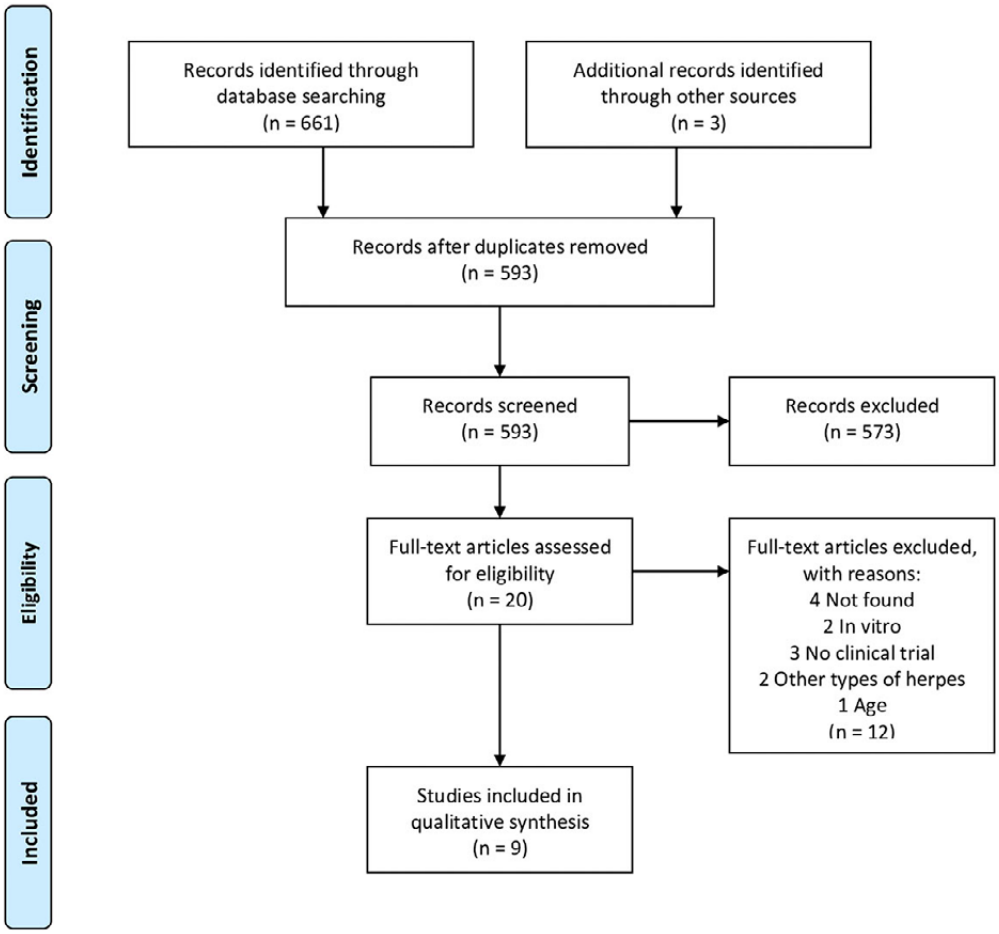

Figure 1. — Study selection diagram
Source: authors' elaboration

The risk of bias in the included studies was assessed by the Cochrane risk-of-bias tool for randomized trials (RoB 2) (48). The following items were evaluated: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. The outcome in the included studies could be graded as low risk of bias, high risk of bias, and unclear risk of bias (48). Two researchers blindly and independently assessed the risk of bias in the included studies. Discrepancies between the review authors during the risk of bias assessment were solved with the opinion of a third researcher.

We used the Review Manager software (Review Manager (RevMan) – A computer program. Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). A qualitative synthesis of the data was performed.

The certainty of the evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (49). A summary of findings was created using GRADEPro GDT (McMaster University, ON, Canada). GRADE evaluates the number of studies incorporated into

the analysis, design, risk of bias, inconsistency, indirectness, imprecision, and publication bias for the outcomes assessed. The certainty of the evidence could be downgraded by one or two levels and result in very low, low, moderate, or high (49).

RESULTS

We found 665 references, of which nine were included in the qualitative analyses (45,50–57). We excluded duplicates and articles that did not comply with the inclusion criteria (Figure 1). In the nine included studies, 668 individuals were assessed. In five studies (50–52,55,57), the outcome evaluated was the healing time in days. In three studies (45,54,56), the outcome assessed was the recurrence of HSV-1. In the study of Schindl and Neumann 1999 (53), the outcome was the median healing time in weeks. In four studies, the lesion size was evaluated (51,55–57).

Regarding the type of intervention, González, Hernández, and Estevez 2008 (45) used laser therapy of 650 nm, Ramalho *et al.* 2021 (57) used laser therapy of 660 nm, Muñoz Sanchez *et al.* 2012 (54) used laser therapy of 670 nm, Schindl and Neumann 1999 (53), used laser therapy of 690 nm, De Carvalho, *et al.* 2010 (56), used laser therapy of 780 nm and the others three studies employed laser therapy of 1072 nm (50–52). Six studies compared the intervention with Acyclovir (45,51,54–57). Four studies used a placebo as a control group (50,52,53,55). One article (45) reported gastrointestinal disturbances, rashes, and fatigue as adverse effects of Acyclovir. In two studies, there were no adverse effects (53,54). The other studies did not present data (50–52,55,56) (Table 1).

Table 1. Characteristics of included studies

Author	Country	Age	Sex (m)	Sex (f)	Outcome	Group 1 (G1)	Mean G1	SD	Group 2 (G2)	Mean G2	SD	Group 3 (G3)	Mean G3	SD	Events (G1)	n (G1)	Events (G2)	n (G2)	Events (G3)	n (G2)	p
Schindl & Neumann. 1999	Austria	Lser therapy: 31.3 ± 12.1. Placebo: 36.6 ± 14.8	11	37	Median Healing time (weeks)	Laser therapy Wavelength: 690 nm (48 J/cm2)	Median: 37.5 wk	Range: 2.0 - <52 wk	Placebo	Median: 3.0 wk	Range: 1-20 wk	_	_	_	_	24	_	24	_	_	<0.001
Dougal & Kelly. 2001	UK	Laser therapy: 41.8 (24±66). Acyclovir: 40.3 (23±54).	11	40	Mean Healing time (Days)	Laser therapy Wavelength: 1072 nm	4.3	1.8	Topical Acyclovir	8.5	3.0	_	_	_	_	25	_	26	_	_	0.005
					Lesion size (mm)		2.91	1.53		3.0	1.23	_	_	_	_	25	_	26	_	_	0.82
Dougal & Lee. 2013	UK	Laser therapy: 40.2 ± 12.9 (20–65). Placebo: 42.8 ± 11.2 (20–65)	16	71	Mean Healing time (Days)	Laser therapy Wavelength: 1072 nm	6	2.6	Placebo	7.5	3	_	_	_	_	35	_	45	_	_	0.01
Hargate. 2006	UK	_	_	_	Mean Healing time (Days)	Laser therapy Wavelength: 1072 nm	6.3	2.99	Placebo	9.4	4.58	_	_	_	_	12	_	15	_	_	0.048
Honarmand et al., 2017	Iran	Laser therapy: 31.30 ± 10.032 Acyclovir: 31.35 ± 6.862 Placebo: 32.85 ± 6.808	44	16	Mean Healing time (Days)	Laser therapy Wavelength: 870 nm (4.5 J/cm2)	2.20	0.41	Topical Acyclovir	3.40	1.042	Placebo	4.30	1.03	_	20	_	20	_	20	<0.001
					Lesion size (mm^2)		25.55	15.99		25.90	15.05		25.75	12.74	_	20	_	20	_	20	0.997
de Carvalho et al., 2009	Brazil	28.8	20	51	Recurrence	Laser therapy Wavelength: 780 nm (3-4.5 J/cm2)	_	_	Topical Acyclovir	_	_	_	_	_	3	41	4	30	_	_	0.076
					Lesion size (monthly avarage size)		_	_		_	_	_	_	_	0.122	41	0.223	30	_	_	0.013
González et al., 2008	Cuba	>18	13	47	Recurrence	Laser therapy Wavelength: 650 nm (8 J/cm2)	_	_	Topical and systemic Acyclovir	_	_	_	_	_	4	30	12	30	_	_	_
Muñoz et al., 2012	Cuba	18-59	_	_	Recurrence	Laser therapy Wavelength: 670 nm (2.04 J/cm2)	_	_	Topical and systemic Acyclovir	_	_	_	_	_	0	116	6	116	_	_	_
Ramalho et al., 2021	Brazil	>18	_	_	Lesion size (Lesion size reduction)	Laser therapy Wavelength: 660 nm (120 J/cm2)	Median (lesion size reduction): 1	Range: -2/2	Acyclovir	Median (lesion size reduction): 0	Range: -6/2	Laser therapy + Acyclovir	Median (lesion size reduction): 1	Range: 0/3	_	25	_	16	_	18	0.0131 (Between Acyclovir and Laser therapy + Acyclovir)

Source: authors' elaboration

The studies found presented an intention-to-treat (ITT) analysis. Only the Hargate. 2006 (50) reported a per-protocol analysis. The risk of bias assessment in the included studies with an ITT analysis is displayed in Figures 2 and 3. Five outcomes presented a low risk of bias for the randomization process (51,52,57), and the other nine showed some concerns (45,53–56). Five outcomes were graded as low risk of bias for deviations from intended interventions (51,52,55): three showed a high risk of bias (45,57), and six had some concerns (53–56). For missing outcome data, eleven outcomes presented a low risk of bias (51–55,57), one outcome was a high risk (45), and two showed some concerns (56). For measurement of the outcome, eight outcomes showed a low risk of bias (51–53,55), four with high risk (45,54,56), and two with some concerns (57). For the selection of the reported result, ten outcomes presented a low risk of bias (51–53,55,57), three were high risk (54,56), and one presented some concerns (45). Finally, we found eight outcomes with some concerns (51–53,55) and six with a high risk of bias in overall bias (45,54,56,57). The Hargate. 2006 study (50) with a per-protocol analysis had some concerns in the randomization process and selection of the reported result. The deviations from intended interventions, missing outcome data, and outcome measurement presented a low risk of bias. Hence, the overall bias assessment showed concerns for the only outcome assessed. The bias with the higher low-risk evaluation involved the missing outcome data. The measurement of the outcome bias presented the highest proportion of the high risk of bias, and the randomization process showed the highest proportion of some concerns.

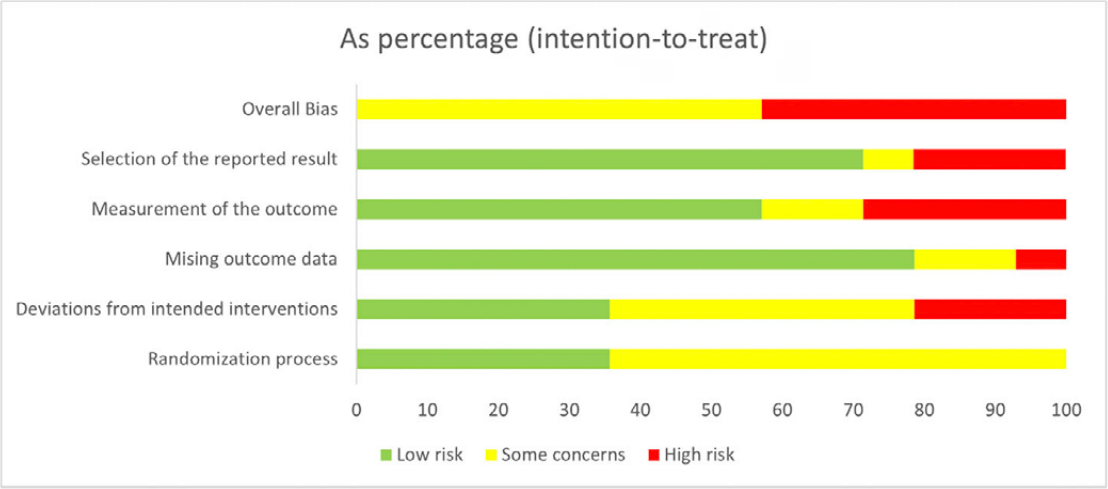

Figure 2. Risk of bias within the studies ITT

Source: authors' elaboration

Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Dougal & Kelly. 2001	Laser therapy 1072nm	Topical Acyclovi	Mean Healing time (Days)	+	+	+	+	+	!
Dougal & Kelly. 2001	Laser therapy 1072nm	Topical Acyclovi	Lesion size	+	+	+	+	+	!
Dougal & Lee. 2013	Laser therapy 1072nm	Placebo	Mean Healing time (Days)	+	+	+	+	+	!
de Carvalho et al., 2009	Laser therapy 780 nm	Topical Acyclovir	Recurrence	!	!	!	-	-	-
de Carvalho et al., 2009	Laser therapy 780 nm	Topical Acyclovir	Lesion size (monthly avarage size)	!	!	!	-	-	-
Muñoz et al., 2012	Laser therapy 670 nm	Topical and systemic Acyclovir	Recurrence	!	!	+	-	-	-
Schindl & Neumann. 1999	Laser therapy: 690 nm	Placebo	Median Healing time (weeks)	!	!	+	+	+	!
Honarmand et al., 2017	Laser therapy: 870 nm	Topical Acyclovir	Mean Healing time (Days)	!	!	+	+	+	!
Honarmand et al., 2017	Laser therapy: 870 nm	Placebo	Mean Healing time (Days)	!	+	+	+	+	!
Honarmand et al., 2017	Laser therapy: 870 nm	Topical Acyclovir	Lesion size (mm2)	!	!	+	+	+	!
Honarmand et al., 2017	Laser therapy: 870 nm	Placebo	Lesion size (mm2)	!	+	+	+	+	!
González et al., 2008	Laser therapy: 650 nm	Topical and systemic Acyclovir	Recurrence	!	-	-	-	!	-
Ramalho et al., 2021	Laser therapy: 660 nm	Acyclovir	Lesion size reduction	+	-	+	!	+	-
Ramalho et al., 2021	Laser therapy: 660 nm	Laser therapy + Acyclovir	Lesion size reduction	+	-	+	!	+	-

Figure 3. Risk of bias among the studies ITT

Source: authors' elaboration

Recurrence of the HSV-1

We found three studies in the analysis comparing the intervention (laser therapy) and Acyclovir concerning the outcome recurrence of HSV-1 (45,54,56). De Carvalho *et al.*, 2009 show no significant differences (p=0.076) between the intervention and Acyclovir. The other studies did not present association results.

Intervention comparison for outcome healing time

Laser therapy vs. Placebo

We found three studies in the analysis comparing the intervention (laser therapy) and placebo (50,52,55). In the three studies, the mean healing time in days was significantly longer in individuals with a placebo than in individuals with laser therapy. Additionally, Schindl & Neumann. 1999 (53) presented that the median healing time in weeks was significantly longer in individuals among whom the placebo had been used than in individuals with laser therapy (p<0.001).

Laser therapy vs. Acyclovir

We found two studies in the analysis comparing the intervention (laser therapy) with another intervention (Acyclovir) (51,55). In the two studies, the mean healing time in days was significantly longer in individuals with Acyclovir than in those with laser therapy. Ramalho *et al.* (57) described non-statistically significant differences in healing time but did not report the results.

Lesion size

Dougal and Kelly, and Honarmand *et al.* (51,55) did not find significant differences between laser therapy and Acyclovir. Ramalho *et al.* (57) noted differences in lesion size on day 1 of treatment. The

Acyclovir group showed less lesion reduction than the group receiving laser therapy and acyclovir. Only De Carvalho *et al.* (56) reported a significantly smaller lesion size in the laser therapy group than in the Acyclovir group. Outcome measures for lesion size were not comparable.

Evaluation of publication bias and the funnel plot was not possible. In the publication bias, the effect calculated will tend to overestimate the effect of the intervention. However, our search strategy includes gray literature and clinical trial protocols, actions that control for this bias. Additionally, the results of studies do not highlight the effect of the intervention, so bias is unlikely. In the same way, to guarantee the validity of the study, we performed the risk of bias and the certainty of the evidence assessment.

A summary of the evaluation of the certainty of the evidence with GRADE was provided in Table 2. The outcomes were 1) Recurrence of the HSV-1, 2) healing time in the comparison between two interventions (Laser therapy and Acyclovir), 3) healing time in the comparison between the laser therapy and placebo, and 4) lesion size. The studies were designed as randomized clinical trials. The level of certainty of evidence was downgraded by three degrees because of very serious concern regarding the risk of bias and serious indirectness and imprecision for the outcomes. Publication bias was unsuspected. Therefore, the certainty of the evidence was very low for the outcomes.

Table 2. GRADE evaluation between Laser therapy compared to another intervention (Acyclovir) or a control (Placebo) for treatment of Herpes Simplex virus type 1

Certainty assessment							Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
3	randomised trials	very serious [45,50,51 a]	serious [b]	serious [c]	not serious	undetected	⊕○○○ VERY LOW$_{a.1}$
2	randomised trials	serious [52, 53 d]	serious [b]	serious [c]	not serious	undetected	⊕○○○ VERY LOW$_{a.2}$
4	randomised trials	serious [54, 55, 56 d]	serious [b]	serious [c]	not serious	undetected	⊕○○○ VERY LOW$_{a.3}$
4	randomised trials	very serious [51, 52, 54, 57 a]	serious [b]	serious [c]	not serious	undetected	⊕○○○ VERY LOW$_{a.4}$

Explanations

a. The evidence has been downgraded by two-levels because the studies presented a high risk of bias
b. The evidence has been downgraded by one level because the studies presented inconsistency with high clinical heterogeneity
c. The evidence has been downgraded by one level because the studies presented indirectness, there are differences in doses and times of interventions.
d. The evidence has been downgraded by one level because the studies presented a considerable risk of bias

Impact

a.1) One study found an association between laser therapy and less recurrence of HSV-1. The other studies did not present association results.
a.2) In the two studies, the mean healing time in days was significantly longer in individuals among whom the acyclovir had been used than individuals with laser therapy.
a.3) In three studies, the mean healing time in days was significantly longer in individuals among whom the placebo had

been used than individuals with laser therapy. Additionally, Schindl & Neumann. 1999 presented that the median healing time in weeks was significantly longer in individuals among whom the placebo had been used than individuals whit laser therapy.
a.4) One study found an association between laser therapy and the smaller size of the lesion. The other studies did not present an association.
Source: based on references 45, 50, 51, 52, 53, 54, 55, 56 and 57

Fi-index tool

This manuscript has been checked with the Fi-index tool and obtained a score of 0 for the authors only on 31/07/2023, according to SCOPUS®. The fi-index tool aims to ensure the quality of the reference list and limit any autocitations.

DISCUSSION

Compared to Acyclovir, we found a reduction in the recurrence risk of HSV-1 and a smaller lesion size when laser therapy is used. Alternatively, we detected a shorter mean healing time for laser therapy than placebo, which could decrease symptoms such as pain, itching, and ulcers, improving the quality of life of patients.

The placebo substance is considered pharmacologically inert with no expected clinical effect in treatment; consistently, laser therapy shows significant effectiveness. For its part, laser therapy has been shown to have the ability to boost electron transport, the release of nitric oxide from adenosine triphosphate (ATP), blood flow, increase reactive oxygen species, and activation of various signaling pathways, whereby stem cells can be activated to facilitate tissue repair and healing in the application area (34). Even though laser therapy showed promising results in decreasing recurrence compared to Acyclovir, it is a treatment that has yet to be studied in-depth. Acyclovir has been the gold standard for years. It has shown high efficacy results in a short time (18,25–27). However, the favorable results of laser therapy may represent less risk of adverse effects than systemic Acyclovir. Although topical Acyclovir may be less toxic and with fewer adverse effects, inadequate penetration of the mucosa may limit its efficacy (58). Regarding practicality, Acyclovir can be self-administered by the patient. However, it requires frequent topical application (five or six times a day). A careful intake of the systemic drug dose, which can turn it annoying (58), requires a sense of coherence and adherence to treatment on the part of the patient. Professional-led laser therapy may prove to be a good treatment option, relieving the patient of responsibility for self-administration of therapy.

Within the limitations found, the wavelength used in clinical trials and the intensity of the laser have not been standardized; this could seriously affect the results. In the literature, there is no consensus regarding the wavelength. Wavelengths of 390nm to 600nm are used to treat surface tissue, and wavelengths from 600nm to 1,100nm are used to treat deeper tissues. Additionally, it has been reported that wavelengths in the 700 nm to 750 nm have limited biochemical activity and are not frequently used (34). Accordingly, the clinical trials included in this study used wavelengths from 650nm to 1072nm. No study used wavelengths between 700nm and 750nm. Similarly, the dose for laser therapy is disputed. It uses relatively low fluences of 0.04–50 J/cm^2; the included studies described amounts from 2.04 to 48 J/cm^2; only Ramalho *et al.* (57) reported 120 J/cm^2. Doses of 0.001 to 10 J/cm^2 have been reported to provide biostimulation (23,59).

The results in this systematic review are consistent with Chi *et al.*, 2015 (16) and Al-Maweri *et al.,* 2018 in their systematic reviews (23). Although Chi *et al.,* 2015 (16) only include two studies with laser therapy intervention (53,56), they found a significantly longer median recurrence-free interval

in the laser group, according to Schindl *et al.,* 1999 (53). They also reported no differences between the interventions in the number of recurrences but found a significantly smaller average lesion size in the laser group, according to Carvalho *et al.,* 2010 (56). Al-Maweri *et al.,* 2018 (23) also reported that laser therapy effectively reduced pain, healing time, and the recurrence rate of cold sores. Landis 2017, in her review for the Master of Science degree, documented that the study by Dougal and Lee, 2013 showed a significant difference in healing time between the groups (Laser therapy and placebo) (60).

For this analysis, few studies with small sample sizes have been included. The differences between the interventions, the different wavelengths, and the difference in doses represent high clinical heterogeneity, so it was impossible to perform a quantitative analysis or meta-analysis, which is one of the limitations of this study. Additionally, some of the experiments evaluated in this review have not been adequately described; consequently, the risk bias may have been overestimated. However, the Cochrane tool used for experimental studies that assess the risk of bias is consistent (48). Despite the findings, no previous reviews evaluated the variety of laser therapies to treat HSV-1. Therefore, it is essential to identify the weaknesses in the existing literature to find the necessary standards for future research that allow more accurate results. We recommend producing high-quality research with larger sample sizes allowing the evaluation of the effectiveness of laser therapy for HSV-1 treatment, with standardization in the dose, in terms of wavelength and treatment times. We suggest randomized controlled experimental studies with well-implemented guidelines reporting adverse effects.

CONCLUSIONS

The mean healing time for treating HSV-1 was shorter for laser therapy in comparison with the placebo and Acyclovir. Compared to conventional treatment, better results were described in the disappearance of signs and symptoms. Although, the findings should be interpreted with caution due to the lack of quantitative synthesis of the information, and the certainty of the evidence was very low for the outcomes. Future research with less heterogeneity between studies and standardization of dose, wavelength, and treatment times are required to provide more accurate results to help healthcare systems in decision-making and health service delivery when considering alternative therapies to treat HSV-1 in any patient.

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflict of interest.

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