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REVIEW

Laser therapy for recurrent aphthous stomatitis: an overview

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Abstract

Objectives To evaluate therapeutic effects of laser therapy on patients with recurrent aphthous stomatitis assessing evidences from previously published systematic reviews.

Materials and methods An overview of systematic reviews was conducted based on PRISMA checklist. Search strategies were developed and adapted for six different electronic databases and a gray literature search was also performed. The methodology quality of the included systematic reviews was assessed by the Measurement Tool to Assess the Methodological Quality of Systematic Reviews 2 (AMSTAR 2).

Results After a two-step selection, five systematic reviews were included. Methodology quality was considered as a high risk of bias in two systematic reviews, while in the other three were graded as moderate. The systematic reviews' conclusions demonstrated that all included systematics reviews showed positive effects of laser therapy for pain relief, and most of them demonstrated healing improvement. A meta-analysis was not feasible due to heterogeneity in treatments parameters.

Conclusions Evidence suggested that laser therapy is an effective tool to treat recurrent aphthous stomatitis; nevertheless, more randomized clinical trials should be conducted to compare different lasers parameters.

Clinical relevance The present overview evaluated recent evidence about laser therapy for recurrent aphthous stomatitis management in order to contribute for evidence-based dentistry and decision-making. This overview suggests that laser therapy is a safe and promising alternative to treat recurrent aphthous stomatitis, since it promotes wound healing and pain relief.

Keywords Lasers · Oral ulcer · Oral medicine · Systematic review · Evidence-based medicine · Overview

Introduction

Recurrent aphthous stomatitis (RAS) is a common chronic inflammatory disease of the oral mucosa characterized by rounded ulcers that usually present first in childhood or adolescence [1, 2]. These lesions might disturb speaking and eating activities and even impact the quality of life [2]. RAS can be classified into three subtypes: minor (MiRAS), major (MjRAS), and herpetiformis ulcers (HUs) [3, 4]. MiRAS is the most common subtype, comprising about 80–90% of RAS cases. MiRAS usually presents with less than 1 cm in diameter and healing time usually takes 4–14 days without scarring. MiRAS occurs on non-keratinized mucosa; therefore, it is uncommon on gingiva, palate or dorsum of tongue surfaces, appearing more often in labial, buccal and floor of mouth mucosa. MjRAS ulcers arise in approximately 10% of cases, they exceed 1 cm in diameter, persist up to 6 weeks and may heal with scarring. HUs affect about 1–10% of individuals with RAS and it is characterized by multiple ulcers with 2–3 mm in diameter that can coalesce into a large and irregular ulcer, taking approximately 15 days to heal, with or without scarring [1].

RAS therapy aims to alleviate pain sensation and decrease wound healing time, trying to reduce frequency and acute phases [5]. Conventional treatments are topical or systemic interventions including analgesics, systemic immunomodulators, anti-inflammatory drugs, chemical cauterizers, and

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others [6]. However, some of these treatments have shown disadvantages related to overdose and side effects, with little effect on recurrence [7, 8].

Laser is an acronym of "Light Amplification by Stimulated Emission of Radiation" and Laser therapy (LT) has demonstrated positive effects on cell metabolism, inflammatory modulation, edema reduction, tissue regeneration, healing time, and pain relief [9, 10]. Its application can be defined as photobiomodulation (PBM) when used in a low intensity, wavelengths between 600 and 1070 nm [11–13]. However, studies using laser in a wavelength outside this range have also been evidenced, including carbon dioxide laser (CO_2) that operates in 10.600 nm of wavelength [11, 14]. Some systematic reviews (SRs) were conducted regarding LT therapy for RAS management, suggesting a satisfactory response due to biostimulation effects [5, 15–18].

There is a considerable number of SRs investigating LT for RAS management; however, the potential effects of laser therapy are still unsettled. In addition, there is a need for established protocols that could be applied in other studies and on clinical practice. Therefore, the range of laser applications on health science has been considered of broad and current interest. Thus, this overview aims to summarize and critically appraise available evidence from SRs by answering the following question: "What are the therapeutic effects of LT for RAS?"

Materials and methods

Protocol and registration

This overview was reported accordingly the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [19]. The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) database under registration number CRD42018102772 [20].

Study design and eligibility criteria

This is an overview that assessed the therapeutic effects of LT on individuals with RAS. Systematic reviews or meta-analysis that synthesized data about LT effects on pain relief and/or on wound healing of RAS were included in the overview. The acronym PICOS (Population, Intervention, Comparison, Outcomes, and Studies) was used to formulate the question of this overview, in which: (P) individuals with RAS; (I) LT; (C) other therapies; (O) effectiveness on treatment for RAS; (S) systematic reviews and meta-analysis. No publication time or language restrictions were applied.

Information sources and search strategy

Search strategy was developed and adapted for each electronic database: Cochrane Library, LILACS, EMBASE, PubMed, Scopus, and Web of Science. A gray literature search was performed on Google Scholar, OpenGrey, and ProQuest Dissertations & Theses Global (Online Resource 1). Duplicated references were removed by reference manager software (EndNote®, Thompson Reuters, Philadelphia, PA). Moreover, the reference lists of selected articles were hand screened to identify potential additional manuscripts that could have been missed during the electronic database searches. Experts were also consulted in order to improve search findings.

Study selection

The study selection was performed in two phases. Phase I was carried out in a web application specific for systematic reviews (Rayyan®, Qatar Computing Research Institute), in which two authors (JAS and AGCN) independently screened titles and abstracts identified in all electronic databases for eligible studies. Any disagreements were mutually discussed and, if a consensus was not achieved, a third reviewer was involved (IPT). In phase II, the same authors (JAS and AGCN) performed a full-text reading of eligible articles and excluded those not meeting inclusion criteria (Online Resource 2) and, if necessary, the third reviewer was consulted to make a final decision.

Data collection

One author (JAS) collected pertinent data from each SR. A second reviewer (AGCN) cross-checked the collected information to confirm its accuracy. The main records from SRs were reported in Table 1. Characteristics of primary studies included in the selected SRs and also LT therapy parameters used are available in Online Resources 3 and 4, respectively.

Risk of bias in individual studies

The risk of bias (RoB) of included SR was assessed by the Measurement Tool to Assess the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) [21]. Risk of bias was categorized as *High* when the study reached up to 49% score "yes," *Moderate* when the study reached 50 to 69% score "yes," and *Low* when the study reached more than 70% score "yes." Two reviewers (JAS and AGCN) independently scored each item as "partial yes," "unclear," "yes" or "no" to classify the RoB of selected studies and then cross-checked the information (Online Resource 5). Disagreements were resolved by a third reviewer (IPT).

Table 1 Summary of overall descriptive characteristics of included systematic reviews (n = 5)

Author, Year, Country and Journal (2016 IF)	Aim	Databases searched (Search date)	Primary studies design (n)/ Laser types used	Outcomes	Main results	Conclusion
Han et al. 2016; China Scientifica (0.91)	To evaluate the clinical effect and security of laser treatment on RAS.	1. Medline (PubMed) 2. Embase 3. Cochrane Library 4. Science Direct 5. Web of Science 6. Manual search	10 RCTs/ CO_2 GaAIAs Nd:YAG InGaA1P Diode	1. Pain reduction 2. Wound healing 3. Adverse reactions	1. 4 of 5 studies that assessed changes in pain level found significant difference between laser and placebo groups. When compared to traditional medication, the laser group presented statistically reduced pain in 2 of 3 studies that assessed this outcome. 2. All 3 studies that assessed healing time found significant difference between laser and placebo groups. When compared to traditional medication, the laser group had statistically reduced healing time in 1 of 2 studies. 3. Any adverse effects were reported.	Laser treatment seemed to alleviate pain and accelerate healing compared to placebo. No adverse reactions or clinical complications were reported. Therefore, long-term, randomized, controlled, and large sample-sized clinical trials should be conducted to confirm the effectiveness of LT on RAS.
Najeeb et al. 2016; Saudi Arabia, United Kingdom Medicina (Kaunas) (1.429)	To evaluate and summarize clinical studies to ascertain whether laser therapy is an effective treatment option for treating RAS.	1. Medline (PubMed) 2. Embase 3. Cochrane database 4. Web of Knowledge (ISI) (1995 – 2015)	7 RCTs 2 Case report-s/ CO_2 GaAIAs Nd:YAG Diode	1. Pain reduction 2. Wound healing 3. Reduction of episodes frequency	1. Studies showed significant pain relief, compared to control group. 2. The authors who assessed wound healing, found faster healing time in lasers groups. 3. One study followed-up the patients for 2 months after laser application, and no recurrence of ulceration was reported.	All LT types have succeeded in immediate pain relief. However, more clinical trials should be conducted in order to ascertain their efficacy in clinical setting.
Pavlic et al. 2015; Bosnia and Herzegovina, Japan Vojnosanit Pregl (**0.405**)	To determine the clinical effectiveness of laser therapy in treatment of RAS lesions.	1. Medline (PubMed) 2. Science Direct 3. Cochrane Library (Until 31 December 2013)	3 RCTs 1 NRCT/ CO_2 InGaA1P	1. Pain reduction 2. Wound healing 3. Adverse reactions	1. The assessed literature demonstrated significant pain reduction. 2. The authors who assessed healing time, confirmed statistically significant differences in RAS faster wound healing following LT. 3. Any adverse effects were reported.	LT seems to be an appropriate therapy for RAS; however, additional studies are recommended since few studies were included and they presented problems of design and heterogeneity of parameters.
Suter et al. 2017; China, Switzerland Lasers Med Sci (1.949)	Evaluate the effect of laser therapy (LLL/hard laser) on RAS in terms of pain relief, duration of wound healing and reduction in episode frequency.	1. Medline 2. Embase via OVID 3. Cochrane database 4. Manual search of selected core journals in the field of interest	10 RCTs 1 NRCT/ CO_2 GaAIAs Nd:YAG InGaA1P Diode GaAs	1. Pain reduction 2. Wound healing 3. Reduction of	1. Significant immediate pain relief was found in five out of six studies that assessed this outcome. The late effect on pain relief was analyzed in nine studies of which seven showed a significant pain reduction for laser group. 2. Nine studies evaluated wound healing and five of them found faster wound healing in laser group.	Laser application relieves symptoms and promotes wound healing of RAS with low risk of side effects. However, it is not possible to consider a standard laser application for the treatment of RAS, due to the high variation of laser types and settings used. Therefore, more studies using similar parameters, with larger samples and uniform methodologies should be conducted.

Table 1 (continued)

Author, Year, Country and Journal (2016 IF)	Aim	Databases searched (Search date)	Primary studies design (*n*)/ Laser types used	Outcomes	Main results	Conclusion
				epi-sodes fre-quency	3. This outcome could not be evaluated because the study that assessed it did not discriminate between LT and control groups.	
Vale et al. 2015; Brazil The Scientific World Journal (1.55)	Assess studies of LLLT used for the treatment of RAS in terms of pain reduction and wound healing.	1. Medline (PubMed) 2. Embase 3. Cochrane Database 4. LILACS 5.Google Scholar	2 RCTs/ GaAlAs Diode	1. Pain reduc-tion 2. Wound healing	1. Both selected studies showed a statistically significant reduction in pain comparing experimental and placebo groups 2. One of the selected studies found complete healing time for the LT group to be highly significant faster compared to placebo group. The other one did not assess this outcome.	A specific protocol could not be proposed; however, LT can be suggested as an alternative to treat RAS. Additional studies should be performed to establish a clinical protocol in order to elucidate the specific mechanisms of LT in RAS.

Abbreviations: *CONSORT*, Consolidated Standards of Reporting Trials; *GaAlAs*, gallium-aluminum-arsenide; *IF*, impact factor; *LLL*, low-level laser; *LLLT*, low-level light therapy; *LT*, laser therapy; *Nd:YAG*, neodymium-doped yttrium aluminum garnet; *NRCT*, non-randomized clinical trial; *NR*, not reported; *RAS*, recurrent aphthous stomatitis; *RCT*, randomized clinical trial

Summary measures

The primary outcome in this overview was the effectiveness of LT on management of RAS, in terms of pain relief and wound healing. Secondary outcomes were the effects on RAS prognosis (reduction of episode frequency), LT adverse reactions or complications.

Graphics

Data were collected from the included randomized clinical trials (RCTs) or non-randomized clinical trials (NRCTs). In order to group and compare the studies, they should report data on mean pain reduction and wound healing, mean at baseline compared to different analyze post-treatment periods and how long the ulcers took to fully heal in days, respectively.

Results

Study selection

In phase I, 399 records were identified and after removing duplicates, 182 references remained. After titles and abstract screening, ten articles were selected to phase II. In addition, only one reference from gray literature was included. Thereafter, a full-text reading was conducted and six SR were excluded according to eligibility criteria. Finally, five SR were selected for qualitative synthesis, of which 15 included primary studies were identified. A flowchart detailing the process of identification, screening, and inclusion of studies is presented in Fig. 1.

Studies characteristics

Synthesis of systematic reviews

All of the selected studies had as outcome the LT effects on pain reduction and wound healing of RAS [5, 15–18]. Two included studies reported evaluation of adverse reactions/ complications as an outcome [15, 17] and two others as well as the reduction of episode frequency [5, 16].

Pain relief was found as a main result in all included synthesis of systematic reviews (SRs), with statistical significance in the majority of the assessed primary studies. However, conflicting results were found in two SRs regarding effects on wound healing [5, 17]. The other three SRs [15, 16, 18] reported that laser group presented faster healing compared to controls in all included studies assessing this outcome. No adverse effects caused by LT were reported [15, 17].

Regarding reduction of episodes' frequency, Najeeb et al. [15] reported that only one primary study had appropriate

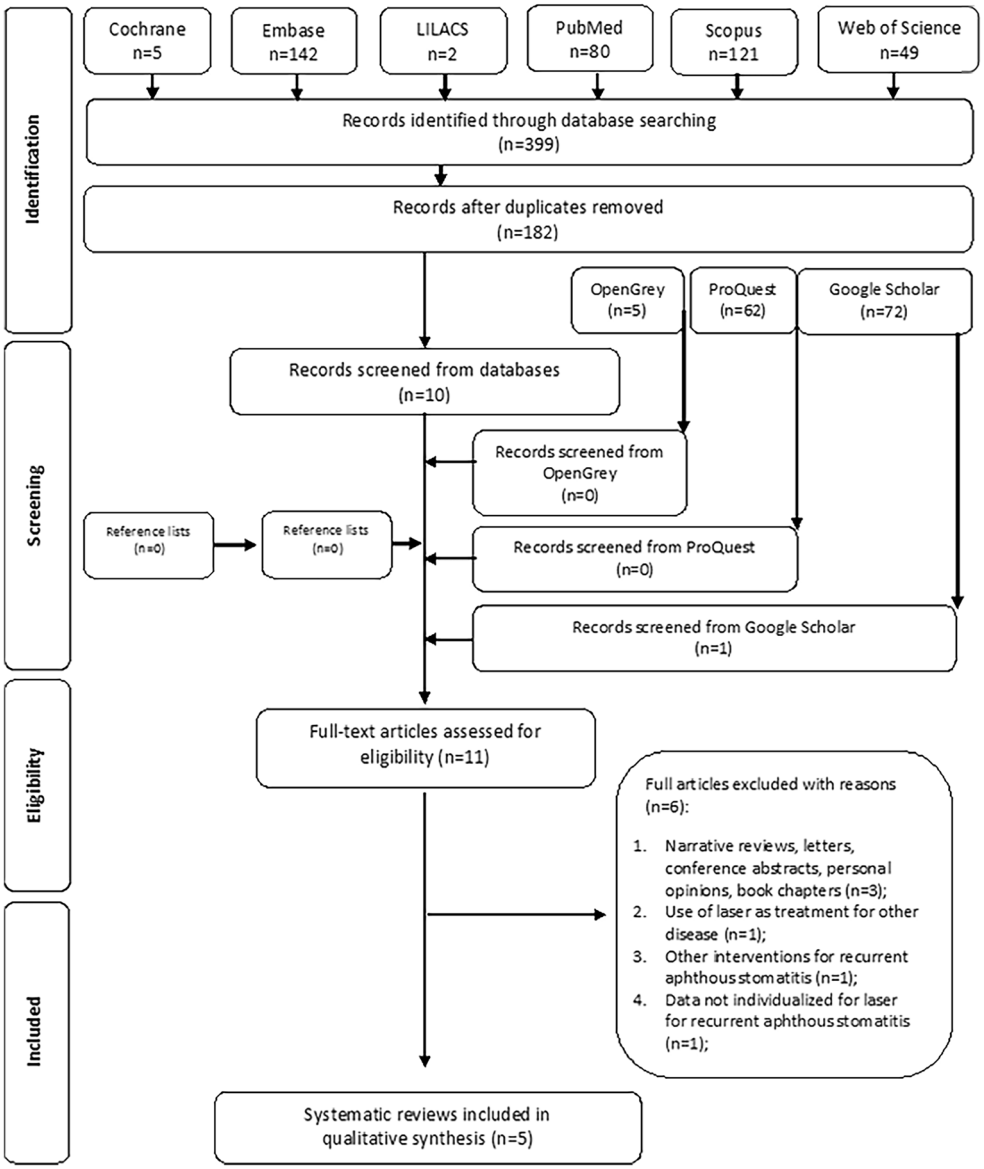

Fig. 1 Flow diagram of literature search and selection criteria adapted from PRISMA [19]

follow-up after laser application, showing no recurrence of ulceration. Suter et al. [5], on the other hand, could not evaluate this outcome due to the lack of data. As main conclusion, all SRs suggested that LT seems to be an appropriate therapy for RAS; however, further clinical studies with similar parameters should be performed (Table 1).

Graphics

Fifteen different primary studies were found in the included SRs. Eight of the fifteen primary studies reported data similarly, making it possible to group them, and were included in graphics to present data of different studies [14, 22–29] (Fig. 2). Data about mean healing time, as well as data on mean pain score of participants in the laser and control groups were collected. Two mean graphics were performed: healing period (Fig. 2a) and pain relief (Fig. 2b), which showed positive effects on both outcomes promoted by LT, compared to control.

Risk of bias

RoB assessment of the five included SRs is summarized in Fig. 3. Two SR were considered as a high risk RoB [15, 18], while the other three were graded as moderate RoB [5, 16, 17]. Items 1 to 7 of AMSTAR assess SRs methodology and protocol, in which no SR achieved score "yes" in all items. Items 11, 12 and 15 from AMSTAR were classified as not applicable for all SR, since none conducted a meta-analysis. However, as shown in item 14, four SR [5, 15, 17, 18] provided a satisfactory discussion of heterogeneity observed, explaining reasons to avoid a meta-analysis.

Discussion

Summary of evidence

Evidence-based practice has increased, leading clinicians to assess health care literature at decision-making moment [30]. The increasing number of SRs being published demands an appropriate mechanism to compare findings of existing evidence and then being strongly useful for clinicians' decisions [31]. An overview is a recent methodological approach that systematically retrieves, critically appraises and synthesizes the results of multiple SRs related to the same topic [32]. The present overview evaluated recent evidence regarding LT for RAS.

Lasers are a light emitting device that can be classified in low or high levels, depending on power output [33]. Low-level lasers operate in the milliwatt range, 1 to 500 mW, while high-level lasers, can be used at high powers, ranging from fractions of a watt to 25 W or more [34]. The term PBM refers to a drug-free, non-invasive clinical application of light emission that stimulates and modulates biologic processes and operates with wavelengths between 600 and 1070 nm [10, 11]. Although high-level lasers are mainly used in an ablation mode on surgery, its use has also been suggested as an alternative to accelerate healing and relieve pain. In this technique, known as non-ablative CO_2 laser therapy (NACLT), the laser is applied defocused through a water content gel to produce a non-thermal, non-ablative reaction, resulting in a low-power use of a high-level laser [5, 14, 22]. PBM and NACLT mechanisms of action are based on emitted radiation that increases cells metabolism, enhances reepithelization and improves microcirculation, tissue oxygenation and growth stimulation [12, 34]. It also seems to have effects on pain relief by modulating the release of inflammatory mediators, changing lymphocyte metabolism and decreasing the nociceptors conduction of impulse [34].

Based on SRs results and related primary studies, LT presented positive effects on pain relief and wound healing for RAS. The studies showed comparisons between high- or low-level lasers and placebo or no therapy [14, 22–26, 28], which aimed to assess LT effectiveness and safety, and also comparisons to medication [29, 35–38] to appraise if lasers can complement or substitute conventional treatment, since it has shown some

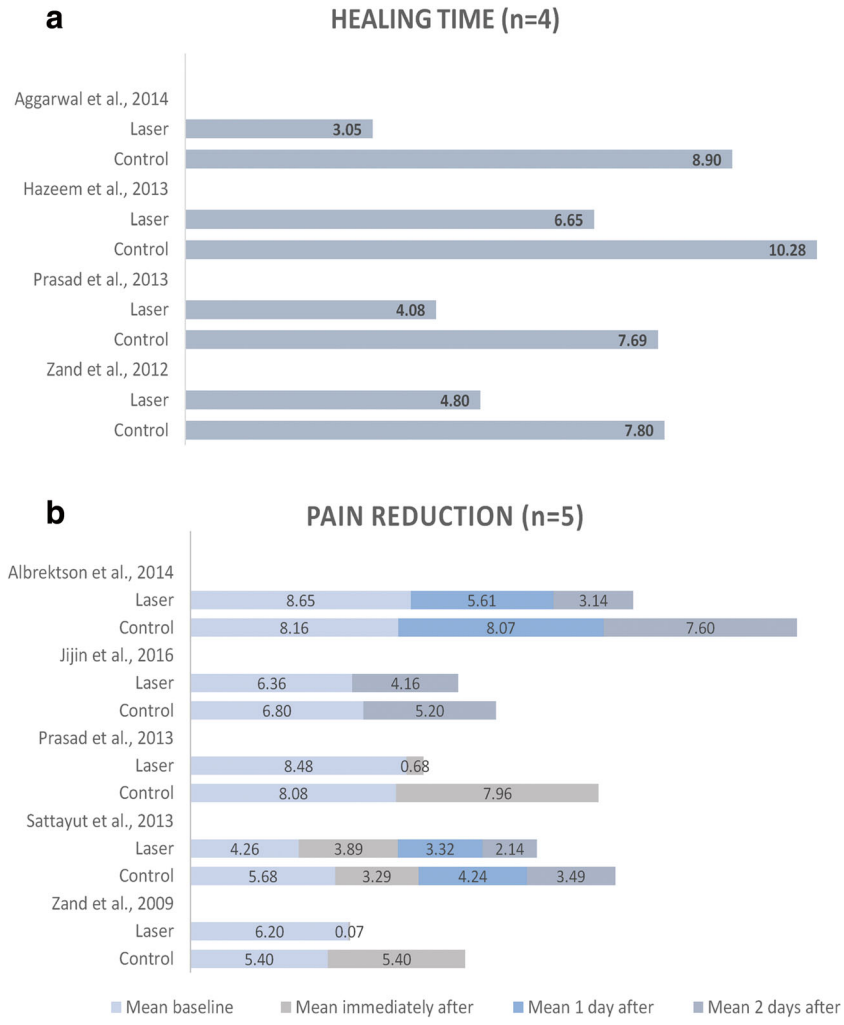

Fig. 2 Laser therapy effects. **a** Laser therapy effects on wound healing for recurrent aphthous stomatitis compared to control. Results from each study evaluated mean healing time in days, considering how long the ulcers took to fully heal. **b** Pain reduction for recurrent aphthous stomatitis compared to control. Results from each study measured pain at baseline and then compared to different analyze periods to assess pain relief using VAS scale (1–10)

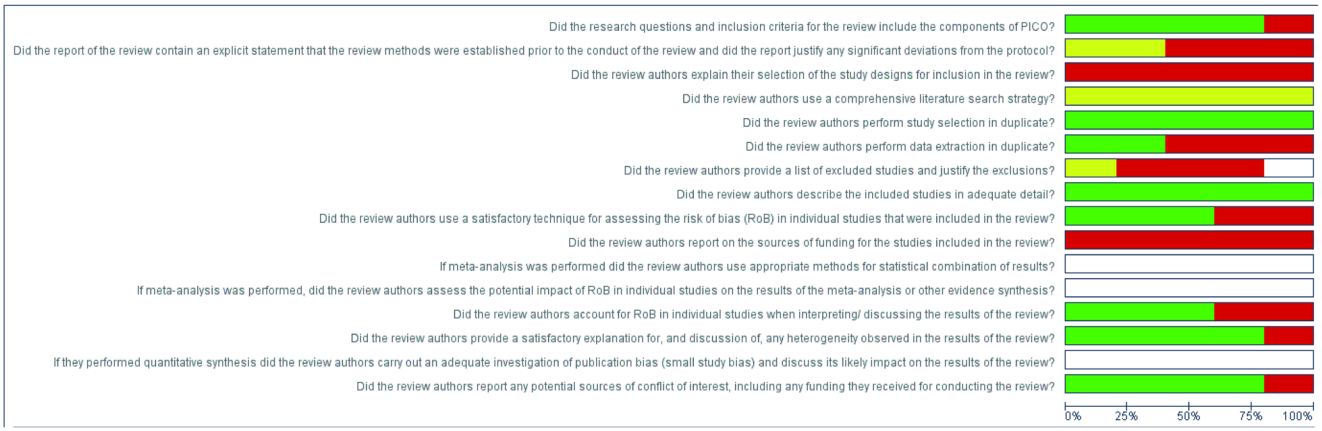

Fig. 3 Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included systematic reviews assessed by AMSTAR 2 [21]

disadvantages in terms of overdose and adverse reactions [39]. The results presented by primary studies were controversial; however, LT was not statistically inferior to control in any clinical trial, it consistently presented similar or superior effects, further, no adverse reactions were reported by participants. Since the effects seems to be equivalent to conventional managements and the application of different laser parameters seems to be safe, the included SRs suggested that LT should be considered in the settings of RAS therapies, nonetheless, authors could not report sound conclusions [5, 15–18]. The uncertain conclusions, added to impossibility of grouping evidence in a meta-analysis, can be associated to the lack of high-quality studies, added to reduced samples sizes and the absence of uniform laser parameters in studies included in the systematic reviews.

Even all included SRs concluded there is still no established protocol for LT, the present overview suggests that LT can be effective in both high- or low-level laser settings and the positive trend in results was the same regardless of lesion extensions, laser type or protocol used. In addition, two identified laser settings seem to present a well-defined protocol under development [14, 22, 23, 25, 27, 36]. CO_2 laser was used with similar parameters in four clinical trials, the NACLT protocol, in a single application [14, 22, 23, 25]. It was effective in all studies that evaluated pain reduction [22, 23, 25] and in just one it showed not significant difference between laser and placebo on wound healing [25]. Nd:YAG was used with the exactly same parameters and the protocol applied showed effectiveness in terms of pain relief in both studies [27, 36] and also on wound healing and prognosis for a one followed-up month in the study that assessed these outcomes [36].

Notwithstanding LT seems to present positive effects, there is a need for more accurate studies to improve evidence. Researchers should conduct studies with similar methodology and comparisons and longer follow-up in order to better evaluate the effects on recurrence. To establish superiority of lasers settings, considering both high- and low-available lasers, more RCTs are requested to analyze cost benefits and effects between different protocols. In addition, authors have to report complete protocols since laser parameters are extremely variable in terms of type, wavelength, dose, distance from ulcer, tip diameter, power, and frequency of treatment.

Clinical practice

Since LT has shown superior effects, large indication and professional controlled application, this technique seems to be a promising approach. The cost can be the hardest challenge for its clinical recommendation. It demonstrates the importance of consider this treatment in public health service, whereas is possible to expend US$ 1000 to purchase a device that could be used for a long time. Since low-level lasers units' price is more accessible then high-level [40], PBM could be easier applied. Considering primary studies results and the conducted graphics for its analyses, the following protocols were suggested to present the best results found in this overview:

For wound healing:

1. Diode laser with 810 nm of wavelengths, 0.5 W power, applied 4 times with a gap of 30–40 seconds between each application in a continuous mode and 2–3 mm of distance to lesion, for 180 seconds per application in a single session.
2. Non-ablative CO_2 operated in a single session, with 10,600 nm of wavelengths, power range from 0.7 W to 1 W and applied defocused trough a water-based non-anesthetic gel in a single application continuous mode and 5–7 mm of distance to lesion, for 5 seconds.

For pain relief:

1. GaAIAs laser with 809 nm of wavelengths, 0.06 W power, applied once a day for two days in a pulsed mode and direct contact to lesion, for 80 seconds per application.

2. Non-ablative CO_2 operated in a single session, with 10,600 nm of wavelengths, power range from 0.7 W to 1 W and applied defocused trough a water-based non-anesthetic gel in a single application continuous mode and 5–7 mm of distance to lesion, for 5 seconds.

Limitations

Some methodological limitations of this overview should be pointed out. First, all included SRs presented moderate or high risk of bias. Methodological flaws indicated incomplete literature search strategy, absence of a pre-defined review protocol and explanation of the selection design for inclusion. A high heterogeneity regarding to study design, LT parameters, protocols of administration and control group intervention were found, which reduced the number of studies that could be considered for a meta-analysis. Therefore, this analysis could not be conducted, which resulted in the graphics developed to compare the outcomes between groups. In addition, a short follow-up time was considered in the included studies, limiting the outcome of LT effects on RAS prognosis (reduction of episode frequency).

Conclusion

Recent evidence suggests that LT is a safe and promising alternative to treat RAS since it seems to reduce wound healing time and promote pain relief. Therefore, more RCTs should be conducted comparing different lasers settings to formulate a well-defined protocol and also to analyze the cost-benefit of available laser therapies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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