Tikrit Journal
for
Dental Sciences
https://tjo-ds.com

Impact the Role of Diode Laser on Management of Herpes Labialis

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Article Info:
-Article History:
-Received: 15/6/2020
-Accepted: 12/7/2020
-Available Online: */7/2020
Keywords:
Diode,Laser,Herpes labialis, Oral Medicine, Viral, Dentistry.
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Abstract
Recurrent herpes labialis is a worldwide life-long oral health problem that remains unsolved. It affects approximately one third of the world population and causes frequent pain and discomfort episodes, as well as social restriction due to its compromise of esthetic features. In addition, the available antiviral drugs have not been successful in completely eliminating the virus and its recurrence. Currently, different kinds of laser treatment and different protocols have been proposed for the management of recurrent herpes labialis. Therefore, the aim of the present article was to review the literature regarding the effects of laser irradiation on recurrent herpes labialis in comparison to the effect of acyclovir. The literature was searched with the aim of identifying the effects on healing time, pain relief, interval of recurrence. According to the literature, none of the laser treatment modalities is able to completely eliminate the lesion and its recurrence. However, laser phototherapy appears to strongly decrease pain and the interval of recurrences without causing any side effects.

Introduction:

Recurrent herpes labialis (RHL) occurs in 20% to 40% of the young adult population. The lesions have prodromal symp-toms, including itching, tingling or burning in 50% of cases and eventually develop papules, vesicles, ulcers, and crust. The pain often exists during the first two days [(1)]. Internal or external stimuli such as stress, immunosuppression, high fe-ver, trauma, and ultraviolet light can trigger recurrences[(2)]. The lesions usually resolve within 7 to 10 days [(3)]. Although RHL is a self-limiting condition, the use of topical antiviral medications reduces viral shedding and infectivity. These agents also decrease pain level, lesion size and duration of symptoms [(1)]. Antiviral medications such as acyclovir cream 5% and docosanol cream 10% can be beneficial if initiated during the onset of lesions. Since these agents have relatively a short half-life, they should be used several times throughout the day [(1)]. Risk of drug nephrotoxicity should be considered for systemic administ-ration [(4,5)]. Low level laser therapy (LLLT)

has been considered as a possible treatment for herpes labialis in recent years. The laser phototherapy has analgesic and anti-inflammatory properties and stimulates tissue regeneration, fibroblast proliferation and neo-vascularization potential [6]. Many studies have examined the influence of LLLT wavelengths on herpes labialis. Dougal and Lee [2] as-signed 87 patients with herpes labialis randomly in two groups. They used a low level laser, 1072 nm, for the experi-mental group. The control group was treated with the laser turned off. The experimental group showed a significant reduction in healing time. Muñoz Sanchez et al. [7] conducted a study in 2012 in which they compared the effect of LLLT, 670 nm, on herpes labialis with acyclovir. They reported that LLLT was an effective therapy with no side effects. This study aimed to evaluate the effect of Low level laser therapy on the treatment of patients with herpes labialis compared to acyclovir cream.

Conventional antiviral therapy

The conventional treatment for RHL is based on the prescription of antiviral compounds. The available treatments do not cure latent HSV infections, but rather palliate symptoms or prevent recurrences. Most drugs developed to act against HSV are antiviral agents called nucleosides and nucleotide analogs, which block viral reproduction. The most prescribed medications against RHL include acyclovir, valacyclovir, and famciclovir. The antiviral drugs are effective and reasonably safe when properly administered. However, these medications differ in their chemical structure, dosage and cost [8, 9– 12]. Topical and systemic acyclovir, at a variety of concentrations and dosages, has been used in the treatment of RHL with variable outcomes. For most dentists, selecting an appropriate type and drug delivery format (intravenous, oral, or topical) can present a dilemma because the intermittent administration of antiviral medications does not alter the frequency of recurrences and usually only demonstrates a good response when applied before the onset of vesicles [9,11,13,14]. There are antiviral medications available in pill form that were particularly developed for genital herpes treatment but are also used for herpes labialis [10]. The oral medication acts by stopping virus growth [10]. These medications may also significantly decrease the severity of a primary outbreak and the number of days that the virus can be transmitted. In addition, the medications reduce the healing time, which consequently decreases painful symptoms. Nevertheless, antiviral medication is most effective if it is taken when the patient first notices the prodromal symptoms (tingling and pain) of RHL outbreak and if medication is taken for the next 5–7 days or until the symptoms are gone [10, 18–20, 22, 23]. Although most patients with RHL do not have a need for systemic medication, it can be prescribed to patients with frequent recurrences (>6 per year) who experience severe pain or disfigurement, have difficulty in swallowing, or have experienced a protracted disease course [18]. Of all patients with herpes labialis, 5– 10 % have frequent recurrences [19]. When the recurrences affect the patient's quality of life, ad-ministration of systemic medication may be appropriate for those psychologically distressed by their disease [4, 20]. The development of new compounds that are effective against HSV is still a challenge for the scientific community and pharmaceutical industry. The development of a vaccine would be the most effective management of HSV infections Nevertheless, the HSV candidate vaccines developed until now have mostly been purified subunit vaccines and/or recombinant envelope glycoproteins (such as gB and gD) that, in different animal model experiments, resulted in protection against acute virus challenge along with a reduction in latency [21]. The immunotherapeutic effects of herpes vaccines are still not reliable. Therefore, the addition of adjutants that shift cytokine production of helper T cells towards stimulation of cytotoxic T Cells (TH1-type cytokine response) may be more promising [27]. Existing efforts for the most favorable combination of HSV-1 glycoproteins, presented as recombinant

proteins or DNA vaccines, with immunostimulatory cytokines are yielding incremental, yet significant, gains in biological activity in animal models [10, 21]. Antiviral agents reduce viral replication by inhibiting viral DNA synthesis, which is essential for viral reproduction. Limiting reproduction helps to keep the virus inactive or la-tent. Acyclovir and penciclovir have a similar mechanism of antiviral action against HSV, as extensively reported in the literature [16,22,23]. The resistance of HSV to acyclovir can happen, and almost all resistance occurs as a result of adeficiency in thymidine kinase [7]. Nearly all clinical HSV isolated with resistance to acyclovir have been obtained from patients who have received prolonged acyclovir therapy [7, 24–27]. Essential to a successful therapeutic intervention for RHL is an accurate anamnesis for assessment of the patient's overall health and the extent of clinical disease [20, 28]. There is a requirement for additional randomized controlled trials to establish the most appropriate means of treating and preventing HSV-1 infection in both immune competent and immunocompromised individuals [10]. As mentioned previously, many antiviral agents are available for the treatment of HSV-1 infection. Despite these treatments being effective, drug-re-sistant strains have been found, and there is no available vaccine for this troublesome viral infection. Recently, laser phototherapy has been suggested as a promising therapeutic measure for both the prevention and episodic management of outbreaks.

Laser phototherapy—mechanisms of action

HSV treatment with lasers is based either on heat production (high-power lasers) or on the photochemical and photobio logical effects of laser light (low-power lasers or "defocused" high-power lasers). Regarding laser phototherapy (LPT; without heating), it has been suggested that its effect is based on its capacity to modulate various metabolic processes by the conversion of the laser light energy into useful energy to the cell. Visible laser light is absorbed by chromophores in the respiratory chain of the mitochondria, leading to fundamental changes, such as increasing reactive oxygen species (ROS), ATP synthesis, cell membrane permeability changes, and nitric oxide release [29]. These effects produce a number of secondary effects: changes in extracellular matrix synthesis, in-creased action potential of nerve cells and new formation of capillaries through the release of growth factors, local effects on components of the immune, vascular and nervous system, and an increase in intracellular Ca2+ and cyclic adenosine monophosphate levels [30], which are related to various bio-logical processes such as RNA and DNA synthesis, cell mitosis, and protein secretion [31, 32]. This cascade of cellular events accelerates cell proliferation, which promotes healing. The laser differ in wavelengths that used for therapeutic purposes as follow:

Low power diode lasers (MediCom a.s., 2012) BioScan – 670 nm/70 mW for superficial applications

The energy of a red light-emitting laser is absorbed in superficial layers of skin and tissue (penetrating to less than 1 cm). A 70 mW output provides a sufficient power reserve to achieve biostimulating effects. Most suitable for: corrective dermatology, cosmetology, dermatology, aesthetics, plastic surgery, and surgery. Frequent applications: acne, biostimulation of skin, burns, decubitus, dermatitis, eczema, Laser Mask application, post-op treatment, scar treatment, and ulcus cruris.

BioScan – 830 nm/450 mW for deep-seated applications

An infrared laser is an ideal tool for the irradiation of deep-seated tissue structures. A high power output makes even the most demanding pathologies treatable in a relatively short time. A simultaneously irradiated red-laser pilot beam pro-vides exact control over the treated area. Most suitable for: physiotherapy, rehabilitation, rheumatology, sports medicine, and orthopaedics. Frequent applications: arthritis, arthrosis, back and neck pains,

locomotive apparatus disorders, post-traumatic conditions, and myorelaxation.

High-power 980 nm surgical laser system Quanta – Polysurge (Quanta Systems S.p.a., 2012)

A high-power 980 nm surgical laser system which can deliver optical power up to 200 W at an output of 600 μm fibre. The emission mode can be pulsed or continuous. The 980 nm wavelength has a particular characteristic: it can be absorbed in a similar way by water and haemoglobin. Because tissues contain a high percentage of water, it is important for a surgical laser to be absorbed by water to ablate tissues properly. The light absorption of the same wavelength by haemoglobin is also important for coagulation and successful haemostasis [(48)]. The effect of LPT depends on the physiological state of the cell at the moment of irradiation [(33, 34)]. This suggests that laser therapy works with a considerable effect in cases of stressed cells. Injuries can be induced in many ways, including physical agents (e.g. skin incisions) and infections [(30)]. LPT can be advantageous because its therapeutic window for anti-inflammatory actions overlaps with its ability to improve tissue repair and pain relief. In addition to these benefits, LPT has been shown to be a simple and atraumatic technique in the treatment of oral lesions and is well tolerated by patients. The anti-inflammatory effect of LPT could be partially due to an increase in circulation and inhibition of PGE2 synthesis [(35, 36)]. The analgesic effect of LPT is still not totally clear in the literature. It has been shown that peripheral nerve stimulation by a laser alters the hyperpolarization of the cellular membrane and increases the concentration of ATP, which could contribute to maintaining the stability of the membrane and increase the pain threshold [(37)]. The enhancement of ATP production has also been shown to lead to the restoration of neuronal membranes and decreasing pain transmission. Moreover, LPT can enhance peripheral endogenous opioid production [(38)] and decrease serum prostaglandin E2 [(39)]. In addition, Chow et al. have shown that infrared laser light is able to block fast axonal flow, providing a mechanism for a neural basis of laser-induced pain relief the mechanism of action of laser therapy for both the prevention and reduction of the severity of the oral manifestation of the herpes labialis virus is not completely understood. Dannarumma et al. [(41)] investigated the effect of LPT on HSV-1 replication and evaluated the modulation of expression of certain proinflammatory cytokines (TNF-α, IL-1 β, and IL-6), antimicrobial peptide HBD2, chemokine IL-8 and the immunosuppressive cytokine IL-10. The authors suggested that LPT acts in the final stage of HSV-1 replication by limiting viral spread from cell to cell and that laser therapy also acts on the host immune response, unblocking the suppression of proinflammatory mediators induced by the accumulation of progeny virus in infected epithelial cells. It is important to note that LPT follows the Arndt– Schultz law, which means that low doses of irradiation cause no reaction and high doses can elicit an inhibition. Still, a reasonable knowledge of the various parameters involved in LPT is necessary to obtain consistent clinical results [(32)].

Materials and Methods:

1. **Search strategy**

A bibliographical search was performed in google scholar, researchgate, science direct and elsevier using combinations of keywords relating to “laser treatment of herpes labialis”, “Acyclovir treatment of herpes labialis” and “comparing the effectiveness of laser and acyclovir in the treatment of herpes labialis”.

1. **Data collection**

From the initial search, 9 papers were studied and subdivided into 3 different categories:

1. 5 papers about the treatment of herpes labialis using laser therapy.

2. 3 papers about the treatment of laser using acyclovir anti-viral drug.

3. 1 paper comparing the effectiveness of both laser therapy and acyclovir drug in the treatment of herpes labialis.

Results:

Overview of the included studies.

A total of 9 articles were included in this review, characteristics of these articles are included in Table (1). On the Table (1) the last column on the right will be filled numbers, each number will represent the article on the other tables. Table (2) contains the outcomes of each article included in this review.

Discussion:

The results of this study show that oral acyclovir treatment effectively reduces the risk for recurrent herpes labialis in otherwise healthy patients who have frequently recurrent dis-ease. Patients enrolled in the (R8) article had a 53% reduction in the mean number of recurrences while on acyclovir therapy compared with placebo. If herpes labialis is correctly diagnosed, and the appropriate acyclovir dosage delivered early in prodrome, we expect to see a significant clinical effect. Treatment would appear to be more successful the sooner the patient begins with the laser treatment after the start of the herpes infection. Acyclovir is an effective treatment for herpes labialis with a short halflife. In general, these difficulties with conventional medications have directed investigators toward other therapeutic approaches. Attention has been given to laser therapy as a new treatment method for herpes labialis. Low level laser therapy has physiological effects such as anti-inflammatory, analgesic and healing-stimulating characteristics [(6)]. Many studies have evaluated different wavelengths of low level laser on herpes labialis [(7-10)]. This study also aimed to evaluate the effect of diode laser on treatment of patients with herpes labialis compared with acyclovir. The low level laser therapy (LLLT) significantly de-creased the healing time, and pain intensity compared to acyclovir and turned-off laser groups, which is consistent with previous studies. In a study conducted in 2013 by Dougal and Lee [(2)], the ef-fect of diode laser (1072 nm) on herpes labialis was assessed. The results showed that the crust time and healing time for herpes labialis decreased in the laser group compared to the control group.

In a study conducted in 2006 b

The main advantages of laser treatment appear to be the absence of side effects and drug interactions, which are especially useful for older and immunocompromised patients. Although these results indicate a potentially beneficial use of lasers in the management of HSV-1 oral manifestations, they are based mostly on case reports.

Conclusion

There have been a lot of efforts to develop new ways to treat the herpes labialis, decrease the unsatisfied sensation the patient feels during the treatment, eliminating the postoperative complications as well as reducing its recurrence rate. After reviewing all of the included articles we can say that both the laser and acyclovir will treat the herpes labialis but the laser will overcome the acyclovir when it comes to sensation the patients feel, the postoperative complications and the recurrence rate as we mentioned earlier that some studies reported common side effects when using acyclovir cream such as headache, cracked lips and dry lips, and one of the study reported that there has been a serious condition where one of the patient has been adopted to the hospital due to chest pain, while no study reported a single side effect during or after treating herpes labialis using laser therapy. We can say that combining laser and acyclovir will boost the treatment as well as reducing the recurrence rate even more but that we cannot neglect the side effects that may rise from the usage of the acyclovir.

Table (1): Characteristics of the 9 articles.

Authors	Year published	Article title	R
DrSimoneSuppelt	2015	The treatment of herpes labialis with a diode laser (970 nm)	1
Cp Eduardo, Alyne Simoes, et al.	2013	Laser treatment of recurrent herpes labialis	2
Dennis Carvalho Ferreira, Helena Lucia Barroso Reis, et al.	2011	Recurrent herpes simplex infections: laser therapy as a potential tool for long-term successful treatment	3
Arturo Guerra Alfonso, Pedro José MuZoz	2010	Laser Therapy of Human Herpes Simplex Lesions	4
Dr Igor Cernavin	2010	Low-level laser therapy in the treatment of herpes labialis	5
Spotswood L. Spruance, Rob- ert Nett, et al.	2002	Acyclovir Cream for Treatment of Herpes Simplex Labi alis: Results of Two Randomized, Double-Blind, Vehicle Controlled, Multicenter Clinical Trials	6
G. Wayne Raborn, W. T. McGaw, M. Grace, et al.	1987	Oral acyclovir and herpes labialis: a randomized, double- blind, placebo-controlled study	7
James F. Rooney, Stephen E. Straus, Margaret L. Mannix, Charles R. Wohlenberg, et al.	1993	Oral Acyclovir To Suppress Frequently Recurrent Herpes Labialis	8
Marieh Honarmand, Leila Far- hadmollashahi, Ehsan	2017	Comparing the effect of diode laser against acyclovir cream for the treatment of herpes labialis	9

Table (2): The outcomes of each article.

R	Patient Sensation	Number of patients	Post operative Recurrence	Complications
1	Warm, some felt tingling and etching.	22	Some patients required to be treated two, three and some six times.	No complications.
2	Warm, some felt tingling and etching.	322	After one year: 84 recurrences(laser group) ×114recurrences (controlgroup).	No complications.
3	Warm, some felt tingling and etching.	2	No recurrences were observed during the 17 month follow-up period.	No complications.
4	Warm, some felt tingling and etching.	232	2 of the laser treated patients had a recurrence once after one year.	No complications.
5	Warm, some felt tingling and etching.	1	No recurrence on the follow up.	No complications.
6	A little burning sensation.	1051	Recurrence was decreased.	The most commonly reported adverse events in patients using either ACV cream or vehicle cream in each study were headache, cracked lips, and dry lips. One serious adverse event occurred in study 2: a patient treated with ACV cream was hospitalized with chest pain.
7	A little burning sensation.	210	Recurrence was decreased.	One female patient had arthritis like pain in the fifth finger, proximal joint, of the right hand 2 days after treatment began and Another female patient believed that her lesions were getting worse after therapy.
8	A little burning sensation.	56	53% reduction in the mean number of clinically documented recurrences	No adverse effects were noted
9	----------	60	They suggested that laser therapy reduced recurrence rates, relieved symptoms.	Has no side effects.

Table (3): The conclusion from each article.

R	Articles about laser treatment	R	Articles about acyclovir treatment
1	Significantly decreased recurrence in comparison to acyclovir.	6	Patients treated in one week with decreased recurrence.
2	Interim between the relapses increased significantly in patients treated with laser in relation to patients treated with acyclovir.	7	Patients treated in one week with decreased recurrence.
3	Medications and laser therapy (LLLT) could reduce the severity and recurrence of lesions, however Acyclovir remains the drug of choice for HVS, but it is expensive and may induce viral resistance.	8	53% reduction in the mean number of clinically documented recurrences.
4	Laser is much more effective in the treatment of herpes labialis.		
5	Found that low-level lasers had an effect similar to Acyclovir on labial and facial areas as well as on genital areas.		
9	It is noteworthy that in the turned-off laser group on the fifth and sixth days, only 2 patients were still under treatment, respectively. The other participants' lesions had developed crust on the fourth days	9	On the fourth, fifth, and sixth days, only 3 patients were still under treatment, respectively considering their lesion, and the other patients of this group had recovered during the first three days of treatment.

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