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Review

Management of recurrent aphthous ulcers using low-level lasers: A systematic review

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ABSTRACT

Background and objective: The exact etiology of recurrent aphthous ulcers (RAS) is unknown. The management of RAS is not always straightforward. The aim of this review is to critically analyze and summarize the clinical literature focusing on the management of aphthous ulcers using low-level lasers.

Materials and methods: The Medline (PubMed), Web of Knowledge (ISI), Cochrane Central Register of Controlled Trials (CENTRAL) and Embase databases were searched electronically for studies published in last 20 years (1995–2015) using the keywords “recurrent aphthous stomatitis,” “aphthous ulcers,” and “laser.”

Results: A total of 85 articles were found during the initial search; 76 studies were excluded for not fulfilling the criteria whereas nine studies were deemed suitable for this review. Among the included studies, two articles were case reports and seven were randomized clinical trials. Study design, sample size, type of intervention and control of each study were critically analyzed and summarized according to the CONSORT protocol. In majority of the patients, immediate pain relief and accelerated ulcer healing was observed following irradiation with lasers.

Conclusions: Although various types of lasers have succeeded in providing immediate pain relief to patients, carbon dioxide (CO₂) lasers have the unique advantage of requiring a short

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exposure time (5–10 s). In order to ascertain the efficacy of laser for treating ulcers in the clinical setting, more clinical trials are required.

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1. Introduction

Recurrent aphthous stomatitis (RAS) is a pathological condition that is characterized by recurrent ulceration of oral mucosa [1]. These ulcers are usually ovoid or round lesions, having yellow or gray floors and erythematous haloes [1]. According to Shulman, RAS is the most common ulcerative affliction of the oral mucosa in the United States of America [2]. Although a variety of predisposing factors such as immunity, systemic diseases and local factors have been thought to cause RAS. However, the exact etiology of RAS remains unknown [3,4]. There are three main types of RAS have been documented in the literature: minor, major and herpetiform [4]. Minor RAS, the most common form, is characterized by small, recurrent and round ulcers that heal within 10–14 days without leaving any scars in the oral cavity. Major RAS is characterized by painful ulcers greater than 5 mm in diameter that heals within 6 weeks, frequently leaves scars. Herpetiform RAS is described as clusters of numerous pinpoint ulcers that heal in approximately 10 days. Management of RAS mainly consists of supportive therapy including administration of systemic and local corticosteroids, antiseptic, analgesics, antibiotics and immunomodulatory drugs [5]. No precise etiology is known for RAS. Its management mostly consists of symptomatic treatment and patients have to undergo considerable amount of discomfort due to the ulceration for several days even following administration of aforementioned drugs [6].

Laser is an acronym of “Light Amplification by Stimulated Emission of Radiation” and is based on the principles laid down by Albert Einstein. Lasers function by emitting light through optical amplification of a medium RAS. Each type of laser is named according to the active medium present. For example, CO₂ laser uses carbon dioxide [7], Nd:YAG laser uses neodymium-doped (Nd) yttrium aluminum garnet (YAG) crystals [8], diode laser uses a semi-conductor diode [9] and a GaAlAs laser uses aluminum gallium arsenide as an active medium [10]. More recently, lasers have been used to treat various forms of oral lesions including RAS [11,12]. Studies have suggested that low-level laser therapy (LLLT) has the potential to treat aphthous ulcer and related lesions [13]. In addition to reducing the pain and discomfort, LLLT also stimulates healing of ulcers [14]. To the best of our knowledge, no reviews summarizing the efficacy of lasers in treating aphthous ulcers have been published to date. Therefore, the aim of this review is to critically evaluate and summarize clinical studies to ascertain whether laser therapy is an effective treatment option for treating aphthous ulcers.

2. Materials and methods

The search methodology employed for this review to find relevant articles is summarized in Figure. The Medline (PubMed), Web of Knowledge (ISI), Cochrane Central Register of Controlled Trials (CENTRAL), and Embase databases were searched electronically for studies published in the last twenty years (1995–2015) using the keywords “recurrent aphthous stomatitis,” “aphthous ulcers,” and “laser.” The primary and secondary searches were conducted by two researchers (S.N. and Z.K.) independently. Any disagreements were resolved by mutual agreement via discussion. Both the researchers also assessed the quality of the studies included according to the CONSORT (Consolidated Standards of Reporting Trials) statement [15].

The inclusion criteria for our search comprised of the following:

1. Randomized clinical trials (RCT)
2. Retrospective studies
3. Case series and reports
4. Laser treatment of only oral aphthous ulceration
5. Articles in English

The exclusion criteria for our search comprised of:

1. Animal studies
2. Laser treatment of extra-oral ulceration and wounds
3. In vitro studies
4. Laser treatment of non-aphthous lesions
5. Letters to the editor

The titles and abstracts of studies obtained in our primary search were read thoroughly to search for further articles meeting our inclusion criteria. Furthermore, the studies cited in the articles were also scanned to find any more published research suitable for this review.

Following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16], a focused question was produced according to the Participants, Interventions, Control and Outcomes (PICO) principle [17]. The focused question for this review was “In RAS patients, compared to placebo and conventional treatment, what is the efficacy of low-level laser therapy effective in promoting the healing of oral ulceration?”

3. Results

A total of 85 articles were found during the initial search. Upon applying the aforementioned exclusion and inclusion criteria,

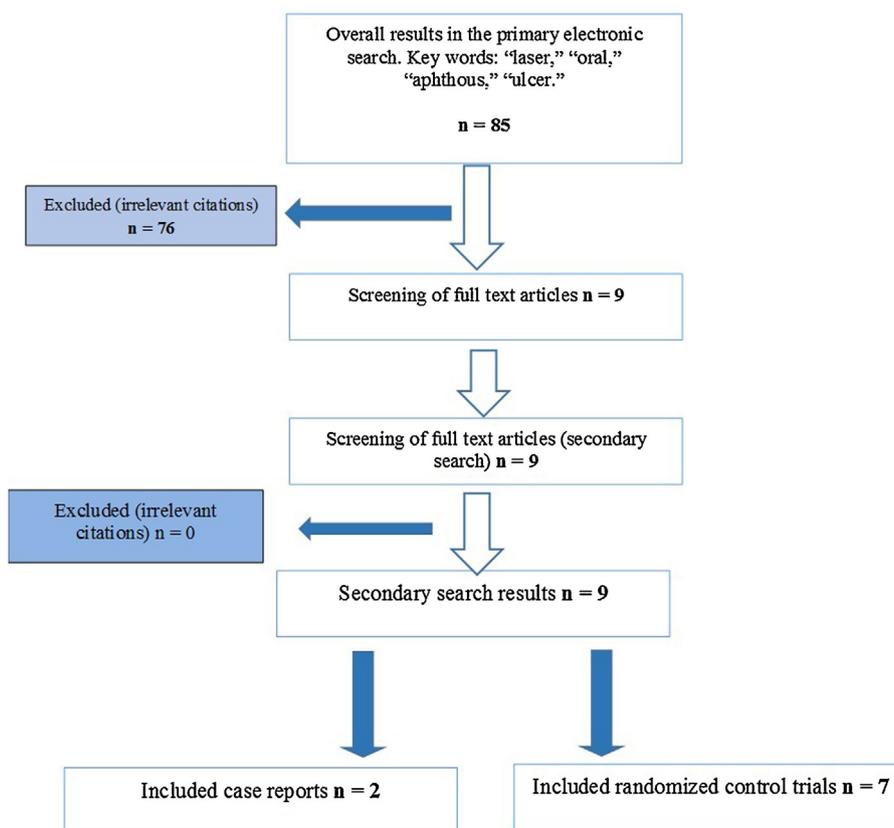


Figure – The literature search methodology used for this review.

76 studies were excluded for not fulfilling the criteria whereas 9 studies were deemed suitable for this review. Among the included studies, two were case reports [12,13] and seven were randomized clinical trials (RCTs) [14,18–23]. Study design, sample size, type of intervention and control of each study were critically analyzed and summarized according to the CONSORT protocol (Table). Since majority of the data was extracted from RCTs, the level of evidence in this systematic review was deduced as Level I [24].

All 9 studies evaluated the effects of low-level laser therapy on the pain levels related to aphthous ulceration in human subjects [12–14,18–23]. Three studies [18,19,22] assessed the pain levels of patients while 6 studies assessed both, healing times and pain levels [12–14,20,21,23]. The first case report of laser treatment of aphthous ulcers included accounts of ulceration treated using low-power CO₂ laser in two patients [13]. Just a 5-s exposing the ulcers to the laser resulted in immediate pain relief and healing of ulcers in one week time. The other case study demonstrated treatment of ulceration by exposing the lesions to a 940 nm diode laser for 60 s [12]. Following exposure, patient experienced immediate pain relief and the ulcers healed completely after 4 days. At 2-month follow-up, no recurrence of ulceration was reported.

In three randomized control trials (RCTs), ablation of ulcers using low-power CO₂ laser was compared to ulcers receiving no treatment [18,20,21]. Immediate pain relief was reported by majority of patients in all three studies [18,20,21]. In addition, tissue healing was significantly accelerated in laser-treated

patients compared to controls [20,21]. The difference was statistically significant in all the studies involving CO₂ lasers. When Nd:YAG laser were used to treat aphthous ulcers [14,19], immediate pain relief was reported which was not evident in the control group treated with conventional topical medications. In one study, the healing time of ulcers after Nd:YAG laser therapy was also evaluated [14]. Significantly faster healing was observed in ulcers exposed to Nd:YAG lasers compared to topical medicaments. An exposure time of 2–3 min was required to provide pain relief [14,19]. In one study [22], a significantly higher pain relief following exposure of ulcers to a 60 mW GaAlAs laser for 80 s compared to placebo. However, the study did not assess the healing times. Another study reported an immediate pain relief and healing stimulation of ulcers in response to 1 min 14 s irradiation using a 658 nm diode laser [23].

4. Discussion

Exposure to low powered lasers is thought to stimulate reepithelization of wounds [25,26]. Numerous theories have been proposed to explain the mechanism of their action. It has been suggested that low-power lasers may enhance reepithelization by increasing respiratory metabolism that in turn upregulates the mitotic activity, collagen synthesis and epithelial proliferation [27]. Recently, a spectroscopic study has strongly suggested that exposure to helium neon (He-Ne)

Table – The studies included in this review.

Study and year	Type of study	Number of patients (n)	Female (n or %)	Age (mean years)	Cause of aphthous	Laser used	Control	Blinding	Frequency (Hz)/wavelength (nm/ μ)	Power (W)	Energy	Duration of exposure to laser	Dose (J/cm ²)	Follow-up	Pain relief	Healing time
Sharon-Buller et al., 2004 [13]	Case report	2	n = 1	57.5	Stress and radiation therapy	CO ₂	N/A	N/A	10,600 nm	1.0–1.5 W	N/A	5 s	Not stated	1 week	Immediate pain relief more in test group	Complete healing in both patients after 1 week.
Arabaci et al., 2008 [14]	RCT	28	11	30.6 ± 4.1	Behcet's disease	Nd:YAG	Corticosteroids, Orabase	None	F = 20 Hz	2 W	2 mJ	2–3 min	Not stated	1 month	Pain relief more in test group (<i>p</i> < 0.001)	Faster healing in test group
Tezel et al., 2009 [19]	RCT	20	13	Not stated	RAS	Nd:YAG	Topical steroid	None	F = 20 Hz, 1.064 nm	2 W	100 mJ	2–3 min	Not stated	7 days	Pain relief more in test group (<i>p</i> < 0.05)	Not assessed
Zand et al., 2009 [18]	RCT	15	13	37.9 ± 10.9	RAS	CO ₂	Placebo	Single	10,600 nm	1 W	Not stated	5–10 s	Not stated	96 h	Pain relief more in test group (<i>p</i> < 0.001)	Not assessed
Zand et al., 2012 [20]	RCT	10	Not stated	35.6	RAS	CO ₂	Placebo	Single	10,600 nm	1 W	Not stated	5–10 s	Not stated	Until healing completed	Pain relief more in test group (<i>p</i> < 0.001)	Faster healing in test group (test: 4.8 ± 2.4 days, control: 7.6 ± 2.5 days) (<i>p</i> < 0.001)
Misra et al., 2013 [12]	Case report	1	0	25	RAS	Diode	N/A	N/A	940 nm	0.1 W	Not stated	1 min	3	2 months	Pain relief more in test group	Complete healing after 4 days. No recurrence after 2 months.
Prasad et al., 2013 [21]	RCT	25	Not stated	Male = 28.20 ± 6.11, female = 26.40 ± 7.99	RAS	CO ₂	Placebo	Single	Not stated	0.7 W	Not stated	5–8 s	Not stated	2 weeks	Pain relief more in test group (<i>p</i> < 0.001)	Healing faster in test group than control (test: 4.08 ± 0.81 days, control: 7.84 ± 0.90) (<i>p</i> < 0.001)
Albrektson et al., 2014 [22]	RCT	40	Not stated	22.5	RAS	GaAlAs	Placebo	Single	809 nm	60 mW	Not stated	80 s	6.3	3 days	Pain relief more in test group (<i>p</i> < 0.001)	Not assessed
Lalabonova et al., 2014 [23]	RCT	180	82.8%	43.01 ± 1.25	RAS	Diode	Placebo	Single	658 nm	27 mW	Not stated	1.14 min	2	5 days	Pain relieved more in the test group (<i>p</i> < 0.001)	Complete epithelization in 75.6% test group and 37.8% in control. (<i>p</i> < 0.001)

RCT, randomized control trial.

lasers increases collagen turnover in wounds [28] and enhances activity of mitochondrial enzymes [29]. Studies conducted using animal models have shown faster wound healing upon exposure to low-level lasers [30,31]. There has been abundant clinical evidence that low-level lasers can help wound repairing and healing in human subjects [32,33]. A possible mechanism of pain relief due to laser exposure of wounds is the alteration of the electrical activity in the nerve cells [34,35]. Four types of low-level lasers have been used to treat aphthous ulcers: CO₂, Nd:YAG, diode and GaAlAs lasers. Therefore, it is not unexpected that all studies investigating the effects of low-level lasers on oral ulcers reported reduced pain perception immediately upon irradiation [14,18-23].

Clinical trials by Zand et al. [18,20] and Prasad et al. [21] have demonstrated that exposure of only a few seconds with CO₂ lasers can induce immediate pain relief. However, none of these studies have compared the efficacy of the lasers with conventionally available topical drugs that are used to treat aphthous ulcers. Nonetheless, CO₂ lasers also appear to stimulate quick healing of ulcers compared to placebo controls at much lower power settings [20,21]. Accordingly, healing times of CO₂ laser therapy compared to topical medicaments have yet to be evaluated. Because CO₂ lasers can be used to treat aphthous ulcers at a much lower power setting and very short exposure duration, these lasers can be considered generally safer to be used in the clinical setting when compared to other lasers.

Nd:YAG lasers have also been used to treat aphthous ulcers [14,19]. However, a major disadvantage of these lasers is a requirement of prolonged irradiation times (2-3 min) that may be a health hazard to the patient as well as the practitioner. Nevertheless, studies comparing the efficacy of Nd:YAG with topical steroids have reported faster healing times in addition to immediate relief [14,19]. However, none of the studies evaluating the efficacy of Nd:YAG were blinded to the patients that could be a cause of bias while assessing pain on a visual scale. Diode lasers can treat aphthous ulcers at a very low-power setting albeit at a considerably long exposure time [12,23]. Lalabonova et al. have used diode laser at 27 mW for 1 min 14 s in a clinical trial study [23]. However, there have been no other similar trials conducted to ascertain the feasibility of using diode lasers in the clinical setting. An obvious disadvantage of diode lasers is the prolonged exposure time needed for the intended therapeutic effects. The case report by Misra et al. [12] and clinical trial by Lalabonova et al. [23] document exposure times of 1 min and 1 min 14 s respectively that was much longer than studies assessing CO₂ lasers [13,18,20,21]. A low-level GaAlAs laser has been used by Albrektsen et al. to treat ulcers in a clinical trial but, similarly to Nd:YAG and diode lasers, ulcers require a much longer exposure [22].

All studies adequately described the inclusion criteria of the patients, the randomizing protocols and the selected parameters of the laser [12-20]. However, there were a number of limitations in the methodology of the studies included in this review [14,18-23]. Only two studies compared the efficacy of LLLT with that of corticosteroids [14,19]. Hence, the difference in the effectiveness of conventional treatment and LLLT has not been ascertained yet. Furthermore, not all studies observed the healing after laser exposure. Hence, more

histological studies need to be conducted to investigate the effect of LLLT on healing of ulcers. Additionally, none of the studies included smokers and only two studies included patients with systemic conditions [13,14]. Therefore, future studies need to observe the efficacy of LLLT on ulcers in patients who are smokers and those with systemic conditions which may lead to manifestation of oral ulceration. Also, more studies with long follow-up periods are vital to assess the long-term efficacy of LLLT in treating oral ulcers. Another factor that may lead to examiner bias is the lack of double-blinding, observed in all RCTs [14-20]. Moreover, two RCTs did not describe any blinding protocols at all [14,16] and 4 studies [15,17-20] only followed single-blinding, both of which may have led to biased observations.

5. Conclusions

Considering the fact that the precise etiology of RAS is not known, the clinical management of these lesions is challenging. Although many modalities have been employed to deal with the severe discomfort due to aphthous ulcers, patients have yet to be provided with an effective, immediate therapeutic regimen. Studies suggested that low-level laser therapy a suitable alternative or adjunct treatment option for RAS. In the literature, four types of lasers have been used to treat aphthous ulcers: CO₂, Nd:YAG, diode and GaAlAs. Although all of them have succeeded in providing immediate pain relief to patients, CO₂ lasers have the unique advantage of requiring a very short exposure time (5-10 s). However, more clinical trials are required to be conducted to compare the efficacy of these lasers with the currently available treatment modalities in order to ascertain their efficacy in the clinical setting.

Conflict of interest

The authors state that they have no conflicts of interest to declare.

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