



Treatment of recurrent aphthous stomatitis by laser therapy: A systematic review of the literature

Lečenje recidivirajućeg aftoznog stomatitisa primenom lasera: sistematski pregled literature

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Abstract

Background/Aim. Recurrent aphthous stomatitis (RAS) is defined as multifactor immunologic inflammatory lesions in the oral cavity, characterized by painful, recurrent single/multiple, shallow, round or ovoid ulcerations of mucosal tissues. To date, a considerable number of RAS treatment protocols have been suggested, but since the etiology of RAS is idiopathic, these treatment options have symptomatic rather than curative or preventive effect. Recently, it has been suggested that laser therapy could be successfully used as an efficient treatment approach in therapy of RAS. Therefore, the aim of this review was to estimate the effects of laser therapy in treatment of RAS analyzing results of clinical studies published in peer reviewed journals. **Methods.** The studies published until 31 December 2013 were obtained from the Medline/PubMed, Science Direct and Cochrane Library of the Cochrane Collaboration (CENTRAL) online databases, using following search terms and key words: “laser”

AND “recurrent aphthous stomatitis”, “laser” AND “aphthous”, and “laser” AND “aphthae”. In total 4 original research articles met the all required inclusion/exclusion criteria, and were used for this review. The main outcome measures assessed were: a reduction of pain associated with RAS and a reduction in episode duration (faster RAS healing). **Results.** The assessed literature demonstrates the benefits of laser therapy mainly due to immediate analgesia and ability to speed up a RAS healing process. **Conclusion.** Even though the assessed literature suggests beneficial outcomes of laser therapy in treatment of RAS, these results should be interpreted with caution. The issues related to the study designs and different sets of laser irradiation parameters of a limited number of available studies with the same treatment outcomes prevent us from making definite conclusions.

Key words: laser therapy, low level; stomatitis aphthous; recurrence; treatment outcome.

Apstrakt

Uvod/cilj. Rekurentni aftozni stomatitis (RAS) definisan je multifaktorskim imunološkim zapaljenskim lezijama u usnoj duplji, koje se karakterišu bolnim, recidivirajućim pojedinačnim/multiplim, plitkim, okruglim/ovoidnim ulceracijama sluzokože. Do danas je predstavljen niz protokola o terapijskom zbrinjavanju RAS, ali kako je oboljenje idiopatske etiologije, predložene terapijske opcije su simptomatske, a ne preventivne ili kurativne. Nedavno je laseroterapija predstavljena kao veoma efikasna opcija terapijskog zbrinjavanja RAS. Cilj ovog rada bio je procena efekata laseroterapije u terapijskom zbrinjavanju RAS na osnovu rezultata kliničkih studija objavljenih u recenziranim

časopisima. **Metode.** Analizirani su radovi objavljeni do 31. decembra 2013, dobijeni pretraživanjem Medline/PubMed, *Science Direct* i *Cochrane Library* of the *Cochrane Collaboration* (CENTRAL) online baza podataka, ukucavanjem ključnih riječi: *laser* i *recurrent aphthous stomatitis*, *laser* i *aphthous* i *laser* i *aphthae*. Ukupno 4 originalna naučna rada, koji su zadovoljili sve kriterijume uključena/isključenja u ovu studiju podvrgnuta su daljoj analizi. Poseban akcent stavljen je na efekte laseroterapije na ublažavanje bola (analgeziju), te na skraćivanje trajanja RAS epizode, odnosno na ubrzanje zarastanje lezija. **Rezultati.** Dostupna literatura ukazuje na prednosti korišćenja laseroterapije u zbrinjavanju RAS, i to u neposrednoj analgeziji, te sposobnosti ubrzanja zarastanja rana. **Zaključak.** Iako podaci

iz dostupne literature ukazuju na prednosti upotrebe laseroterapije u zbrinjavanju RAS, ove rezultate trebalo bi interpretirati uz oprez. Naime, različiti dizajn kliničkih studija, različiti iradijacijski parametri lasera korišćeni u tim studijama, te veoma mali broj dostupnih studija u kojima su praćeni isti terapijski ishodi, sprečavaju nas da donese-

mo konačne zaključke o prednostima laseroterapije u lečenju RAS.

Ključne reči:

laseri male snage; stomatitis aftozni, recidiv; lečenje, ishod.

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most frequent pathologic conditions in the oral cavity in an otherwise healthy individual. It is defined as multifactor immunologic inflammatory lesions that affect 10–20% of the population, mainly in developed parts of the world^{1–4}. RAS has three main clinical subtypes – minor (miRAS), major (maRAS) and herpetiform ulcers^{1–4}. Minor ulcers (Mikulicz ulcers) are the most common subtype, which comprise over 80–90 % of cases. They are usually less than 1 cm in diameter, last up to 7–14 days, and heal without scar. Major ulcers (Sutton's ulcers) are over 1 cm in diameter, their healing may take 20–30 days at a time, and often with scarring. Herpetiform ulcers (HU) are multiple, clustered, 1–3 mm lesions that may integrate into larger ulcers. They typically heal with scar within 15 days^{1–4}. Although the majority of cases are benign and heal in less than two weeks, these ulcerations may be indicative of underlying systemic diseases ranging from vitamin deficiency to autoimmunity, especially pointing on immunodeficiency^{2,3}. Awareness of these correlations can help the dentist make the diagnosis of potentially serious conditions. RAS can also have clinical and histological aspects in common with Behcet's, Sweet's, Stevens-Johnson and Reiter's syndrome³.

Even though exact underlying etiology of RAS is unknown, many etiologic, predisposing factors have been suggested. Several microbial agents such as *Herpes Simplex*, *Varicella Zoster*, *Coxsackie A* and other viruses, *Toxoplasma gondii* and organisms which cause Vincent's angina, *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Actinomyces*, *Neisseria* and other bacterial agents including the pleomorphic, transitional L-forms of *Streptococcus sanguis* have been mentioned^{1–5}. The current literature also suggests correlation of RAS with fungal agents, such as *Coccidioides immitis*, *Cryptococcus neoformans* and protozoans such as *Entamoeba histolytica*. Also trauma, physical or psychical stress, hematological deficiencies, chemical injuries, hormonal changes (mostly in women), allergy, vitamin C, B₁ and B₁₂, iron and folic acid deficit and smoking are potentially related to RAS^{2,3}. Moreover, there is considerable evidence that aphthous ulcers are related to a focal immune system dysfunction in which T-lymphocytes have very important role^{2,3}.

A considerable number of treatment protocols for RAS have been described, but since the etiology of RAS is unknown, none of these treatment options have curative or preventive effect⁶. The basic of the treatment is focused on pain relief and promotion of the healing in order to reduce the duration of the disease and its recurrence^{3,6–8}. Therapy of RAS includes topical (e.g. triamcinolone acetonide) or systemic

corticosteroids (e.g. prednisolone), systemic immunomodulators (e.g. thalidomide), antibacterial (e.g. tetracycline), non-steroidal anti-inflammatory drugs (e.g. pentoxifylline-PTX, colchicine, 5% amlexanox), antimicrobials (e.g. chlorhexidine gluconate), chemical cauterizers and/or cryotherapy. Further, nonprescription options, such as vitamin supplements, herbal supplements and/or local anesthetics gels or pastilles can be often used to reduce discomfort^{5, 7–13}. Recently, it has been suggested that statins – cholesterol lowering drugs, whose immuno-modulatory and anti-inflammatory actions have been proven in local¹⁴ and systemic inflammation, particularly by inhibition of pro-inflammatory cytokines production¹⁵ could be successfully used in several inflammatory diseases. Auto-inflammatory disease, such as RAS, is predominantly mediated by pro-inflammatory cytokines of the innate immune system, particularly IL-1 β and TNF- α ¹⁶, suggesting potential therapeutic benefits of blocking these cytokines. Although, it has been showed that simvastatin exerts anti-inflammatory properties in experimental periodontitis¹⁷, and reduces IL-1 α -induced production of inflammatory cytokines by human oral epithelial cells¹⁸, the therapeutic effectiveness of statins in the treatment of RAS remains to be established. Even though widely accepted, conservative/pharmacological therapeutics is often disappointing and palliative, and recurrences of the lesions are common after the therapy is ceased. The need for better treatment alternatives was obvious, especially for patients unresponsive to conservative therapy of RAS.

Low-level laser therapy (LLLT) is nondestructive amount of energy that occurs at the periphery of the target tissue, simultaneously along high-level laser irradiation ("simultaneous LLLT"), or as independent ("pure LLLT") amount of power and energy density below the destructive level¹⁹. It has bioactivating effects, such as increase of cell metabolism and/or tissue regeneration, thereby accelerating healing of the tissue^{20–24}, anti-inflammatory effects on the targeting tissues and cells, as well as reduction of pain of various etiologies^{25,26}. Since it has been recently reported that LLLT can be successfully used as an advanced treatment modality in therapy of RAS, the aim of this study was to determine the clinical effectiveness of laser therapy in treatment of RAS lesions.

Methods

Search strategy

The studies published until 31 December 2013 were obtained from the Medline/PubMed, Science Direct and Cochrane Library of the Cochrane Collaboration (CENTRAL)

online databases, using following search terms and key words: “laser” and “recurrent aphthous stomatitis”, “laser” and “aphthous” and “laser” and “aphthae”. Screening and study selecting process was performed independently by two authors to avoid the potential for reviewer bias. Further, the references of all selected articles were scanned. The corresponding authors were contacted in case of missing and insufficient data reported originally in studies. The online databases’ search initially yielded a total of 228 publications. On the basis of title and abstract evaluation, authors agreed by discussion to exclude 204 publications. Remaining 24 publications in full-text format (relevant or possibly-relevant) were retrieved for more detailed analysis.

Study inclusion and exclusion criteria

The selected publications were further analyzed according to the following inclusion criteria: 1) publication in an international peer reviewed literature; 2) English language publications; 3) randomized controlled clinical trials (RCTs) and/or comparative clinical studies; 4) studies on RAS lesions, regardless clinical subtype (miRAS, maRAS, HU); 5)

any type of low-level laser therapy, as an intervention to at least one of the treatment groups; and 6) presence of at least 5 patients in test and/or control group.

The studies that fulfilled the inclusion criteria were further analyzed according to the following exclusion criteria: 1) no definition of inclusion and/or exclusion criteria; 2) no sufficient information on laser parameters’ settings; 3) no outcome of interest.

In total, 4 original research articles were identified as appropriate (met the required inclusion/exclusion criteria) for this review. The main outcome measures assessed were a reduction of pain associated with RAS and a reduction in episode duration (faster RAS healing).

Quality assessment

After establishing the scores of quality assessment (Table 1), the overall estimation of risk of bias (low – all of criteria met, moderate – one or more criteria partly met and high – one or more criteria not met) was determined²⁷ for each selected study (Table 2). A quality assessment of all the selected studies was performed independently by two authors (V. P. and V. VA.).

Table 1

Categories used to assess the quality of the selected studies		
Category	Category description	Grading
A	Sample size calculation (minimal number of participants, in order to achieve a stat. significant difference among compared groups)	0 = not mentioned 1 = reported, but not confirmed 2 = reported and confirmed
B	Randomization and allocation concealment methods	0 = clearly inadequate 1 = possibly adequate 2 = clearly adequate
C	Clear definition of inclusion and/or exclusion criteria	0 = no 1 = yes
D	Completeness of follow-up	0 = no 1 = yes
E	Experimental and control group comparable at study baseline	0 = no 1 = unclear 2 = clearly adequate
F	Presence of masking	0 = no 1 = unclear 2 = yes
G	Appropriate statistical analysis	0 = no 1 = unclear 2 = yes

Table 2

Quality assessment of the selected studies								
Author and the year of the publication (reference)	A (0–2)*	B (0–2)*	C (0–1)*	D (0–1)*	E (0–2)*	F (0–2)*	G (0–2)*	Estimated risk of bias
Zand et al. 2009. ⁵	2	2	1	1	2	0	2	Low
de Souza et al. 2010. ⁶	2	2	1	1	2	0	2	Low
Zand et al. 2012. ²⁸	2	2	1	1	2	0	2	Low
Prasad et al. 2013. ²⁹	2	2	1	1	2	0	2	Low

*For explanation see Table 1.

Results

De Souza et al.⁶ compared InGaAlP (670 nm) diode laser therapy to conventional therapy (topical corticosteroids-triamcinolone acetonide). Both treatments were applied until the complete resolution of RAS lesions. The study evaluated 20 miRAS patients (12 females and 8 males), with the mean age of 23.65 (Table 3). Laser parameters employed were: power output 50 mW; energy density 3 J/cm² per point; and exposure time 1 min. Irradiation was applied daily (once *per* day) on consecutive days. The distance between a laser beam and the mucosa was constant (laser pen touching the surface of

Zand et al.⁵ analyzed 15 patients (13 female and 2 males), with their mean age of 37.9 years, while in another study 10 patients (9 females and one male) with the mean age of 35.6 years were enrolled²⁸. Prasad et al.²⁹ conducted a study on 25 patients, mean age 27.48 years (Table 3).

Regarding the effects of CO₂ laser therapy on pain relief, Zand et al.⁵ operated at power of 1 W, while Prasad et al.²⁹ employed even lower power settings of 0.7 W (Table 4). As the result, Zand et al.⁵ reported pain levels of 6.2 ± 1.3 preoperatively and 0.07 ± 0.3 postoperatively (immediately after 4 h, 8 h, 12 h, 24 h, 48 h, 72 h and 96 h following irradiation), which was similar to Prasad et al.²⁹ pain reports of 8.48 ± 0.71

Table 3

General information on the selected studies

Author and the year of the publication (reference)	Study design/ Number of patients	RAS clinical subtype	Exp.group	Control group
Zand et al. 2009. ⁵	RCT (15 patients)	miRAS	Laser	Placebo
de Souza et al. 2010. ⁶	Comparative study (20 patients)	miRAS	Laser	Topical corticosteroids (triamcinolone acetonide)
Zand et al. 2012. ²⁸	RCT (10 patients)	miRAS	Laser	Placebo
Prasad et al. 2013. ²⁹	Prospective clinical study (25 patients)	miRAS	Laser	Placebo

RCT – randomized controlled clinical trial; miRAS – mirror recurrent aphthous stomatitis.

the lesion). As the result, a reduction of pain (75% of the patients) in the same session after laser treatment was demonstrated. Further, a total regression of the lesion was achieved 4 days following laser irradiation (40% of the patients) compared to prolonged time (5–7 days) required to obtain the same results in the corticosteroid group. The authors concluded that under the conditions administered in the study, InGaAlP laser therapy can be safely used as the advanced RAS treatment technique in order to achieve immediate analgesia and faster healing of RAS lesions⁶.

Other selected studies reported the effects of non-contact, non-ablative CO₂ laser (10,600 nm) therapy on pain relief and faster tissue healing of RAS lesions compared to placebo in patients with 2 miRAS lesions present at the same time (Table 3). Randomly allocated miRAS was treated with laser, while another served as placebo^{5,28,29}. As a precaution to prevent thermal damage to the mucosa due to the heat produced by CO₂ laser, a thick layer of high water content transparent non-anesthetic gel (3–4 mm thickness) on RAS lesion prior to CO₂ laser irradiation was applied^{5,28,29}. As the result, authors claimed that no side effects, such as warmth on laser targeted spot, erythema, carbonization or vaporization had been reported^{5,28,29}. Further, these procedures were pain-free and did not require anesthesia prior to irradiation.

The selected studies used defocused (angulated) hand-piece for scanning over RAS lesion at the distance of 5–7 mm (circular motion) for about 5–10 seconds^{5,28,29}. The study sample size and its characteristics varied from study to study:

before treatment and 0.68 ± 0.63 24 h following irradiation. In total, both studies^{5,29} demonstrated similar results measured by the visual analog scale (VAS) in the statistically significant difference in pre- and postoperative pain levels in CO₂ laser group, whereas no such difference was observed in the placebo groups. As the result, the authors suggested the use of CO₂ laser therapy in significant immediate and dramatic reduction of idiopathic and contact RAS pain, with sustained analgesic effect^{5,29}. As for enhanced RAS wound/tissue healing following CO₂ laser therapy, Zand et al.²⁸ assessed healing every day after irradiation until complete re-epithelization of RAS lesion, while Prasad et al.²⁹ assessed healing at days 3 and 4 following CO₂ laser irradiation, and every 2 days until 14 days. Zand et al.²⁸ reported main healing score of 4.8 ± 2.4 days in the laser group compared to 7.6 ± 2.5 days in the placebo group. These results were similar to what Prasad et al.²⁹ reported: the mean healing score was 4.08 ± 0.81 and 7.84 ± 0.90 days for the laser and placebo treatment groups, respectively. Both authors^{28,29} confirmed statistically significant differences in RAS faster wound healing following CO₂ laser therapy (Table 4).

Discussion

Combined problems of unknown etiology, lack of specific therapy and the frequency of recurrence of RAS have made the management of these patients a difficult problem to general dentist. All the three clinical types of RAS are as-

Table 4

Effects of low-level laser therapy (LLLT) treatment of recurrent aphthous stomatitis (RAS)								
Author and the year of the publication (reference)	Laser device (wavelength, emission mode)	Laser parameters	Anaesthesia prior to irradiation	Oral gel prior to irradiation	Laser distance (between laser and RAS lesion)	Laser application	Observation period and follow-up	Treatment outcome
Zand et al. 2009. ⁵	CO ₂ laser (10.600 nm) continuous emission mode	Power: 1W Irradiation time: 5-10 s	No	Yes	5-6 mm (circular motion)	Single	Before Immediately after, and 4h, 8h, 12h, 24h, 48h, 72h and 96h after irradiation	Immediate pain relief
de Souza et al. 2010. ⁶	InGaAlP diode laser (670 nm) continuous emission mode	Power: 50 mW Energy density: 3 J/cm ² Irradiation time: 60 s	No	No	Touching the surface of RAS	Daily (once per day) on consecutive days	Before Immediately after irradiation and every day up to 10 days	Immediate pain relief Enhanced healing
Zand et al. 2012. ²⁸	CO ₂ laser (10.600 nm) continuous emission mode	Power: 1W Irradiation time: 5-10 s	No	Yes	5-6 mm (circular motion)	Single	Before Immediately after irradiation and every day until the resolution of signs	Enhanced healing
Prasad et al. 2013. ²⁹	CO ₂ laser (10.600 nm) continuous emission mode	Power: 0.7 W Irradiation time: 5-8 s	No	Yes	5-7 mm (spiral motion)	Single	Pain: Before Immediately after and 24h after irradiation Healing: Before-3-4 days after irradiation and up to 14 days	Immediate pain relief Enhanced healing

sociated with painful, recurrent, single or multiple, shallow necrotizing ulcerations of mucosal tissues. Although patients in most of the cases have spontaneous healing within 14 days, treatment is often indicated to mainly control pain and to reduce the duration and severity of symptomatic outbreaks, especially during the periods of quiescence and exacerbation (period of increased pain and sensitivity) of RAS lesions³⁰. Pain usually reduces after 4-5 days, but during this period it can cause discomfort to a patient during eating, swallowing, speaking and wearing dental prostheses¹⁻⁵. Pain control is also very important in order to maintain patient physical and mental condition, further improving effectiveness of the therapy. To date, it is widely accepted that the first-line therapy for patients with RAS are topical corticosteroids, even though the evidence of their efficiency is not overwhelming. Recently, laser as a new treatment modality has been introduced. To date, lasers are widely used in dentistry, namely due to beneficial clinical outcome achieved in shorter time and with a better patient acceptance. Lasers are successfully used in surgical (ablative) and non-ablative (LLLT) manner to treat painful RAS lesions. In ablative manner lasers are used to remove as much of necrotic RAS tissue as possible, including the inflamed halo around the aphthae^{31,32}. Patients feel mild warmth on the targeted place; therefore anaesthesia is required prior to irradiation, as a part of surgical proce-

dure. One of the biggest concerns in ablative manner is laser-related hazard-plume (having a potential for carrying viral particles). Also, a potential for pseudoisomorphic (Köebner) phenomenon in susceptible persons with ulcerations (seen in Behcet's disease) after laser irradiation, as trigger, has been mentioned³³. In contrast to ablative lasers, LLLT is non-destructive, non-thermal and pain free procedure, which usually does not require anaesthesia and do not carry any potential of plume hazard to the surgeon and personnel⁵. Further, it does not produce visual effects of thermal damage to the oral mucosa such as ablation, coagulation, vaporization or erythema⁵. Therefore, LLLT is described as more convenient to use, with a fewer possible adverse events and it became a treatment of choice, when it comes to the use of lasers in therapy of RAS.

It is well-known that LLLT causes immediate analgesia in various painful oral lesions³⁴⁻³⁶. For that indication³⁷ LLLT have been approved for marketing by the U.S. Food and Drug Administration through the premarket notification/510(k). To date, there are several suggested mechanisms for pain reduction following LLLT application, such as effect in modulating key factors of inflammation, reduction of the prostaglandin E₂ level, inhibition of cyclo-oxygenase, and/or lymphocyte metabolism that could lead to reducing of edema, and further reduction of inflammatory processes^{38,39}.

Also, release of endogenous pain relievers – endorphins and enkephalins⁶, the increase in production of serotonin and suppression of bradykinin activity^{5,40,41} has been suggested. It has been also shown that laser therapy increases systemic microcirculation by nitric oxide synthesis, causing the reduction in swelling and pain⁴⁰. Even though, there are several potential mechanisms proposed, the real underlying mechanism following laser therapy for pain reduction is yet to be determined. It is believed that not just one, but two or more coexisting mechanisms or their combination are responsible for the beneficial outcome of LLLT in achieving analgesia. Apart from documented analgesic effect, LLLT is successfully applied for tissue healing, mainly due to successful hemostasis, decontamination (sterilization) and anti-inflammatory effect³⁸. Further, a potential biostimulation of underlying and surrounding cells, increased collagen organization and promoting of growth factors and cytokines in response to laser irradiation have been demonstrated^{19–24}.

Although the assessed literature demonstrated significant analgesia and enhanced RAS tissue healing following laser therapy without any reported side effects (Table 4), the results should be interpreted with caution due to insufficient evidence (small number of studies available for evaluation). Firstly, selected studies employed different sample size (number of patients enrolled) with further varieties, such as female/male ratio and patients' main age. Secondly, beneficial results of the laser therapy were only reported on miRAS lesions. The miRAS could be considered as a prototype of painful RAS lesions, but it would be of a great interest to report laser therapy

effects in the treatment of the maRAS and HU, too. Thirdly, laser devices employed were different (InGaAlP and CO₂), with different wavelengths and completely different characteristics and biological effects on targeted tissues. Further, laser irradiation protocol (power, dose, observation period/follow up) was also inconsistent. Since there is no firm proof-backed framework for treatment of RAS, it is really difficult to support the effectiveness of any specific laser therapy approach presented, as being superior. In order to determine the real efficacy of laser therapy in treatment of RAS lesions, further carefully designed clinical studies with precise sample standardization (number of patients, gender and age) as well as the type of laser and clinical subtype of RAS should be rigorously studied in order to further evaluate the obtained results.

Conclusion

Low-level laser therapy of selected wavelengths used at the documented energy settings seems to be the appropriate procedure in therapy of recurrent aphthous stomatitis. This fact was evidenced by significant analgesia and enhanced wound healing, without any major adverse effects reported. However, issues related to the design and laser irradiation parameters of a limited number of studies prevent us from making definite conclusions. Therefore, further research, especially long-term follow up randomized control trials with a larger number of patients are required in order to determine the optimal laser therapy protocol in treatment of recurrent aphthous stomatitis.

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