Lasers in Medical Science (2022) 37:3393–3402
https://doi.org/10.1007/s10103-022-03653-6

REVIEW ARTICLE

Is low-level laser therapy effective in the treatment of herpes labialis? Systematic review and meta-analysis

Ana Waleska Pessoa Barros[1] · Pedro Henrique da Hora Sales[1] · Paulo Goberlânio de Barros Silva[2] · Ana Claudia Amorim Gomes[3] · Alessandra Albuquerque Tavares Carvalho[4] · Jair Carneiro Leão[4]

Received: 24 January 2022 / Accepted: 4 October 2022 / Published online: 10 October 2022

Abstract

The objective of this systematic review is to evaluate the effectiveness of low-level laser therapy in the treatment of herpes labialis. The searches were carried out independently by 2 researchers and the articles were selected through the electronic databases according to the inclusion and exclusion criteria previously established. Initially, 480 articles were found, of which 7 randomized clinical trials and 1 clinical trial were selected. In total, 928 patients were included. In the meta-analysis, the mean healing time for laser use was significant, showing a mean reduction of 1.37 [CI 95% = 0.92 to 1.82] days for tissue healing ($p < 0.0001$). In the meta-analysis to evaluate the time for crust formation, there was no significant difference between the groups and no significant reduction in the mean time for crust formation ($p = 0.150$). Only one of the selected studies had a low risk of bias. The use of low-level laser proved to be effective in the treatment of herpes labialis. However, due to the high risk of bias in the included studies, there is a need to carry out new standardized studies to prove the effectiveness of this therapy.

Keywords Herpes labialis simplex · Low-level laser therapy · Photodynamic therapy

Introduction

Herpes simplex virus 1 (HSV-1) is the etiological factor of one of the most prevalent viral infections that affect the orofacial region, the herpes labialis (HL) [1, 2]. And, it is through contact with lesions or contaminated body fluids, such as exudate from active lesions, saliva, and genital secretions that this virus replicates and infects only the superficial mucosa. After this primary infection, the virus enters the sensory nerve endings and is transported to the neural cell bodies, most often causing latent infection of these neurons and being able to reactivate periodically [1, 2].

The initial forms of HSV-1 contagion, a special emphasis, should be given to the lesions caused by this virus, which are highly contagious and include stages, such as prodromal, which does not show any physical sign of the disease but can cause symptoms such as itching, pain, and tingling; vesicle, appearing as a small superficial blister; pustules or ulcers; crust, which may be softened or hardened; and finally, the healed stage, in which there is a return to normal mucosa/skin, and there may be residual erythema. However, the vesicle phase is more associated with high rates of contagion, as the fluid from the vesicle stores millions of viral particles [1, 3, 4].

HSL is a benign, self-limiting lesion, which spontaneously disappears between 7 and 10 days after the appearance of the first vesicles; however, especially in immunocompromised patients, it may require a longer time for its disappearance, in addition to presenting more recurrences in a shorter period of time [1, 2].

Although spontaneous healing usually occurs, there are therapeutic options to accelerate this process and reduce the

✉ Pedro Henrique da Hora Sales
salespedro@gmail.com

1 Department of Prothesis and Oral and Maxillofacial Surgery, Federal University of Pernambuco (UFPE), Av. Prof. Moraes Rego 1235 – Cidade Universitária, Recife, Pernambuco Zip: 50670-901, Brazil

2 Department of Oral Pathology, CHISTHUS University, Fortaleza, CE, Brazil

3 Department of Oral and Maxillofacial Surgery, University of Pernambuco, Recife, Pernambuco, Brazil

4 Department of Clinical and Preventive Dentistry, Federal University of Pernambuco (UFPE), Recife, Pernambuco, Brazil

pain caused by the injury. The standard therapeutic option for the treatment of HLR is the antiviral acyclovir. Which provides symptomatic relief, but is not able to cure the latent infection. Acyclovir is administered topically, intraorally, and intravenously [5]. Among these, topical use is considered the least effective, reducing the symptoms associated with HLR [6] more slowly; however, it has the fewest side effects. Intraoral or intravenous use is prescribed for individuals with a high recurrence of these lesions, or in immunocompromised individuals, because their indiscriminate use can generate side effects such as phlebitis, nausea, and increase in liver enzymes, urea, and creatinine in addition to being related to increased resistance of HSV-1 [5].

An excellent alternative that has been successfully used in patients with HSL, both for the treatment of their symptoms and to reduce the chances of recurrence of the lesion, is the use of laser, especially photodynamic therapy with low-level laser (LLLT). The latter acts on the final stage of HSV-1 replication, thus limiting viral replication from one cell to another and also acting on the host's immune response, unblocking the suppression of pro-inflammatory mediators [7, 8]. The use of LLLT associated with a chromophore agent, such as methylene blue, has been used in the healing of lesions such as those caused by HRL and mucositis [8–10].

Thus, due to a closer relationship with accelerated wound healing, pain reduction and a possible stimulation of the patients' immune response, the use of low-level laser has gained prominence as a therapeutic option for these patients [4, 11–15]. However, although the low-level laser represents a promising alternative for the treatment of HSL, there is still no consensus on the standardization of its use and which wavelength or period of application is more effective for the treatment of this clinical condition [10, 15–18]. Thus, the objective of this systematic review is to answer the following research question: Is low-level laser therapy effective in the treatment of herpes labialis?

Materials and methods

This study was designed and conducted in accordance with the guidelines of the PRISMA [19] and registered in international prospective register of systematic reviews (PROSPERO) with registration number CRD 42,021,264,802.

Research strategy

The search was carried out in six databases including the gray literature (Medline via PubMed; Scopus; Central Cochrane; LILACS; Embase; and Sigle via Open grey) until September 2021. The descriptors were used "herpes labialis"; "laser"; and "herpes simplex," in order to include as many articles as possible for the initial evaluation. Through these descriptors, a search with a specific algorithm was performed in each database as shown below (Table 1). A manual search was also carried out in the references of the selected articles and in the researchers' scientific article archives.

Selection of studies

The article search process was conducted by two reviewers (AWPB) and (PHHS), and a third reviewer (JCL) was consulted for cases of disagreement in which there was no consensus between the first two reviewers. These reviewers performed a screening by reading the titles and abstracts; these articles had their eligibility assessed by reading them in full in order to select the articles included and submit them to the risk of bias assessment. After the selection process, an

Table 1 Specific search terms for each database. Search Terms Specific for Each Database and Truncations

Electronic database	Search strategy used	Items found
Keywords	Herpes labialis; Herpes simplex; Lasers	
PubMed	((“herpes labialis”[MeSH Terms] OR (“herpes”[All Fields] AND “labialis”[All Fields]) OR “herpes labialis”[All Fields]) AND (“lasers”[MeSH Terms] OR “lasers”[All Fields])) OR ((“herpes simplex”[MeSH Terms] OR (“herpes”[All Fields] AND “simplex”[All Fields]) OR “herpes simplex”[All Fields]) AND (“lasers”[MeSH Terms] OR “lasers”[All Fields]))	391
Scopus	TITLE-ABS-KEY (*herpes* AND *labialis* AND *laser* OR *herpes* AND *simplex* AND *laser*)	50
COCHRANE	IDSearchHits #1 “herpes labialis OR herpes OR labialis”:ti,ab,kw (Word variations have been searched) #2″Lasers OR laser” ti,ab,kw (Word variations have been searched) #3 “herpes simplex OR herpes OR simplex” ti,ab,kw (Word variations have been searched) #4 #1 AND #2 OR #3 and #2	32
LILACS	herpes labialis AND laser OR herpes simplex AND laser AND (db:(“LILACS”))	7
Grey literature		
OpenGrey	Herpes labialis and laser or herpes simplex and laser	0

evaluation of the kappa index was carried out in order to assess the level of agreement between the evaluators.

Inclusion criteria

Studies with randomized and observational clinical trials (prospective and/or retrospective) that evaluated the effectiveness of low-level laser in the treatment of herpes simplex labialis. This effectiveness was evaluated through the reduction of signs and symptoms of HLR in studies carried out in humans without restriction of age, sex, and ethnicity; no language restriction was performed.

Exclusion criteria

Exclusion criteria are as follows: report studies or case series, cross-sectional studies, systematic reviews; duplicate studies and/or that did not report results after the end of the research; and preclinical studies.

Variables

The primary variable of this study was the effectiveness of low-level laser in reducing signs and symptoms caused by HLR. These data were expressed in absolute values and percentages.

The secondary variables were healing time, crusting time, use of red or infrared laser, laser exposure time, and effects of laser on recurrence of HLR lesions, as well as the use of antivirals, concomitant, or not to treatment.

Assessment of risk of bias and quality of studies

The tool *Revised Cochrane risk-of-bias tool for randomized trials* (RoB 2.0) was used to assess the risk of bias of the randomized controlled trials that were selected. This tool assesses five domains: bias in the randomization process, deviations from the intended intervention, bias due to missing data, bias in measuring outcomes, and bias in reporting outcomes. Each domain determines whether there was a low risk of bias, some concerns, or a high risk of bias. Enabling the realization of judgment increases the risk of bias arising from each domain through the use of an algorithm, which helps reviewers to assess the important factors in the evaluation of each domain.

Meta-analysis

Data were tabulated in Microsoft Excel and exported to Revman in which the meta-analysis of the difference of means by inverse variance and fixed effect method. Additionally, the I^2 heterogeneity coefficients were calculated.

Results

In the initial search, 480 results were found: 391 in Medline via PubMed, 50 in Scopus, 32 in Central Cochrane, 7 in LILACS, and 0 in Sigle via Open grey. Of these, 73 were excluded after removing duplicate articles, and another 391 after reading the titles and abstracts. The remaining 16 were read in full and 8 more were excluded. The reasons were case report/case series ($n=2$) [20, 21], use of high-power laser ($n=1$) [22], incomplete article ($n=1$) [10, 23], observational study ($n=1$) [24], study without a control group ($n=1$) [25], study without presentation of results ($n=1$) [26]; at the end of this selection, stage 08 was chosen to compose this systematic review [15–18, 27, 28]. The Kappa index among the evaluators was 0.93 (CI 95%: 0.91; 0.95). The details of the selection process can be seen in Fig. 1 (flowchart).

Risk of bias assessment

All articles selected were prospective studies, 07 of which were randomized clinical trials and 01 clinical trial. The eight were submitted for evaluation of bias through RoB 2. Through the tool's criteria, it was observed that three articles had a high risk of bias [18, 28, 29], four articles had some concerns at risk of bias [15–17, 27], and only one with a low risk of bias [30]. The complete data can be seen in Fig. 2.

Country of studies

The studies evaluated came from eight countries, one study carried out in Spain, one in Austria, two in England, one in Brazil, one in Cuba, one in Serbia, and another in Iran.

Patients

The selected studies worked together with a sample of 928 patients, 295 (31.8%) men, and 333 (35.9%) women and 300 not reported (32.3%). Two studies used oral acyclovir [18, 27], and one of them used topical acyclovir [27], with a total of four studies using topical acyclovir [15, 18, 28, 29]. Regarding the use of placebo laser in control groups, five of the 09 studies reported use. The follow-up time of these individuals ranged between 06 and 1825 days. One of these studies carried out a pilot study previously and these data, which were reported independently, allowing different analyses in the same study [18]. Four studies did not analyze the effectiveness of laser [15, 16, 18, 29], such as healing time and crust formation. However, another five studies [17, 18, 27, 29, 30] (including the pilot study by [18] performed such an

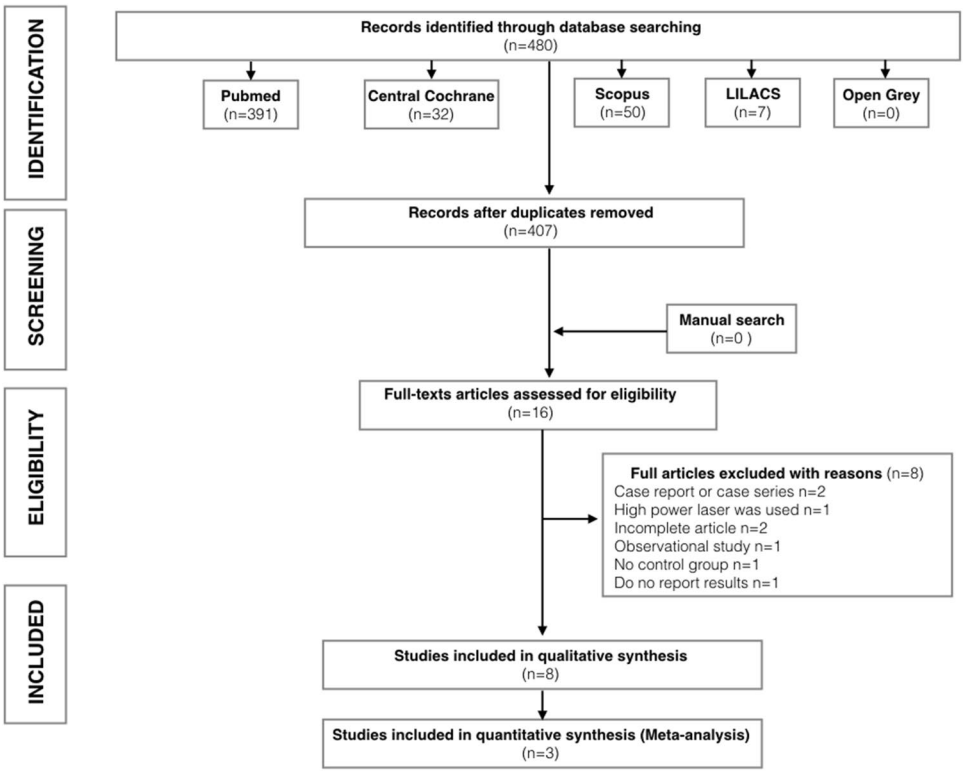

Fig. 1 Flowchart of the study selection process

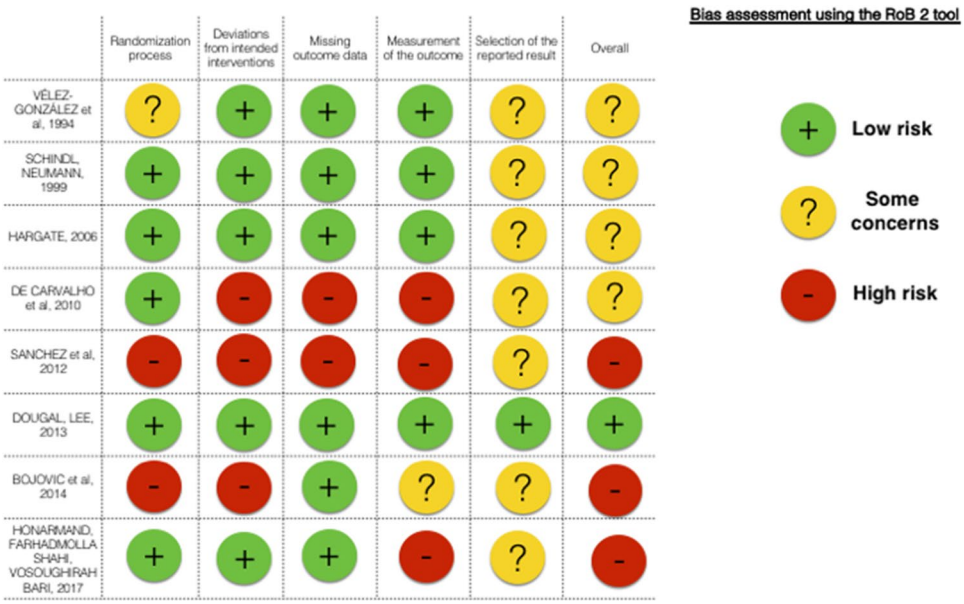

Fig. 2 Bias assessment using RoB 2 tool

evaluation and one of them was able to verify[18] the onset of crust formation in 29 h with the use of laser [30]. Another study found that the total healing time together with the end of the signs of the disease was 7 days for patients using laser and that for the same time, 77 of 116 patients using topical acyclovir still had vesicles [18]. This data can be seen in full in Tables 2 and 3.

Pain analysis with the VAS scale

Three of the eight studies used the VAS scale for pain analysis [15, 28, 29]. In the group that performed only the laser in the study by [29], the scale result on the second day was 2 to 1 on the fifth day; in the control group, which used topical Acyclovir, the scale went from 3 on

Table 2 Systematized table referring to the sample, therapy genre, and laser property of the included studies

Authors and year	Type of study	Sample	Gender	Mean of age (y)	Standard therapy (ST)	Follow-up (D)	Type of laser	Pulse energy	Wavelength	Probe diameter	Exposure time / Interval	Country
VÉLEZ-GONZÁLEZ et al., 1994	RCT	36 10 (ST1) 12 (ST2 + L) 24 (ST3 + L)	NR	NR	ST1: acyclovir (200 mg orally) + laser (placebo) ST2: acyclovir (placebo) ST3: acyclovir (200 mg orally)	775	Red	8 J/cm^2 20 mW	632.8 nm	2 mm	NR	Spain
[16]	RCT	48 24 (L) 24 (ST)	M 5/F 16 M 6/F18	31.3 ± 12.1 36.6 ± 14.8	ST1: dummy laser	364	Red	48 J/cm^2 80 mW	690 nm	1 cm^2	10 Min Once a day for 2 weeks	Austria
[17]	RCT	32 14 (L) 18 (ST)	NR	NR	ST1: dummy laser	12	Infrared	NR	1072 nm	NR	3 Min 3 times a day for 2 days	UK
[15]	RCT	71 41 (L) 30 (ST)	M 20 F 51	28.8	ST1: acyclovir (topic)	480	Red	4.5 J/cm^2 60 mW	780 nm	0.4mm^2	2–3 M 10 Sects. 1 per week	Brazil
[18]	RCT	322	M 189/F 133	NR	NR	1825	Red	2.04 J/cm^2 40mW	670 nm	0.79 cm^2	2,4 min 40 s. It does not report for how many days	Cuba
[18] (pilot*)	RCT	232 116 (L) 116 (ST)	NR	NR	ST1: acyclovir (topic and tablets)	365	Red	2.04 J/cm^2 40 mW	670 nm	0.79 cm^2	2,4 Min 40 s. It does not report for how many days	Cuba
[30]	RCT	87 41 (L) 46 (ST1)	M 16 F 71	26.8	ST1: dummy laser	480	Infrared	NR	1072 nm	NR	3 Min 3 times a day for 2 days	UK
[29]	CT (pilot)	43 23 (L) 20 (ST1)	M 15 F 28	34	ST1: acyclovir (topic)	9	Red	NR	670 nm	2 mm	4 Min NR the interval	Sérvia
[28]	RCT	60 20 (L) 20 (ST1) 20 (ST2)	M15/F5 M15/F5 M14/F6	31.30 ± 10.03 32.85 ± 6.80 31.35 ± 6.86	ST1: acyclovir (topic) ST2: dummy laser	6	Red	4.5 J/cm^2 80 mW	870 nm	6–8 mm	NR	Iran

RCT, randomized clinical trial; *CT*, clinical trial; *L*, laser; *M*, male; *F*, female; *Y*, years; *D*, days; *ST*, standard therapy; *Med*, medication; *NR*, not reported; *Min*, minutes; Sec, seconds

Table 3 Laser effectiveness analysis (healing time and crust formation time)

Authors and year	Healing time				Crusting time	
	Just laser (L)	Standard therapy 1 (ST 1)	Standard therapy 2 (ST 2)	Standard therapy 3 (ST 3)	Just laser (L)	Standard therapy 1 (ST 1)
VÉLEZ-GONZÁLEZ et al., 1994	UN	9.16 days	9 days	7.85 days	UN	UN
[16]	UN	UN	UN	UN	UN	UN
[17]	6.3 days (SD 2.99)	9.4 days (SD 4.58)	UN	UN	48 h (SD 29.04)	67,2 h (SD 31.44)
[15]	UN	UN	UN	UN	UN	UN
[18]	UN	UN	UN	UN	UN	UN
[18](pilot)*	After 7 days, there were no more signs of the disease	After 7 days, 77 patients had vesicles	UN	UN	After 7 days, there were no more signs of the disease	After 7 days, 29 had crust formation
[30]	5.37 days (SD 2.63)	7.37 days (SD 3.02)	UN	UN	29 h (SD 23.8)	33 h (SD 40.8)
[29]	UN	UN	UN	UN	UN	UN
[28]	2.2 days (SD 0.41)	4.3 days (SD 1.03)	3.4 days (SD 1.042)	UN	UN	UN

UN, unrealized; *L*, laser; *ST1*, standard therapy 1; *ST2*, standard therapy 2; *ST3*, standard therapy 3; *NR*, not reported; *SD*, standard deviation

the second day to 2 on the fifth day and only obtained a null result on the seventh day. These data can be viewed in full in Table 4.

Therapies used and the recurrence of herpes

Four of the eight studies were able to make such an assessment [15, 16, 18, 27]. Schindl and [16] reported the recurrence of herpes during a 10-week follow-up in 04 of the 24 patients who used the laser; in those 24 who used the placebo laser, 21 had recurrence during the first 10 weeks. [18] (pilot*) were able to verify that 84 of the 116 individuals treated with laser had recurrence of lesions in the first year, while all subjects treated with topical acyclovir had recurrence in the first year. These data can be seen in full in Table 5.

Table 4 Pain analysis with the VAS scale

Authors and year	Just laser (L)	Standard therapy 1 (ST 1)	Standard therapy 2 (ST 2)	Standard therapy 3 (ST 3)
VÉLEZ-GONZÁLEZ et al., 1994	NR	NR	NR	NR
[16]	NR	NR	NR	NR
[17]	NR	NR	NR	NR
[15]	0.113 Average pain per month	0.184 Average pain per month	UN	UN
[18]	NR	NR	NR	NR
[18](pilot)*	NR	NR	NR	NR
[30]	NR	NR	NR	NR
[29]	VAS scale Day 2 = 2 Day 5 = 1 Day 7 = 0	VAS scale Day 2 = 3 Day 5 = 2 Day 7 = 0	UN	UN
[28]	VAS scale Day 2 = 0.85 (0.99) Day 5 = 0 (0.0)	VAS scale Day 2 = 3.20 (2.84) Day 5 = 0.0 (0.0)	VAS scale Day 2 = 2.55 (1.82) Day 5 = 0 (0.0)	NR

UN, unrealized; *L*, laser; *ST1*, standard therapy 1; *ST2*, standard therapy 2; *ST3*, standard therapy 3; *NR*, not reported; *NA*, not applicable; *SD*, standard deviation; *VAS Scale*, visual analogic scale

Table 5 Studies that evaluated the effect of the therapies used and the recurrence of herpes and their results

Authors and year	Relapses (year)			
	Just laser (L)	Standard therapy 1 (ST 1)	Standard therapy 2 (ST 2)	Standard therapy 3 (ST 3)
VÉLEZ-GONZÁLEZ et al., 1994	UN	Before: 5.2 After: 2.8 (number/year)	Before: 7.83 After: 1.16 (number/year)	Before: 7.28 After: 1.28 (number/year)
[16]	First 10 weeks: 04	First 10 weeks: 21	UN	UN
[15]	They reported an average of 3116 recurrences per month	They reported an average of 3.48 recurrences per month	UN	UN
[18]	First year: 35 Second year: 42 Third year: 149 Fourth year: 41 Fifth year: 22	NA	NA	NA
[18](pilot)*	84 in 1 year	116 in 1 year	UN	UN

UN, unrealized; *L*, laser; *ST1*, standard therapy 1; *ST2*, standard therapy 2; *ST3*, standard therapy 3; *NR*, not reported; *NA*, not applicable; *SD*, standard deviation

Meta-analysis

It was possible to perform meta-analysis to assess healing time. In this, three studies were included, totaling 75 patients treated with laser and 84 patients treated with dummy laser divided into two subgroups, treated with infrared and red lasers. All studies demonstrated a significant reduction in the mean healing time and the meta-analysis showed a mean reduction of 1.37 [CI 95% = 0.92 to 1.82] days for tissue healing ($p < 0.0001$). There was no significant heterogeneity ($p = 0.200$, $I^2 = 38\%$) or difference between laser types ($p = 0.100$) (Fig. 3).

It was also possible to perform meta-analysis to evaluate the time for crust formation. In this one, only two studies could be included, both using infrared laser and totaling 55 patients treated with laser and 64 with dummy laser. The two studies did not show a significant difference between the groups and the meta-analysis also did not show a significant reduction in the mean time for crust formation ($p = 0.150$). There was no significant heterogeneity ($p = 0.240$, $I^2 = 29\%$) (Fig. 4).

Discussion

Conventionally, topical and/or systemic antiviral drugs such as acyclovir and famciclovir are included for the treatment of HLR. Such medications are responsible for reducing the symptoms and severity of HLR lesions, but they are not capable of curing or reducing the incidence of infections, as they are associated with the emergence of drug-resistant HSV [1]. Thus, the search for new therapeutic alternatives

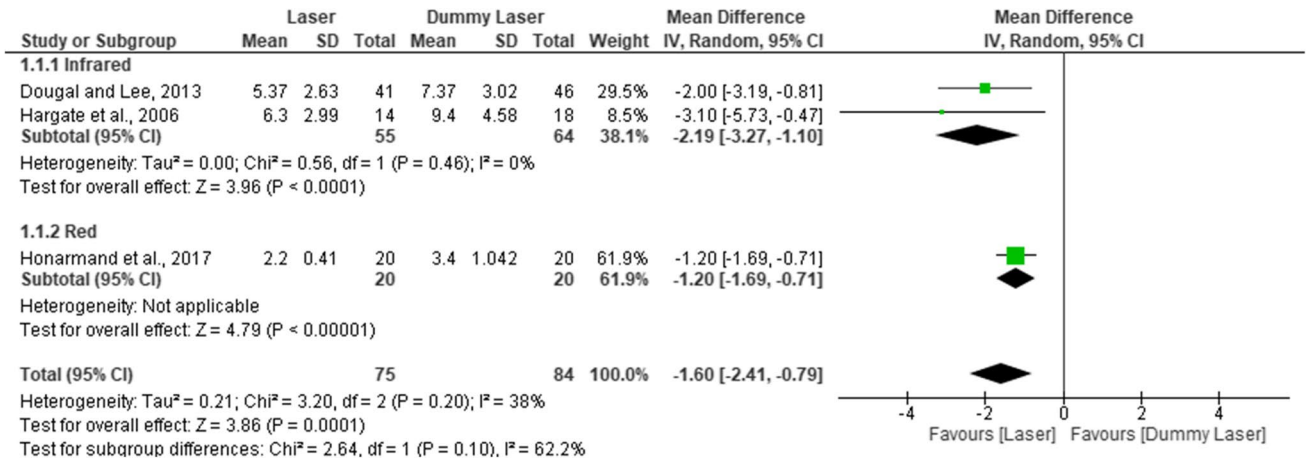

Fig. 3 Meta-analysis comparing healing time between laser and dummy laser

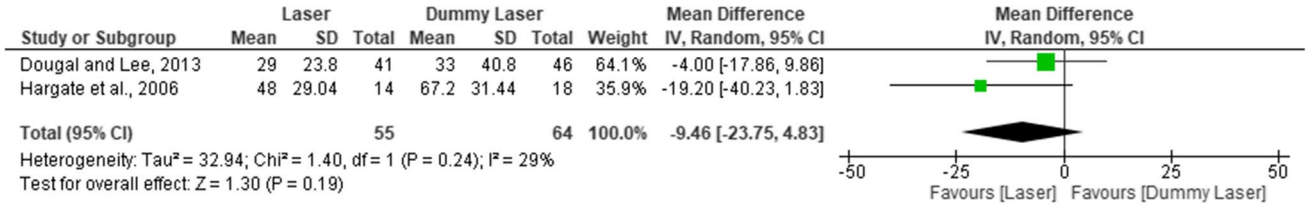

Fig. 4 Meta-analysis comparing crust formation time between laser and dummy laser

that reduce the incidence of lesions, treat the infection, and symptoms of HLR has pointed to photodynamic therapy as a non-invasive and satisfactory therapy [2–4, 7, 10, 14–30].

In a study carried out by [18], when comparing the healing time in 116 patients who underwent laser therapy and 116 who were treated with topical acyclovir, both for 7 days, patients in the laser group had no more lesions, while in the laser group acyclovir 77 patients still had vesicles on the seventh day and 29 patients had crust formation. Such findings were also significant in other studies such as the one carried out by [28] in which the time required for healing of the laser group was almost half (2.2 days) when compared to the group treated with acyclovir (4.3 days).

Regarding the incidence of HLR lesions, a study carried out by [15] did not find statistical significance between the laser and acyclovir groups. However, a study carried out by Schindl and [16] found that laser therapy is effective in preventing HLR lesions since they observed the 24 patients in each group for ten weeks, in which only 4 patients in the laser group had recurrence of lesions, against 21 in the topical acyclovir group. However, the two cited studies used different energy densities: [15] used 3.0 to 4.5 J/cm^2, while Schindl and [16] used 48 J/cm^2; thus, these differences related to the density of energy used have been decisive in the results found.

Although acyclovir therapy is considered the standard therapy for the treatment of herpes simplex labialis [31], in this systematic review, the efficacy of laser in relation to the use of acyclovir could not be proven through meta-analysis. This was because the included studies reported data in a very heterogeneous way, and it was not possible to perform statistics for this outcome; however, it is observed through the meta-analysis that laser was superior to placebo (dummy laser), in relation to healing time and crust formation time, which is extremely relevant in the treatment of this pathology. New studies should be conducted in order to statistically compare the efficacy of laser in relation to acyclovir in the treatment of patients with herpes labialis.

It is also possible to use a chromophore agent such as methylene blue, prior to laser exposure. Such a technique is called photodynamic therapy (aPDT) and has been used in cases of HLR. This photosensitizer is able to absorb light at a certain wavelength (660 nm), so the photosensitizer can lose energy through non-radioactive, radioactive (phosphorescence) processes, or generate reactive oxygen species (ROS). This therapeutic alternative has been pointed out by case reports as being effective in wound healing. However, in the absence of well-designed clinical studies, the efficacy of aPDT for HLR cannot be confirmed [10].

Thus, in the literature, there is a range of photodynamic therapy protocols that can be used like the use of different wavelengths (670–1072 nm), infrared laser or red laser, and yet the possibility of using methylene blue as a photosensitizer. Thus, there is no consensus on the type of laser used, wavelength, and technique necessary for the effective treatment of HLR in the analyzed studies, thus generating different results among the variables analyzed, which is the main limitation of this systematic review, and requiring the establishment of a standard protocol that guides dentists in the effective treatment of patients with HLR with the emergence of new studies that prove such effectiveness.

The main limitations of this study are found in the way the included studies reported their data, which in a very heterogeneous way made statistical analysis difficult, with the only possible meta-analysis being performed only in relation to healing time and crust formation time. Another important limitation is the risk of bias of the included studies, with only one considered at low risk of bias [30].

Given the high heterogeneity between the studies and the different types of protocols used, it is not possible to define the best type of laser to be used in the treatment of this pathology. It was also observed in this meta-analysis that both the red and infrared lasers were superior to the dummy laser in relation to the duration of the lesion; however, a comparison between these lasers and acyclovir was not possible due to important methodological differences between the studies, not allowing the elaboration of statistics for this outcome, so the efficacy of laser when compared to traditional treatment still seems to be open and requires new controlled and standardized studies to determine the best therapeutic method [17, 28, 30].

It is important to note that, in this systematic review, the studies included worked with very different parameters for the low-power laser (pulse energy, wavelength, probe diameter, etc.…), and although it was not possible to carry out a meta-analysis with all the included studies, it was observed

that, in general, the laser was superior to the conventional treatment or placebo and that, therefore, being therefore a viable and promising therapy; however, it is important that the clinician understands that in the literature there are several different clinical protocols for the use of laser in the treatment of recurrent herpes labialis and that therefore it should be used with caution and prudence.

Although there are limitations in the meta-analysis, it is important to note that laser was superior to other treatments in all included studies, both in terms of pain, healing time, crusting time, and recurrence of cold sores. Further studies with more accurate descriptions of the data are needed in order to reliably determine the effectiveness of low-level laser therapy in the treatment of herpes labialis.

Conclusion

The low-level therapy laser was shown to be effective in the treatment of herpes labialis. However, the high risk of bias and the lack of standardization and uniform protocols among the included studies demonstrates that its use should be done with caution. New controlled and standardized primary studies must be carried out in order to safely determine the efficacy of low-level laser in the treatment of herpes labialis.

Funding The present study was financed by the authors.

Declarations

Ethical approval Not applicable.

Conflict of interest The authors declare no competing interests.

References

1. Whitley RJ, Roizman B (2001) Herpes simplex virus infections. Lancet 357(9267):1513–1518. https://doi.org/10.1016/S0140-6736(00)04638-9
2. Arduino PG, Porter SR (2008) Herpes simplex virus type 1 infection: overview on relevant clinico-pathological features. J Oral Pathol Med 37(2):107–121. https://doi.org/10.1111/j.1600-0714.2007.00586.x
3. Fatahzadeh M, Schwartz RA (2007) Human herpes simplex labialis. Clin Exp Dermatol 32(6):625–630. https://doi.org/10.1111/j.1365-2230.2007.02473.x
4. Eduardo CP, Aranha ACC, Simões A, Bello-Silva MS, Ramalho KM, Esteves-Oliveira M, Freitas PM, Marotti J, Tunér J (2014) Laser treatment of recurrent herpes labialis: a literature review. Lasers Med Sci 29(4):1517–1529. https://doi.org/10.1007/s10103-013-1311-8
5. Frobert E, Burrel S, Ducastelle-Lepretre S, Billaud G, Ader F, Casalegno JS, Nave V, Boutolleau D, Michallet M, Lina B (2014) Resistance of herpes simplex viruses to acyclovir: an update from a ten-year survey in France. Antiviral Res 111:36–41. https://doi.org/10.1016/J.ANTIVIRAL.2014.08.013
6. Arain N, Paravastu SC, Arain MA (2015) Effectiveness of topical corticosteroids in addition to antiviral therapy in the management of recurrent herpes labialis: a systematic review and meta-analysis. BMC Infect Dis 15(82):1–8. https://doi.org/10.1186/s12879-015-0824-0
7. Donnarumma G, Gregorio V, Fusco A, Farina E, Baroni A, Esposito V, Contaldo M, Petruzzi M, Pannone G, Serpico S (2010) Inhibition of HSV-1 replication by laser diode-irradiation: possible mechanism of action. Int J Immunopathol Pharmacol 23(4):1167–1176. https://doi.org/10.1177/039463201002300420
8. Prazmo E, Mielczarek A, Kwasny M, Lapin M, Mielczarek A (2016) Photodynamic therapy as a promising method used in the treatment of oral diseases. Adv Clin Exp Med 25(4):799–807. https://doi.org/10.17219/acem/32488
9. Marotti J, Sperandio FF, Fregnani ER, Aranha ACC, Freitas PM, Eduardo CP (2010) High-intensity laser and photodynamic therapy as a treatment for recurrent herpes labialis. Photomed Laser Surg 28(3):439–444. https://doi.org/10.1089/pho.2009.2522
10. La Selva A, Negreiros RM, Bezerra DT, Rosa EP, Pavesi VCS, Navarro RS, Bello-Silva MS, Ramalho KM, Aranha ACC, Braz-Silva PH, Fernandes KPS, Bussadori SK, Horliana ACRT (2020) Treatment of herpes labialis by photodynamic therapy: study protocol clinical trial (SPIRIT compliant). Medicine (Baltimore) 99(12):e19500. https://doi.org/10.1097/md.0000000000019500
11. Walker J (1983) Relief from chronic pain by low power laser irradiation. Neurosci Lett 43(2–3):339–344. https://doi.org/10.1016/0304-3940(83)90211-2
12. Hagiwara S, Iwasaka H, Okuda K, Noguchi T (2007) GaAlAs (830 nm) low-level laser enhances peripheral endogenous opioid analgesia in rats. Lasers Surg Med 39(10):797–802. https://doi.org/10.1002/lsm.20583
13. Reddy GK, Stehno-Bittel L, Enwemeka CS (2001) Laser photostimulation accelerates wound healing in diabetic rats. Wound Repair Regen 9(3):248–255. https://doi.org/10.1046/j.1524-475x.2001.00248.x
14. Al-Maweri SA, Kalakonda B, AlAizari NA, Al-Soneidar WA, Ashraf S, Abdulrab S, Al-Mawri ES (2018) Efficacy of low-level laser therapy in management of recurrent herpes labialis: a systematic review. Lasers Med Sci 33(7):1423–1430. https://doi.org/10.1007/s10103-018-2542-5
15. Carvalho RR, Eduardo FP, Ramalho KM, Antunes JL, Bezinelli LM, Magalhães MH, Pegoretti T, Freitas PM, Eduardo CP (2010) Effect of laser phototherapy on recurring herpes labialis prevention: an in vivo study. Lasers Med Sci 25(3):397–402. https://doi.org/10.1007/s10103-009-0717-9
16. Schindl A, Neumann R (1999) Low-intensity laser therapy is an effective treatment for recurrent herpes simplex infection. Results from a randomized double-blind placebo-controlled study, J Invest Dermatol 113(2):221–223. https://doi.org/10.1046/j.1523-1747.1999.00684.x
17. Hargate G (2006) A randomised double-blind study comparing the effect of 1072-nm light against placebo for the treatment of herpes labialis. Clin Exp Dermatol 31(5):638–641. https://doi.org/10.1111/j.1365-2230.2006.02191.x
18. Sanchez PJM, Femenías JLC, Tejeda AD, Tunér J (2012) The effect of 670-nm low laser therapy on herpes simplex type 1. Photomed Laser Surg 30(1):37–40. https://doi.org/10.1089/pho.2011.3076
19. Moher D, Shamsser L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 Statement. Syst Rev 4:1. https://doi.org/10.1186/2046-4053-4-1
20. Marotti J, Aranha ACC, Eduardo CP, Ribeiro MS (2008) Tratamento do herpes labial pela terapia fotodinâmica. Rev Assoc Paul Cir Dent 62(5):370–373

21. Eduardo CP, Bezinelli LM, Eduardo FP, Lopes RMG, Ramalho KM, Bello-Silva MS, Esteves-Oliveira M (2012) Prevention of recurrent herpes labialis outbreaks through low-intensity laser therapy: a clinical protocol with 3-year follow-up. Lasers Med Sci 27(5):1077–1083. https://doi.org/10.1007/s10103-011-1019-6
22. Bello-Silva MS, de Freitas PM, Aranha AC, Lage-Marques JL, Simões A, Eduardo CP (2010) Low- and high-intensity lasers in the treatment of herpes simplex virus 1 infection. Photomed Laser Surg 28(1):135–139. https://doi.org/10.1089/pho.2008.2458
23. González BM, Hernández A, Estevez A (2008) Tratamiento del herpes simple labial con láser de baja potencia. Colomb med 39(2):175–181
24. Lotufo MA, Horliana T, Ratto AC, Thalita S, Queiroz AC, Gomes AO, Motta LJ, Ferrari RAM, Fernandes KPS, Bussadori SK (2019) Efficacy of photodynamic therapy on the treatment of herpes labialis: a systematic review. Photodiagn Photodyn Ther 29:101536. https://doi.org/10.1016/j.pdpdt.2019.08.018
25. Beeson WH, Rachel JD (2002) Valacyclovir prophylaxis for herpes simplex virus infection or infection recurrence following laser skin resurfacing. Dermatol Surg 28(4):331–336. https://doi.org/10.1046/j.1524-4725.2002.01155.x
26. Ramalho KM, Cunha SR, Gonçalves F, Escudeiro GS, Steiner-Oliveira C, Horliana ACRT, Eduardo CP (2021) Photodynamic therapy and acyclovir in the treatment of recurrent herpes labialis: a controlled randomized clinical trial. Photodiagnosis Photodyn Ther 33:102093. https://doi.org/10.1016/j.pdpdt.2020.102093
27. Velez-Gonzalez M Urrea-Arbelaez A Nicolas M Serra-Baldrich E Perez JL Pavesi M Camarasa JM Trelles MA (1996) Treatment of relapse in herpes simplex on labial and facial areas and of primary herpes simplex on genital areas and "area pudenda" with low-power He-Ne laser or acyclovir administered orally, Proc. SPIE 2630:43–50. https://doi.org/10.1117/12.230040
28. Honarmand M, Farhadmollashahi L, Vosoughirahbar E (2017) Comparing the effect of diode laser against acyclovir cream for the treatment of herpes labialis. J Clin Exp Dent 9(6):e729–e732. https://doi.org/10.4317/jced.53679
29. Bojovic M, Kesic L, Jovanovic G, Buric N, Savic Z, Obradovic R et al (2014) Aplication of soft laser in the treatment of herpes labialis – pilot study. Acta Stomato Naissi 30(69):1342–1347. https://doi.org/10.5937/ASN1469342B
30. Dougal G, Lee SY (2013) Evaluation of the efficacy of low-level light therapy using 1072 nm infrared light for the treatment of herpes simplex labialis. Clin Exp Dermatol 38(7):713–718. https://doi.org/10.1111/ced.12069
31. Siegel MA (2002) Diagnosis and management of recurrent herpes simplex infections. J Am Dent Assoc 133(9):1245–1249. https://doi.org/10.14219/jada.archive.2002.0366