Review paper

Low-level laser therapy in the treatment of recurrent aphthous stomatitis and oral lichen planus: a literature review

Zuzanna Ślebioda, Barbara Dorocka-Bobkowska

Department of Gerodontology and Oral Pathology, Poznan University of Medical Sciences, Poznan, Poland

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Abstract

Recurrent aphthous stomatitis (RAS) and oral lichen planus (OLP) present inflammatory, recurrent diseases of the oral mucosa with not fully understood aetiology. Despite numerous attempts to discover an effective treatment for RAS and OLP, the current main treatment strategies are largely confined to the reduction of symptoms. Low-level laser therapy (LLLT) is of interest as a novel treatment modality. The aim of the paper was to discuss the mechanism of action and the biological effects of LLLT and to critically review and summarize recent clinical reports on the management of RAS and OLP. Most of the studies demonstrated the beneficial effect of LLLT in accelerating the healing process and pain reduction. However, the results should be interpreted with caution due to the limited number of studies available and empirical design using various irradiation parameters.

Key words: low-level laser therapy, recurrent aphthous stomatitis, lichen planus, oral pathology.

Introduction

The use of laser therapy, as a strategy to support the standard dental treatment regimes, has recently become very popular. In dental surgery and endodontic treatment, high-power lasers such as carbon-dioxide (CO_2), neodymium-doped yttrium aluminium garnet (Nd:YAG) or erbium-doped yttrium aluminium garnet (Er:YAG) have been commonly used. Meanwhile, semiconductor, low-power lasers are used in the physiotherapy of the oral mucosa and periodontium [1–5]. The history of clinical laser application dates back to the early 1960s, when the first low-level laser was invented by professor Ali Javan [6]. However, the popularization and the scientific acceptance of this treatment method has occurred-only recently [7, 8].

The aim of the paper was to discuss the mechanism of action and biological effects of low-level laser therapy (LLLT) and to critically review and summarize recent clinical reports on the management of recurrent aphthous stomatitis (RAS) and oral lichen planus (OLP). In this review the studies published up to 2017 and obtained from Medline/PubMed online database were searched using the following key words: "laser", "low-level laser therapy", "recurrent aphthous stomatitis", "oral lichen planus" and "lichen planus". Language was limited to English. Randomized clinical trials, prospective studies and case reports were included in the analysis, while the fundamental experimental studies such as animal or cell studies, abstracts, reviews and editorials were excluded. Papers with insufficient information on phototherapy parameter settings or being duplicate studies were not discussed. The results of 21 full-text papers published in peer-reviewed journals are presented in the final summary.

Mechanism of action and biological effects of low-level laser therapy

Laser biostimulation of tissue is achieved by the application of a laser beam with a wave length from 630 to 1100 nm and with a power between 2 and 200 mW. The laser beam, which is monochromatic, coherent and parallel penetrates the tissue at depths up to 6 cm [2, 7, 9]. The penetration depth depends on the tissue vascularization and the energy dispersion by the erythrocytes. According to the first law of photobiology, molecular photoreceptors or chromophores must have absorption bands coinciding with the laser emissions for the pho-

Address for correspondence: Zuzanna Ślebioda DDS, PhD, Department of Gerodontology and Oral Pathology, Poznan University of Medical Sciences, 70 Bukowska St, 60-812 Poznan, Poland, phone: +48 618547039, e-mail: zuzia_slebioda@o2.pl
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tons to be absorbed in order to induce any effect on the living biological system by the laser red or infra-red light [10, 11]. The basic receptors for the laser light in the body are the proteins. It has not been clearly defined what particular cell structures perform this role; most likely the elements of the mitochondrial-cytochrome system are involved. Changes to the redox state of mitochondria and cytoplasm results in the activation of several biochemical reactions, including increased cell proliferation and migration, changes in cytokine levels, growth factors, inflammatory mediators and increased tissue oxygenation [2, 7, 9].

The biological action of low-level laser therapy is multidirectional, although the mechanism of immunomodulation is not fully understood [12]. The laser irradiation results in the stimulation of blood circulation, revascularization, and the growth of nerve cells, fibroblasts and collagen fibres. It improves haemoglobin dissociation and increases the secretion of biological substances relevant in conducting nerve stimuli. LLLT does not result in tissue damage and overheating and it does not cause pain [7, 9, 13].

LLLT modulates the proliferation of fibroblasts, where the low power doses stimulate this process, while the high power doses result in its inhibition. The stimulation of the fibroblast proliferation occurs due to the increased production of basic fibroblast growth factor (bFGF). After the laser biostimulation, the transformation of the fibroblasts into myoblasts is accelerated, which is essential for the wound closure [14]. Moreover, it modifies the activity of macrophages by stimulating them to secrete several factors enhancing the proliferation of fibroblasts. LLLT increases the chemotactic activity of macrophages at the initial phase of healing [14, 15].

Laser therapy stimulates the differentiation of the epithelial cells while not disturbing the regularity of the process such as keratin synthesis. LLLT in low doses accelerates the collagen production which strengthens the scar. In post-operative wounds treated with LLLT the enhanced production of granulomatous tissue, earlier epithelization, efficient production of fibroblasts and active neovascularization have been observed. These processes result in decreased healing time and faster tissue regeneration [7, 14, 15].

The analgesic effect of LLLT results from the inhibition of several nociceptive stimuli, related to the temperature changes and chemical irritations. An increased pain threshold is also related to the stabilization of the cell membranes and regulation of the resting cell potential. LLLT limits the production of the proinflammatory mediators in the damaged nerve cells and it stimulates their maturation and post-traumatic regeneration [13–16].

The mechanism of action of low-level laser therapy may be very beneficial in the treatment of oral erosions and ulcers. Reports of healing acceleration in erosive mucocutaneous disorders are few and often presented as case series rather than large randomized clinical trials (RCTs). The available results referring to skin wound healing and periodontal inflammation management with laser biostimulation conclude that this treatment modality may also be useful for oral erosive conditions [3, 4, 17–19].

Recurrent aphthous stomatitis and oral lichen planus

Erosions and ulcers of the oral mucosa may be a manifestation of various pathologic conditions. Common oral mucosa diseases that occur with the presence of these lesions include RAS and OLP.

RAS is a chronic, ulcerative, inflammatory disease of the oral mucosa which affects between 5% and 20% of the general population [20, 21]. It manifests with recurrent, painful, round or oval erosions or ulcers surrounded with erythematous halo. The etiopathogenesis of this condition remains unclear, but it is probably multifactorial. In patients with RAS an inadequate immunologic response to certain trigger stimuli occurs. This includes mechanical irritation, stress, bacterial, viral or fungal antigens [22–24]. The inheritance of several gene polymorphisms, especially those related to the cytokine encoding genes, may predispose the development of the disease in one family members [20, 25]. Three clinical types of RAS can be distinguished: minor (Mikulicz's, MiRAS), major (Sutton's, MaRAS) and herpetiform (HeRAS). These types vary with lesion size and number during one flare-up, together with their localization and healing manner. The eruptions are painful and significantly decrease the patients' quality of life [22, 26].

Lichen planus is a chronic inflammatory mucocutaneous disease which manifests with pink, flat, itchy papules on the skin in the area of wrists, forearms, dorsal surface of feet, calves, and lumbar region. Intraoral lesions present as white, non-removable striae composed of small papules, which is a primary eruption of OLP. The adjacent oral mucosa may be affected by the inflammation [12, 26]. While the exacerbations, the erosive or bullous forms may develop. The frequency of this condition is estimated to be 1% of the general population. It develops mostly in patients between 30 and 60 years of age. To date the etiopathogenesis of lichen planus has not been clearly understood and it involves both antigen-specific and non-specific mechanisms that include CD8+ cytotoxic T cells activity against keratinocytes, mast cell degranulation and activation of matrix metalloproteinase, which leads to the damage of the basal cell layer in the epithelium. Environmental factors including stress play a crucial role in the induction of the disease exacerbation [12, 27, 28].

The treatment of RAS and OLP is difficult and not always effective. The standard treatment regime includes the local application of steroids and non-steroidal anti-inflammatory agents, together with agents to enhance the epithelial regeneration. The therapy is mainly symptomatic and may lead to several side-effects, including steroid-induced candidiasis [29, 30]. No effective causative treatment option is currently available [12, 25, 28, 31].

LLLT application in RAS and LP

Several articles describing the effects of laser therapy in patients with RAS and LP have been published in recent years. Most were designed as RCTs, some as prospective studies or case series. Diode, Nd:YAG and CO_2 lasers have been utilized in the trials.

Table 1 depicts the most relevant international publications in this matter.

The beneficial effects of LLLT performed with diode lasers reported in RCTs on RAS included: immediate pain reduction and shorter healing time compared to placebo groups [32–36]. Moreover, faster regression of lesions in comparison to patients treated with corticosteroids (4 days vs. 5–7 days) was reported by De Souza *et al.* [37]. Also in two case series presented by Anand and Babu, pain relief and faster healing time, compared to previ-

Table 1. Studies on laser therapy effects in the treatment of RAS and OLP

Author	Study population	Country	Study type	Laser used	Results	Year
RAS:						
Aggarwal *et al.* [32]	30	India	RCT	Diode	Immediate pain relief and rapid reduction in the lesion size in the test group	2014
Albrektson *et al.* [33]	40	Sweden	RCT	Diode	Significant pain relief in the test group	2014
Al Mulla *et al.* [34]	147	Kuwait	RCT	Diode	Significant pain relief in the test group	2012
Anand *et al.* [38]	2	India	Case series	Diode	Pain reduction and shorter healing time compared to previous episodes	2013
Arabaci *et al.* [46]	28	Turkey	RCT	Nd:YAG	Pain relief and faster healing time in the test group	2008
Babu *et al.* [39]	4	India	Case series	Diode	Pain relief and faster healing time compared to previous episodes	2015
De Souza *et al.* [37]	20	Brazil	RCT	Diode	Pain reduction and reduced healing time in the test group	2010
Kashmoola *et al.* [40]	35	Iraq	RCT	Diode	No significant differences in healing time between study groups and controls	2005
Khademi *et al.* [35]	24	Iran	RCT	Diode	Reduction in healing time, pain intensity and pain relief time in the test group	2009
Lalabonova *et al.* [36]	180	Bulgaria	RCT	Diode	Significant pain relief and reduced healing time in the test group	2014
Muńoz Sanchez *et al.* [58]	252	Cuba	RCT	Diode	Reduced healing time in the test group	2013
Prasad *et al.* [42]	25	India	RCT	CO2	Immediate pain reduction and reduced healing time in the test group	2013
Sattayut *et al.* [43]	14	Thailand	RCT	CO2	Significant pain relief in the test group; no difference in the lesion sizes	2013
Tezel *et al.* [47]	20	Turkey	RCT	Nd:YAG	Significant pain relief in the test group	2009
Zand *et al.* [41]	15	Iran	RCT	CO2	Immediate, significant pain relief in the test group	2009
OLP:						
Cafaro *et al.* [27]	30	Italy	Prospective	Diode	Reduction in clinical symptoms defined by visual analogue scale (VAS)	2014
El Shenawy *et al.* [56]	24	Egypt	RCT	Diode	Laser less effective than conventional steroids in pain reduction	2015
Fornaini *et al.* [52]	19	Italy	Prospective	Diode	Reduction of discomfort according to the NRS scale	2012
Kazancioglu and Erisen [55]	120	Turkey	RCT	Diode	Laser less effective than conventional steroids and ozone in pain reduction	2015
Mahdavi *et al.* [54]	2	Iran	Case series	Diode	Pain reduction, shift from ulcerative LP to reticular LP	2013
Misra *et al.* [59]	1	India	Case report	Diode	Total pain reduction	2013

ous episodes, was reported by all the RAS subjects who underwent diode laser stimulation [38, 39]. Significant advantages of LLLT regarding pain reduction and healing time acceleration were achieved despite the different ranges of power applied, contact or non-contact use of the laser tip and a various period of irradiation. The suggested parameter settings ranged from 40 mW to 0.5 W of power output, wavelength between 670 and 810 nm, energy between 1,.5 and 1.6 J, exposure time between 40 s and 3 min (with short intermissions) [32–39]. Contrary to the above-cited authors, Kashmoola *et al.*, who examined 35 RAS subjects in Iraq, did not observe significant differences in healing time between study groups and controls [40]. The diode laser used in that study had an average diode power of 8 mW and wavelength of 904 nm. Laser irradiation with the energy of 1.5 J for 5 min was applied in the study subgroups on two following days. Considering the results of previously cited studies this observation is unexpected. Lack of any significant difference in the healing time between laser-treated and untreated RAS subjects suggest that the dose and other parameters of LLLT implementation influence the effectiveness of the therapy. It should be also emphasized that most of the cited studies were performed on a relatively low number of patients, therefore for more conclusive results a necessity to perform more extended observation in this field is evident.

Attempts to manage RAS with CO_2 lasers in a non-contact, non-ablative manner, where the mucosa was protected from the heat produced by laser with a thick layer of transparent gel, also resulted in significant pain reduction with sustained analgesic effects and accelerated healing processes [41–43]. Zand *et al.* observed immediate reduction of pain directly after the laser irradiation with the power output after passing through the gel at a level of 2–5 mW. A single session of 10600 nm CO_2 laser operated at 1 W power, 5–6 mm distant from the mucosal surface in a continuous mode and spiral motion of a de-focused hand piece, was used for 5–10 s in this study. The differences remained significant between the study and placebo groups during the next 96 h post-operatively [41]. Also Prasad and Pai who used CO_2 laser with a reduced wattage compared to the previously described study (0.7 W, 5–8 s) reported immediate and significant pain reduction in RAS patients after a single session of laser irradiation. Moreover, the healing time was also significantly reduced in the study group compared to placebo [42]. Suggested mechanisms which explain the analgesic action of non-ablative CO_2 laser include the direct effect on the exposed nerve endings present in the aphthous ulceration, suppression of inflammatory mediators or, less probably, the destruction of the nerve endings. The healing process is supported by the laser irradiation via various paths described in the section "Mechanism of action and biological effects of low-level laser therapy (LLLT)" above. It includes the stimulation of blood circulation, revascularization, and the growth of nerve cells, fibroblasts and collagen fibres. Meanwhile, no differences in the time of lesion size reduction between the tested groups were observed by Sattayut *et al.*, who reported only the analgesic effect of LLLT. However, significant differences in the pain perception appeared not immediately (like in the previous studies) but after 3 days of irradiation with a de-focused 10.6 micron CO_2 laser in a continuous wave mode (2 W, 5 s) [43]. High density of energy used in this study (110.67 J/cm^2) could explain the inhibitory effect of pain relief rather than stimulation of wound healing as in several *in vitro* studies it was demonstrated that while the low doses of low-intensity laser promoted the cellular proliferation, the doses over 16 J/cm^2 inhibited the process. A contrary effect was observed in relation to the prostaglandin E2 production, which was stimulated at lower and inhibited at higher energy density [44, 45].

The use of Nd:YAG laser stimulation in the two RCTs also caused the pain relief and faster healing time in the test group compared to controls [46] and a significant analgesic effect in the study group [47]. Arabaci *et al.* who used the following irradiation parameters: power output: 2 W, energy: 100 mJ, frequency: 20 Hz, emission mode: pulsed, irradiation time: 2–3 min, and a contact mode of application, reported immediate and significantly higher pain reduction in the RAS group treated with laser compared to controls who received topical corticosteroids [46].

Malignant diseases and precancerous lesions are listed as contraindications for LLLT since it stimulates the growth of cells, therefore, according to some authors, the use of this treatment modality should be generally avoided in patients with OLP [9]. The stimulating effect of LLLT on various cell lines is dose-dependent and still not well understood. For example, in a Powell *et al. in vitro* study on selected cell lines, certain doses of laser increased the proliferation of human breast adenocarcinoma, however multiple exposures had either no effect or showed negative dose response relationships and generally no sign of malignant transformation of cells by laser phototherapy was detected in the study [48]. Although a number of studies suggest an increased risk of oral squamous cell carcinoma (OSCC) related to OLP, only a few researches demonstrated significant differences in comparison to a general population [49, 50]. This risk varies between 0% and 12.5% and this large heterogeneity of results is caused, among the others, by ambiguous diagnostic criteria or various follow-up periods used in different medical centres [50]. Based on the recent meta-analysis by Aghbari *et al*., only a small subset of OLP patients (1.1%) develop OSCC [51].

The described effects of LLLT in the treatment of OLP included the reduction of pain and discomfort and – in most cases the remission of exacerbated lesions [27, 52–54]. Soliman *et al.* observed marked clinical improvement in over 60% of examined patients with OLP after diode laser irradiation [53]. In their case report series, Mahdavi

et al. observed a shift from ulcerative OLP to reticular OLP after LLLT [54]. However, in the two described RCTs the analgesic effect of diode laser therapy was less evident than in case of standard topical steroidal treatment [55, 56]. Moreover, Kazancioglu and Erisen found that it was also less effective than ozone therapy [55]. Most commonly used diode laser settings were as follows: output power of 300 mW, wavelength between 630 and 980 nm, the power density of 1 W/cm^2 and repeated mode of application [27, 54, 56]. As in case of RAS, the beneficial effects of LLLT in the treatment of OLP could be explained by dose-dependent lowering of prostaglandin E2 and interleukin 1β levels at the peripheral level, modification of metabolism and release of serotonin and acetylcholine at the central level, and by the reduction of oxidative stress [55, 56].

Although the benefits of using CO_2 lasers in a non-contact, non-ablative manner for several erosive mucosal conditions, such us RAS, Behçet's disease, pemphigus vulgaris or mucositis have been reported, not much is known on the effect of that treatment modality in OLP [7, 9]. Meanwhile, a traditional, high-power CO_2 approach to treat recurrent, erosive OLP was suggested by Mücke *et al*. who observed a decreased risk of malignant transformation and reduced rate of recurrences in subjects who underwent CO_2 laser vaporization compared to controls on topical, symptomatic treatment. The authors defined this treatment option as an independent significant factor reducing malignant transformation in OLP. In this study 9.4% out of 171 OLP subjects developed oral squamous cell carcinoma: 2 (2.9%) patients after continuous defocused CO_2 laser treatment and 14 (13.6%) patients undergoing conservative treatment only [57]. It must be emphasized however that laser vaporization instead of biostimulation was studied in this research, therefore a potential effect of malignant cell growth stimulation was not observed here. The use of LLLT in erosive OLP as a potential premalignant condition remains controversial.

Conclusions

Low-level laser treatment has been used for lesions of an inflammatory nature, not as an inhibitor of the process, but as a modulating action and reparative effect on tissues. Based on the research presented, it seems that LLLT presents as a reasonable treatment modality both in RAS and OLP and could be incorporated into a standard treatment algorithm under these conditions. Based on the studies presented, the beneficial effects of LLLT were more evident in the case of RAS than in OLP, where in the two cited RCTs laser therapy was less effective than topical steroidal treatment. Pain reduction and acceleration of healing in the case of recurrent exacerbations are extremely relevant to the quality of life in patients with RAS and OLP. Further studies are required to define the efficacy of LLLT in the treatment of RAS and OLP in comparison to more traditional, anti-inflammatory treatment modalities that also include topical steroidal therapy. Since lasers were first introduced into dentistry it has become necessary to establish simultaneously most useful and least harmful irradiation parameters, including wavelength, energy density, continuous or pulsed mode, time of exposure and focal spot. A diversity of LLLT parameters used in the presented studies impede the unambiguous interpretation of the results.

It should be emphasized however that LLLT helps to reduce the symptoms of existing diseases without addressing the cause. Therefore, there is an urgent necessity to develop an effective, causative treatment for RAS and OLP.

Conflict of interest

The authors declare no conflict of interest.

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