

Original Article

Low-Level Diode Laser Therapy (LLLT) versus Topical Corticosteroids in the Management of Recurrent Aphthous Stomatitis Patients: A Randomized Controlled Trial

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Abstract:

Objectives: The current study was conducted to evaluate the effect of low-level laser therapy (LLLT) on recurrent aphthous stomatitis for reduction of pain score and ulcer size.

Subjects and Methods: 28 participants with symptomatic minor recurrent aphthous ulcers were randomly allocated into two groups. The treatment group received a 980 nm diode laser and the control group received topical triamcinolone acetonide 0.1%. The measured outcomes included pain score as visual analog scale (VAS) at baseline, second day, and seventh day, and the lesion size at baseline and seventh day.

Results: A statistically significant difference was found between the laser and the corticosteroid groups when comparing VAS scores on day two (pain reduction was -2.2 ± 0.9 and -4.786 ± 1 for corticosteroid and laser groups respectively with a p -value of 0.001) and day seven (pain reduction was -4.643 ± 1.646 and -6.071 ± 1.439 for corticosteroid and laser groups respectively with a p -value of 0.024) in favor of the laser group. Moreover, a statistically significant difference was noticed between the laser and the corticosteroid groups regarding the decrease in lesion size (lesion diameter reduction was -3.036 ± 1.447 and -4.536 ± 1.846 for corticosteroid and laser groups respectively with a p -value of 0.024) in favor of the laser group. Two participants experienced severe mouth dryness after corticosteroid application. None of the laser patients experienced any side effects.

Conclusion: LLLT can be considered a reliable alternative to topical steroids in the management of recurrent aphthous ulcers since it was more effective in reducing both pain intensity and ulcer size.

Keywords: Recurrent aphthous stomatitis; Low-level light therapy; Recurrent aphthous ulcer; Diode laser; Triamcinolone acetonide

Introduction:

Recurrent aphthous stomatitis (RAS) is painful, idiopathic, recurrent, inflammatory ulcerations of the oral cavity. The lesion appears clinically as a round or oval-shaped ulcer with erythematous borders. RAS is classified into minor (<1 cm), major (> 1cm), and herpetiform (Edgar et al.,

2017). As a painful experience, RAS can compromise the quality of life due to its interference with day-to-day life activities (Zwiri, 2015). The mainstay of managing RAS is to decrease the pain sensation and to achieve a more swift healing process in addition to decreasing the number of episodes (Amorim dos Santos et al.,

2020). Treatment of RAS includes many medications such as corticosteroids, antiseptics, and anti-inflammatory agents. Multivitamins are also used based on the evidence of the deficiency of certain nutritional elements in RAS patients. Antibiotics and corticosteroids are provided in both topical and systemic forms. Systemic therapy is reserved for cases with more severe symptoms and more frequent episodes. Nevertheless, some of these agents have limitations due to their side effects or their minimal effect on decreasing recurrence (Huo et al., 2021). Topical corticosteroids are the most widely-used medications for managing RAS (Chiang et al., 2019). They exert a local anti-inflammatory effect with minimal systemic absorption, so they are used for treating many oral inflammatory conditions including RAS (Hamishehkar et al., 2015). However, frequent or long-term use of these medications in the oral cavity can result in undesirable side effects such as oral candidiasis (Oflooglu et al., 2017). Recently, Low-level Laser Therapy (LLLT) has been proven to be effective in treating a multitude of illnesses. This is due to its proven role in inflammatory modulation, improving tissue regeneration, the healing process, and pain relief. These are results of activation of cellular proliferation, changes in levels of inflammatory mediators, and improving tissue oxygenation (Slebioda & Dorocka-Bobkowska, 2020).

The low energy emitted from LLLT can guarantee safety and prevent any complications after therapy (Ahmed et al., 2020). Other types of laser, like Diode, Nd: YAG, and non-contact non-ablative CO₂ lasers have been used in the treatment of RAS (Tezel et al., 2009). This is because the laser enhances both reepithelization and pain relief. Exposure to a low-powered laser is believed to stimulate tissue reepithelization. It has been postulated that a low-power laser may improve tissue reepithelization by increasing respiratory metabolism which upregulates the

mitotic activity, epithelial proliferation, and collagen formation (Tezel et al., 2009). It is suggested that the pain relief caused by laser exposure is due to the electrical activity alteration in the neurons (Aggarwal et al., 2014). Another suggested pain relief mechanism by LLLT is enhanced ATP synthesis in the mitochondria due to the photo-receptors in the mitochondria absorbing the red and infrared wavelengths which result in a hyperpolarization status and the obstruction of action potential and hence the pain sensation (Wei Yu et al., 1997). A third proposed mechanism involves prostaglandin E2 and interleukin-1 (IL-1) beta inhibition (Shimizu et al., 1995). Diode lasers were found to stimulate aphthous ulcers pain relief and re-epithelization at a very low power setting (Jijin et al., 2016).

There are very few trials evaluating the effect of LLLT on the management of oral aphthous ulcers. So, the current study aimed to investigate the effect of LLLT on recurrent aphthous ulcers for pain and lesion size reduction as compared to topical corticosteroids.

Subjects and Methods:

Study Design:

This study was a randomized clinical trial. The Ethical Committee of the Faculty of Dentistry, Cairo University approved the current study, under approval number 19 2 32, and all procedures were following the declaration of Helsinki. Patients signed informed consent and were educated about the nature and objectives of the study.

Participants:

Patients were recruited from the Oral Medicine Clinic of the Faculty of Dentistry, Cairo University between February 2019 until August 2021. Consecutive patients diagnosed with minor aphthous ulcers were evaluated for study eligibility. Medical history was taken and a

thorough medical examination was performed on all the participants.

Laser therapy was carried out at the Medical Application of the Laser Department, National Institute of Laser Enhanced Science (NILES), Cairo University.

The inclusion criteria of the patients involved diagnosis with symptomatic minor aphthous ulcer/s with a diameter smaller than one cm which appeared a maximum of two days before the day of examination.

Exclusion criteria included patients with major aphthous ulcers, pregnant and lactating women, smokers, patients who were treated with any topical or systemic steroids during the previous month. The excluded patients were treated using topical corticosteroids but were not included in the study. Figure 1 demonstrates the study's CONSORT flowchart

Interventions:

The subjects were randomly assigned to receive either LLLT or triamcinolone acetonide. Simple randomization was done using www.randomizer.org. Allocation concealment was done by placing the treatment assignment in sequentially numbered, opaque, sealed envelopes.

Group A (intervention group) included 14 patients treated with a low-level diode laser with a wavelength of 980 nm using a fiber optic diameter of 320 μ m as shown in Figure 2. The laser application was carried out using diode laser apparatus (an Italian system (Quanta system laser). Before starting the treatment, protective eyewear was used by the patient, the dentist, and the dental assistant. The treatment was done in one sitting consisted of four sessions of low-level laser applications. Each session lasted 45 seconds with a gap of 30-60 seconds between the sessions. The total laser application time was about three

minutes. The laser was applied in a non-contact mode with a 2-3 mm between the laser tip and the ulcer. The laser beam was applied in a continuous sweeping circular motion to cover the entire ulcer surface especially when the ulcer is large. Those 30-60 seconds gap, sweeping motion of the laser beam, and the non-contact mode were used to prevent overheating of the oral tissues (Aggarwal et al., 2014).

Follow up session was performed after seven days. The patients were asked to keep a record of any post-procedural adverse effects over the following seven days.

Group B (control group): included 14 patients who were instructed to use triamcinolone acetonide 0.1% (trade name: kenacort in orabase manufactured by GlaxoSmithKline pharmaceutical industry). All patients were instructed to apply the medication four times a day after meals and at bedtime for one week. They were also told not to drink or eat for at least 30 minutes after treatment application. Neither the patients nor the investigators could be blinded in this study due to its nature; however, the outcome assessor was blinded.

Outcomes:

The primary outcome of this study was pain score which was assessed using the visual analog scale (VAS) which is a scale from 0 to 10, in which 0 means no pain and 10 means intolerable severe pain, while the secondary outcome was lesion diameter in mm measured using a periodontal probe. The pain score was assessed at baseline, two days, and after one week. The lesion diameter was the secondary outcome assessed at baseline and one week.

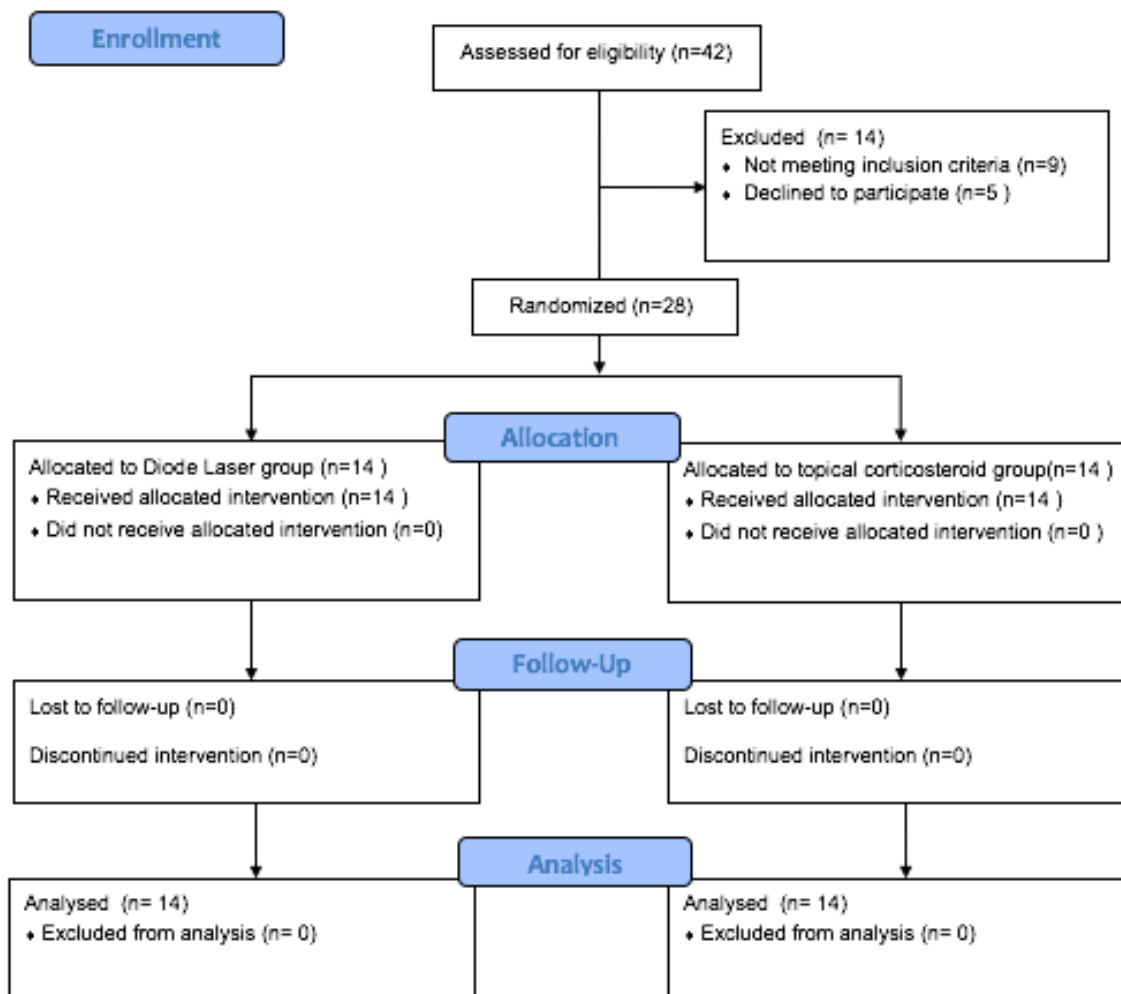


Figure 1: The participants' flow chart

Sample size:

The sample size was estimated based on (Aggarwal et al., 2014). The samples size for each group was 14 participants. Based on (0.02) α error, (95%) power and effect size of (0.4) with two arms and two outcome measures

and expected missing data are around 10% per each group.

Statistical analysis:

Data were explored for normality using the Shapiro-Wilk test. Continuous variables were described as mean and standard deviation if they



Figure 2: Demonstrates the laser device setting (*left*), and the application of the LLLT on the aphthous ulcer (*right*)

were normally distributed or median and range if they were non-normally distributed. The within-group comparison was performed using Wilcoxon signed-rank test

for the diameter and Friedman test for the pain score. The comparison between the two groups was performed using a two-tailed unpaired T-test (for normally distributed data) and a two-sided Mann-Whitney U test (for non-normal data). Confidence interval (CI) was calculated only for the normally distributed data since non-parametric tests are rarely accompanied by CI.

All statistical analyses were done using IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp. Differences were considered to be significant when the *P*-value was less than .05.

Results:

The study comprised 28 patients with the minor type of aphthous ulcer. The demographic data was described in table 1. There was no attrition during the trial. Two participants experienced mouth dryness after corticosteroid application.

No side effects were reported from the LLLT group.

Both groups showed a statistically significant decrease in ulcer diameter compared to the baseline. Also, both groups showed a statistically significant decrease in pain between the different endpoints with a *p*-value <0.001 for the laser group and <0.001 for the corticosteroid group. The comparison between the diameter and VAS at different endpoints for both groups was described in tables 2 and 3.

A statistically significant decrease in lesion diameter was detected between the laser group and the corticosteroid group with a *p*-value of 0.024 as stated in table 4.

A statistically significant decrease in VAS on the second day was detected between the laser and the topical corticosteroid groups with a *p*-value of < 0.001. A statistically significant decrease in VAS on the seventh day was detected between the laser and the topical corticosteroid groups with a *p*-value of 0.024 as stated in table 5.

Discussion:

Laser therapy has been widely used in the dental field due to its unique characteristics of being able to penetrate the tissues and biostimulate numerous beneficial biological processes. LTTT has anti-inflammatory and immunoregulatory capacities with confirmed action in pain reduction, bleeding control, and tissue healing stimulation (De Souza et al., 2010). Many studies demonstrated the use of laser in the management of RAU, but very few compared the effect of LLLT with the topical steroid which is the widely used drug and is considered the first drug of choice in such cases (Agrawal et al., 2019). Hence, this was the rationale behind conducting this study.

Recurrent aphthous ulcer are self- limiting usually heals after 10-14 days (Edgar et al., 2017). Both interventions are hypothesized to shorten the duration of healing. So, seven days interval was chosen to evaluate the effect of both interventions before self-healing. So, day seven timepoint was the most important time point for the lesion diameter evaluation. Regarding pain, many studies as Khaedmi et al., 2009; Aggarwal et al., 2014; Jijin et al., 2016 and Albrektsen et al., 2017 concluded that laser is more significant in reducing the pain after 2-3 days, so say two time point was added for pain score assessment.

Table 1: Demographic data of the two groups

	Corticosteroid group	Laser group	P-value
Age (years)	28.5 ±12.7	30 ± 7.9	0.7
Gender (male %)	36%	14%	0.001*

**Variables are significant when P-values less than .05*

Table 2: Intra-group comparison of the lesion diameter using Wilcoxon signed-rank test

	Lesion diameter (mm)**	
	Corticosteroid group	Laser group
	n=14	n=14
Baseline	3.5 (1,8)	6 (1, 9)
Day 7	0 (0,6)	0 (0, 4)
p-value	<0.001*	<0.001*

**Variables are significant when P-values less than .05*

***Diameter was described as median and range at the timepoints*

Table 3: Intra-group comparison of the VAS differences using Friedman test

VAS**		
	Corticosteroid group n=14	Laser group n=14
Baseline	6.5 (1,8)	6.5 (4,9)
Day 2	3.5 (0,5)	2 (0,4)
Day 7	1 (0,3)	0 (0,2)
p-value	<0.001*	<0.001*

*Variables are significant when P-values less than .05

**VAS (ordinal data) was described as median and range at the timepoints

Table 4: Inter-group comparison of the lesion diameter using unpaired T-test

Lesion diameter difference (mm)**		
	Corticosteroid group n=14	Laser group n=14
Mean ± SD	-3.036 ±1.447	-4.536 ±1.846
p-value	0.024*	
95% CI	[-2.788, -0.212]	

*Variables are significant when P-values less than .05

** Difference in diameter described as mean and SD

Table 5: Inter-group comparison of the VAS using Mann-Whitney test

	Lesion pain difference between baseline and day 2		Lesion pain difference between baseline and day 7	
	Corticosteroid group n=14	Laser group n=14	Corticosteroid group n=14	Laser group n=14
Mean± SD	-2.2 ± 0.9	-4.786 ±1	-4.643 ± 1.646	-6.071 ± 1.439
Median (range)	-1.5 (-1, -4)	-4.5(-3, -6)	-4.5 (-1,-7)	-5.5 (-3, -9)
p-value	0.001*		0.024*	

*Variables are significant when P-values less than .05

The results of the current study showed that there was a statistically significant decrease in lesion diameter and pain scores from baseline to the different study time intervals in each group separately. This is in accordance with the results of the study performed by Arabaci et al., 2009 who compared ND:YAG laser application versus the use of 0.1 % Triamcinolone in the management of aphthous ulcers in patients suffering from Behcet syndrome. They recorded

a statistically significant decrease in pain scores and accelerated ulcer healing in both groups separately after 1, 4, and 7 days.

These results were also confirmed by Khaedmi et al., 2009; Aggarwal et al., 2014; Jijin et al., 2016 and Albrektsen et al., 2017. They all demonstrated the clinical efficiency of LLLT in the reduction of pain intensity with immediate relief on the same day or the few days next to LLLT application. The role of LLLT in

decreasing pain was explained by its action in the increased release of endorphins and enkephalins (Lins et al., 2010). Another postulation is the induced ATP synthesis in mitochondria of neurons, allowing for hyperpolarization and pain stimulus reduction, and even obstruction (Aga, 2007). Furthermore, LLLT was found to cause a reversible change in the voltage-gated Na-K channels leading to inhibition in nerve fibers conduction (Yanagisawa, 2003).

Similarly, the authors also confirmed in their studies the positive impact of LLLT on the acceleration of recurrent aphthous ulcer healing. LLLT application in the management of RAU led to a decrease in the inflammatory cytokines production as IL1, 6, and TNF α . In addition, a significant increase in growth factors and collagen type 1 gene expression, as well as vascular endothelial growth factor (VEGF) production, was detected. Moreover, LLLT was found to induce fibroblast locomotion and promote fibroblast proliferation. (Basso et al., 2016)

In the current study, the lesion diameter decreased more in the laser group than in the steroid group. There was a statistically significant difference between both groups regarding the change in lesion diameter after 7 days in favor of the laser group. Similarly, the decrease of pain scores from baseline to day 2 and from baseline to day 7 was higher in the laser group than the steroid group with a statistically significant difference in VAS scores change in both groups in favor of the laser group whether at second or seventh day. This was confirmed by the randomized controlled trials conducted by Arabaci et al., 2009 and Tezel et al., 2009 who compared the change in pain scores between laser and topical steroid groups in patients suffering from RAU. They found a statistically significant difference in favor of the laser group with immediate and faster relief, while the pain gradually decreased in the steroid group by the

fifth day. Regarding the healing, Tezel et al., 2009 did not evaluate the healing rate nor the lesion size in their study.

In contrast to our study, Arabaci et al., 2009 when compared the healing between both groups, a significant rate of healing was detected in both groups with no statistically significant difference between them. This might be justified by the use of the erythema and amount of exudate to evaluate the healing, unlike our study which used the change in the lesion's actual size. In addition, they applied Nd:YAD laser and the choice in our present study was diode laser.

Moreover, Agrawal et al., 2019 in a prospective clinical study divided 77 patients into two groups, group I was treated with laser, and group II was treated with triamcinolone acetonide 0.1% in orabase. They reported that there was a significant statistical difference in pain score and functional disability between both groups in favor of the laser group whether on the same day or after 3 days. On the opposite side, the healing and reduction in ulcer size in their study showed no statistically significant difference between both groups. The difference between their results and the results of our study concerning the reduction in ulcer size may be attributed to the fact that they monitored the ulcer only 3 days, unlike our study's follow up which was extended to 7 days.

All of these findings confirm the superiority of LLLT over topical steroids in the management of RAU in terms of accelerated pain relief and faster ulcer healing. This goes along with the systematic review conducted by Khaleel et al., 2020 which included five randomized controlled trials comparing laser therapy versus different topical medications which include triamcinolone acetonide among others. In all the included studies, the patients treated with LLLT reported lower pain scores and shorter periods of aphthous ulcer healing.

Conclusions and Limitations:

From the present study results, we can conclude that the laser treatment of recurrent aphthous stomatitis can be an easy, reliable, and effective treatment option with no reported side effects. However, the operator must put into consideration the higher cost of using LLLT when compared to topical steroids and should weigh the benefits in relation to the expenses. In addition, it is recommended to interpret these results putting into consideration the limitations of the study such as the failure of blinding both the investigator and the patients. Further studies with longer follow-up are needed to investigate the impact of LLLT on the recurrence rate of aphthous ulcers.

Conflict of Interest:

The authors declare no conflict of interest

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