Lasers in Medical Science
https://doi.org/10.1007/s10103-020-03166-0

ORIGINAL ARTICLE

Effect of different treatments on recurrent aphthous stomatitis: laser versus medication

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Received: 29 February 2020 / Accepted: 21 October 2020

Abstract

Recurrent aphthous stomatitis (RAS) is a common disease with ulcers in oral cavity which may trigger chewing, speaking, and swallowing difficulties to patients. Treatment of RAS is primarily aimed at pain relief and the promotion of wound healing. However, few agents have been found to have definite effect in the management of RAS and most of the medicinal products may cause adverse reactions or other disadvantages, which makes their clinical usage questionable. The purpose of this randomized controlled clinical trial (RCT) was to assess the clinical effect of diode laser and traditional medication treatment on RAS. In this study, 56 patients were randomly assigned to two groups (n = 28). Laser group was treated using diode laser (810 nm, 1.0 W, CW, irradiation time 20 s for 3 applications) once daily for continuous 3 days. Medication group was treated with triamcinolone acetonide 0.1% three times a day until the lesion was healed. Spontaneous and functional pain level on the third day of treatment was significantly less in the laser group. Significant difference was observed with respect to healing time; however, the order of difference is small albeit of statistical significance. Diode laser with the chosen parameters had better effects on pain relief and no distinct advantage on wound healing comparing with medication. Trial registration number: ChiCTR2000030298; date of registration: 26 February 2020 (retrospectively registered)

Keywords Recurrent aphthous stomatitis · Photobiomodulation · Low level laser therapy · Pain · Wound healing

Introduction

Recurrent aphthous stomatitis (RAS) is a common and frequently encountered disease which develops recurrently, with painful ulcers confined in oral cavity only as clinical manifestation [1]. The ulcers are typically clearly defined, sunken in the central part, round or elliptical in shape, circumscribed by erythematous haloes, and covered by pseudomembrane tissues with grey or yellow in color [2]. RAS is generally identified as three different types respectively named Minor (MiRAS), Major (MaRAS), and Herpetiform (HU) ulcers according to the distinct discrepancy primarily in morphology and prognosis of ulcers [3]. Thereinto, minor aphthous is the most prevalent form which accounts about 70–85% of all RAS lesions [4]. The definite etiology and pathophysiology of RAS remain unclear up to date. However, it is considered to be a kind of multifactorial disease. Predisposing factors like immune system dysfunction, genetic predisposition, endocrine alterations, nutrition deficiencies, microbiological organisms, specific drugs, food allergens, stress or anxiety, and mechanical injuries may contribute to the occurrence of mucosal lesions of RAS [5].

RAS is a self-limited disease and a typical minor aphthous ulcer can spontaneously heal within 4–14 days [4]. However, the lesions in oral cavity may trigger severe chewing, speaking, and swallowing difficulties, which seriously interfere with the normal activities of patients in daily life [6]. The objects of treatment are pain relief, promotion of reepithelialization, and reduction of the frequency [7]. Traditional medications for RAS applied locally or systemically including corticosteroids, anesthetics, antibiotics, anti-inflammatory agents, multivitamins and microelements, and

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Published online: 02 November 2020

immunomodulator drugs [1, 8, 9]. Topical therapy is the fundamental choice for minor ulcers, in comparison with systemic agents applied when the outbreaks are constant and aggressive, with major ulcers or when the patients respond insensitively to topical agents [10].

Although numerous agents available for RAS, only a few are identified though evidence-based processes. Topical corticosteroids perform potent effects on active ulcers and provide a widespread use for treatment of RAS [8]. However, long-term application of such kind of agents may lead to a risk of oral candidiasis [8]. Furthermore, most of the medicinal products may have adverse reactions or other disadvantages, which makes their clinical usage questionable [11]. Thus, medical and dental clinicians have been incessantly seeking for treatment modalities effectively managing symptoms of RAS without adverse effects.

Soon after the discovery of low level laser therapy (LLLT) by Ender Mester in the 1960s, it was rapidly realized that LLLT had the magic potential to treat numerous diseases and unhealthy conditions involving inflammation, pain, wound healing, regeneration, and abnormal immune responses [12, 13]. There has been a widespread application of LLLT in field of dental diseases including endodontics, periodontics, peri-implantitis, diseases of oral mucosa, oral surgeries, temporomandibular disorders, and dental movement [14]. Recently, several different types of laser (Nd:YAG laser, CO2 laser, and diode laser, etc.) have been applied for the treatment of RAS and they indeed demonstrated superiority in pain relief and faster healing comparing with placebo or medical treatment group [15–17]. However, additional high-quality randomized controlled clinical trials (RCTs) are particularly needed to scope the optimal parameters for RAS laser treatment.

The purpose of this RCT was to assess the clinical effect of diode laser and traditional medication treatment on RAS.

Materials and methods

Study design

Ethical approval for the project was obtained from Medical Ethics Committee of Stomatology Hospital of Hebei Medical University. Study subjects were recruited from the pool of patients in the Clinic of Oral Medicine of Hospital of Stomatology, Heibei Medical University between January 2018 and December 2019.

The inclusion criteria were as follows: (1) A minor aphthous ulcer with the size of not more than 10 mm in diameter; (2) The ulcer occurred within 3 days; (3) The visual analog scale (VAS) of functional pain score before treatment was not less than 3; (4) Only one lesion in mouth.

The exclusion criteria were as follows: (1) Patients with systemic disease relating with oral ulcer (such as ulcerative colitis, Crohn's disease, Behcet's syndrome); (2) Pregnant or lactating patients; (3) Patients undergoing orthodontic therapy; (4) Patients accepted other treatments (such as systemic steroids or immunomodulatory agents, nonsteroidal anti-inflammatory drugs) during the previous month; (5) Patients used any topical agents within 1 week before the trial; (6) Patients with the habits of tobacco and alcohol. Oral and written informed consents were obtained from all participants.

The sample size was determined with the method described by Walters for comparing means of ordinal data when the samples display a relatively normal distribution [18]. The significance level was chosen as 0.05, the power of this test as 0.80, the value of the minimal difference in intensity of pain between two treatment protocols as 3.53 [15], and the value of standard deviation of population as 3 (analyzed from preliminary experiment), then $\alpha = 0.05$, $\beta = 0.20$, $\sigma = 3$. When applying a two-sided t test, the sample size was calculated and determined as 24, with 12 participants in each group. Finally, the sample size of the study was determined to be 56, with 28 in each group. After written and verbal informed consent was obtained, the patients were randomly assigned to either laser or medication group using a block of random numbers generated by an assistant by Excel 2007.

Study procedure

Laser group was treated using a calibrated laser source from a diode laser (810 nm, FOX laser, A.R.C., Germany) device with the following irradiation parameters: power output 1.0 W, continuous mode, fiber diameter 320 μm with irradiation performed in scanning mode on an area of 1.5 cm of diameter around the lesion, irradiation time 20 s for 3 applications with 10-s interval, total theoretical fluence 12.9 J/cm^2. The distance between the fiber tip and the surface of ulcer was 1 cm, with the approximate optical spot diameter 7 mm. Laser therapy was implemented once daily for continuous 3 days.

Medication group was treated with Triamcinolone Acetonide Dental Paste (triamcinolone acetonide 0.1%, Bright Future Pharmaceutical Lab. Ltd, Hong Kong) three times a day until the lesion was healed.

The participants were advised not to take any other topical or systemic medications beyond the project during the study.

Clinical assessment

Pain

Spontaneous pain means patient perception of pain without any activity and external stimuli. Functional pain means pain of lesion when chewing, drinking, and speaking. Participants were asked to record the pain intensity using a visual analogic

scale (VAS) before treatment, immediately after laser therapy for the first time, and on days 1, 3, and 7.

Healing

As the criteria for healing of the ulcer, we recorded the day in which the lesion was re-epithelized while a vague outline of the lesion was still visible in clinical examination.

Statistical analysis

Statistical analysis was performed using SPSS 23.0. The descriptive statistics was used for presenting the general data. Chi-square test was used to compare the differences between the groups including gender of the patients and location of the lesions. Mann-Whitney *U* test was used to compare the distribution of the patient age and lesion size before treatment after testing by Shapiro-Wilk's method. In case of non-normal distribution data, Mann-Whitney *U* test was applied to compare the differences of pain scores at each point of assessment and healing days between the two groups. Wilcoxon test was used to compare the differences between before and immediately after treatment in laser group. Values of $P < 0.05$ were accepted as statistically significant.

Results

No complications or side effects were observed in the laser group. One patient missed the recall visit on day 2 and two patients failed to contact after laser treatment. In medication group, one patient discontinued the treatment because of nausea and one subject failed to contact. Among the remaining 51 patients, 25 patients finished their treatment in laser group and 26 in medication group (Fig. 1).

There were no significant correlations between patients' gender, age,, and the studied parameters including lesion size and location within each group. The results from the statistical analysis are presented in Table 1.

Pain VAS scoring results are presented in Table 2.

Spontaneous pain No significant difference was noted in the spontaneous pain before treatment between the two groups ($P > 0.05$). Pain scores were significantly less in the laser group on days 1 and 3 ($P < 0.01$); however, the difference was not significant on day 7 ($P > 0.05$).

Functional pain No significant difference was noted in the functional pain before treatment between the two groups ($P > 0.05$). Immediately after laser treatment for the first time, pain intensity was significantly reduced ($P = 0.000$). However, pain scores picked up subsequently and there was no significant difference between the two groups on day 1. Significant difference was noted between the two groups on day 3 and day 7 ($P < 0.05$).

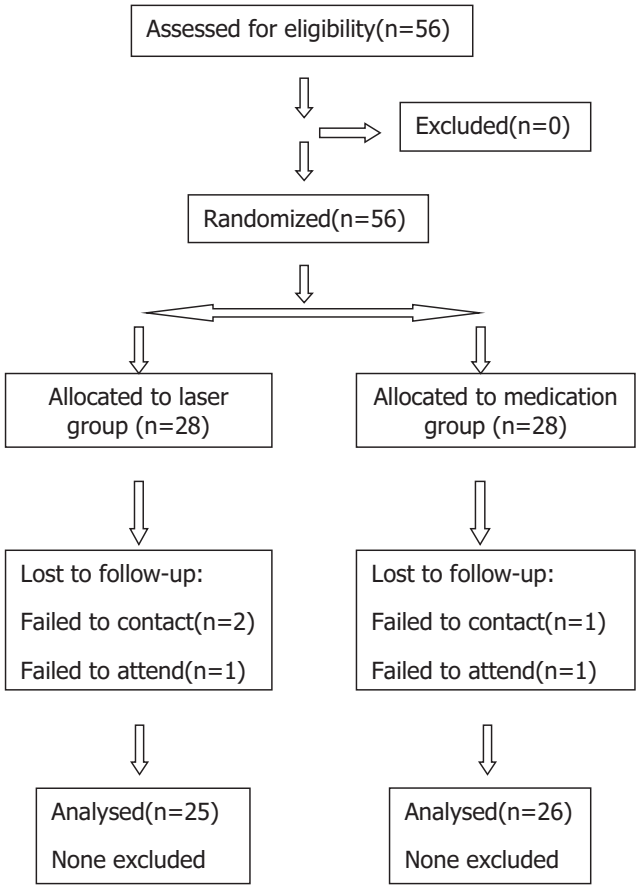

Fig. 1 Consort flow chart for this study

Healing There was a significant difference in the healing time between the two groups; however, the order of difference is small albeit of statistical significance (Table 2).

Discussion

Nowadays, LLLT is commonly known as photobiomodulation (PBM), which includes the therapeutic use of laser and light emitting diode (LED) [19].

Although there have been a considerable number of clinical trials, animal experiments, and in vitro studies demonstrating the positive effects of LLLT on pain relief, inflammation alleviation, and wound healing promotion, the mechanism remains indistinct.

Therapeutic effects by LLLT are initiated by light absorption of photo-acceptors locating in mitochondria which triggers a series of biochemical responses at the molecular, cellular, and tissular levels [20]. Cytochrome c oxidase (CCO) containing two heme-iron centers and two copper centers is

Table 1 Distribution of preoperative clinical factors by groups of treatment

Variables	Categories	Laser (n = 25)		Medication (n = 26)	
		n	%	n	%
Gender	Masculine	8	32.0	9	34.6
	Feminine	17	68.0	17	65.4
Age	Under 40	16	64.0	13	50.0
	Above 40	9	36.0	13	50.0
Location	Gingiva	2	8.0	2	7.7
	Tongue	9	36.0	9	34.6
	Buccal or labial mucosa	13	52.0	14	53.8
	Floor of mouth	1	4.0	1	3.8
Area	Under 5 mm × 5 mm	15	60.0	16	61.5
	Above 5 mm × 5 mm	10	40.0	10	38.5

the primary chromophore [21]. Light activation of CCO provokes the mitochondrial respiratory chain reaction inducing the phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). The phosphorylation produces abundant free radicals such as reactive oxygen species (ROS) and nitric oxide (NO) [22]. Positive effects can be also achieved by dissociation of inhibitory NO from CCO which leads to a boost of ATP production and to a reduction of the oxidative stress by modulating prooxidant and antioxidant mediators [23]. Another hypothesis proposes that laser irradiation can initiate an influx of calcium ions Ca^{2+}, following by activation of a series of signaling pathways [24].

On the whole, laser absorption by the target tissue triggers a chain of events, which accelerates the cell activities stimulating the production of serum reactive factor and superoxide dismutase, increasing the synthesis of serotonin and endorphins, and improving procollagen synthesis and macrophage activation, etc. [25, 26]. These biochemical effects at cellular level are continued with subsequent biological effects at tissue level including but more than pain alleviation, inflammation inhibition, immunomodulation, wound healing, and tissue regeneration.

Table 2 Comparison of the VAS scores and healing time

	Laser	Medication	P
Spontaneous pain (VAS)			
Before treatment	5.12 ± 0.63	5.69 ± 0.46	0.379
After treatment			
1 day	2.04 ± 0.44	4.85 ± 0.40	0.000
3 days	0.60 ± 0.25	3.00 ± 0.44	0.000
7 days	0	0.31 ± 0.17	0.083
Functional pain (VAS)			
Before treatment	7.60 ± 0.30	6.96 ± 0.34	0.292
After treatment			
Immediately after treatment (laser)	3.40 ± 0.49		
1 day	4.60 ± 0.44	5.96 ± 0.35	0.169
3 days	1.36 ± 0.33	4.00 ± 0.46	0.000
7 days	0.20 ± 0.14	1.19 ± 0.38	0.040
Healing time (days)	6.60 ± 0.29	7.77 ± 0.52	0.036

The biological effects by laser therapy are dependent on several protocol parameters such as wavelength, dose, power density, emission mode, irradiation technique, number and timetable of the sessions, and duration of the therapeutic treatment [27]. Different types of laser with various exposition parameters and methods of application were used in former clinical studies on RAS. Nd:YAG laser, CO_2 laser, and diode laser with wavelength in the range of 658 to 10,600 nm and power between 0.005 and 5 W have been reported to treat RAS [15–17]. The type of irradiation can be a continuous wave or a pulsed light consisting of energy density ranging from 3 to 110.67 J/cm^2 [15–17]. Clinical trials demonstrated different conclusions by reason of various designs and devices with diverse parameters. As a whole, most researchers expressed the positive effect of laser therapy on RAS concerning pain relief, wound healing, or both [28]. Tezel et al. compared the effects of Nd:YAG laser (1064 nm, 2 W, 20 HZ in pulsed mode, once at the first visit) and topical corticosteroid, with the results suggesting that laser had lower rates of pain and post-treatment adverse events [15]. De Souza et al. compared InGaAlP Diode laser (670 nm, 50 mW and 3 J/cm^2 in continuous mode) with topical corticosteroid and found that laser therapy effected on immediate pain relief while the later pain relief and improvement in wound healing were not significantly different comparing with topical medication [29]. Lalabonova and Daskalov assessed the therapeutic effect of Diode laser (658 nm, 27 mW, and 2 J/ cm^2 in continuous waveform, once daily until symptoms abated) versus topical granofurin and solcosery, concluding that laser therapy was better in pain management and epithelization acceleration [30]. Jijin et al. compared a diode laser (810 nm, 0.1

W, 6 J/cm^2, irradiation time 30 s for 3 applications daily for three sessions totally) with 5% amlexanox and found both therapies were equally effective in relieving pain and promoting ulcer healing [31]. However, whether laser therapy a better option than traditional medication treatment was still not clear owning to the deficiency of RCTs concerning on this topic.

Recently, diode laser with wavelength of 810 nm, which is in the near infrared (NIR) region, has been widely used and showed positive PBM effects in previous studies. The fact that NIR lights can penetrate tissues well and 810-nm light may arrive at above 5-mm depth beneath the surface although the thickness of oral epithelium is only about 100–800 μm [32, 33]. In our study, we did not limit the irradiation into the lesion but widened the scope to above 0.5 cm beyond the ulcer because healing of ulcers was achieved with great assistance of tissues around the lesion. An 810-nm laser on healing might be attributed to the photo biostimulative effects on healthy tissues around the lesion, which in turn induced migration of the peripheric keratinocytes and endothelial cells into the wounded zone and promoted re-epithelialization and angiogenesis [34]. Asheesh Gupta et al. evaluated the healing effects of LLLT mediated by different wavelengths of light in mice, discovering that cellular proliferation revealed by positive immunofluoresence staining for cytokeratin-14 and proliferating cell nuclear antigen (PCNA) across the wound surface and dermal granulation tissue was more evident under the irradiation of 810-nm laser, which pronounced a better stimulation of wound healing [34].

In our study, we used an 810-nm diode laser with parameters set up according to the instruction of the device. The results suggested that diode laser with the chosen parameters had better effects on pain relief comparing with triamcinolone acetonide 0.1%. Of note, the mean pain scores were significantly lower in the laser group on day 3 in respect of spontaneous pain and functional pain. Pain intensity descended more quickly in laser treatment. In addition, there was a distinct advantage of sharp pain relief in laser therapy, in contrasted with a gradually decline observed in medication group. Although there was a significant difference in functional pain between the two groups on day 7, the total pain intensity actually had descended to a fairly low level at this time point, which was imperceptible or without detriment to patients' chewing and speaking.

Although there was a significant difference concerning healing time between the laser and the medication group, the difference is small. A better outcome might be achieved by adjustment of parameters. According to the Arndt-Schulz law, there is a biphasic response to light irradiation that positive biostimulating effects depend on a proper dose which is neither excessive nor inefficient [35, 36]. Analgesic results have been reported with fluences widely ranging from 1 to 138 J/cm^2, while considering wound healing and anti-inflammatory effect, the effective fluences are suggested to range from few mJ/cm^2 to ten or a little more J/cm^2 to trigger all the biochemical and cellular mechanisms [37–39]. A fluence lower than 12.9 J/cm^2 applied for the RAS laser therapy might result in a more efficient outcome in clinical practice; however, it will be a further study to verify the supposition.

However, we still cannot confirm the proper or optimal parameters of this special device on RAS treatment from only one RCT. Besides, it was not possible to perform a conclusion from the results of the previous studies because there were no researches assessing the efficacy of lasers with similar parameters. Therefore, it is necessary to explore the appropriate parameter list for each optional laser device to promote the application of laser therapy on RAS. Furthermore, there is still a long way to go in laser therapy and more studies concerning ideal parameters (wavelength, power, energy density, etc.) of laser and treatment frequency are particularly needed.

Conclusion

An 810-nm diode laser with the chosen parameters in our study had better effects on pain relief comparing with triamcinolone acetonide 0.1% on RAS. However, there is no distinct advantage concerning on wound healing.

Authors' contributions Huo Xiao: Conceptualization, methodology, software, data curation, writing—original draft preparation, investigation, supervision, writing—reviewing and editing.

Han Ning: Software and data curation.

Liu Li: Conceptualization, writing—reviewing and editing, and project administration.

Funding This work was supported by two funding projects: (1) Project supported by Hebei Key Research Development Program. (Grant No. 18277776D); (2) Project supported by government for cultivating excellent talents in clinical medicine (Grant No. 2019061441-2).

Compliance with ethical standards

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

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and has been approved by Medical Ethics Committee of Hospital of Stomatology, Hebei Medical University.

Consent to participate Both written and verbal informed consent were obtained from every participant.

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