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Does low-level light therapy accelerate healing time of oral herpes simplex lesions?

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine- Georgia Campus
Suwanee, GA

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ABSTRACT

OBJECTIVE: The objective of this selective evidence-based medicine review is to determine whether or not low-level light therapy accelerates healing time of oral herpes simplex lesions.

STUDY DESIGN: Review of three randomized control trials between 2006 and 2013.

DATA SOURCES: Three randomized, double-blind and semi-blind control trials found via PubMed.

OUTCOMES MEASURED: The primary endpoint measured was healing time, which was defined as time for oral herpes lesions to fully resolve and underlying skin to become completely re-epithelialized.^{3,4} The secondary endpoint measured time it took lesions to crust over.^{3,4} One study also measured recurrence of lesions over a one-year time period.⁶

RESULTS: Two randomized control trials showed statistically significant ($P=0.014^3$, $P=0.048^4$) reduction of healing time with direct application of 1072-nm light on the lesion using a Virulite CS device for three minutes, three times daily for two days. This therapy reduced healing time by 48-72 hours compared to placebo.^{3,4} The other randomized control trial found that direct application of a 670-nm diode laser on the lesion, as well as radiation over C2-C3 vertebrae, resulted in completely healed lesions in one week and a large reduction in recurrence over a one-year period compared to treatment with commonly-used agents, including acyclovir cream and tablets.⁶

CONCLUSION: Review of these articles concludes that direct application of low-level light therapy significantly accelerates the healing time of oral herpes simplex lesions. This therapy exhibited great patient satisfaction, as they did not have to endure unsightly facial lesions for a long duration of time, and their symptoms of pain and burning were significantly reduced. Another added benefit of this therapy is patient acceptance, as patients reported simple usage and denied any negative effects of the light therapy.

KEY WORDS: herpes labialis; light therapy

INTRODUCTION

Oral herpes, known more commonly as cold sores or fever blisters, is caused by herpes simplex virus type 1 (HSV-1). These lesions typically present as small vesicles on the vermilion border of the lip atop an erythematous base.³ They can also occur in the perinasal and periorbital areas, however the perioral area is the most common sight of infection.³ Before the lesion becomes visible, people infected by the virus experience a prodrome of burning and tingling at the site of infection.³ Once visible, the blisters can be very painful, but most patients are more concerned about the unsightly appearance of these lesions. The blisters later rupture, creating a crust over the lesion; this crust formation is the beginning of the healing process.³ The average healing time without treatment is 10-14 days.² Because they occur on the face, they are difficult to conceal and can greatly affect patients' self-confidence.

The virus is transmitted via skin-to-skin contact, most likely when one person has an active lesion.³ However, it is still possible to transmit the virus to another person even if there is no blister present, as infected patients continuously shed the virus.⁹ Many patients are unaware of this fact, which likely leads to increased transmission.

This virus is incredibly frustrating for patients, for once they are infected,³ they will never be able to eradicate the virus from their bodies. It lies latent most commonly in the trigeminal nerve dorsal root ganglion.⁶ The trigeminal nerve has three branches, each of which distribute to different areas of the face bilaterally. The virus will establish itself in one of these branches, which is why patients with HSV-1 have unilateral outbreaks in the same areas each time (i.e. the left lower lip, right upper lip).⁹

During times of stress, sun exposure, high fever, or any triggers that cause the patient to become immunosuppressed, the virus can become reactivated and travel down the nerve, which

causes the prodrome and then the lesion appears.⁶ Once the lesion has healed, the virus moves back into the dorsal root ganglion and waits for another episode of immunosuppression, where it can become reactivated again.⁶ Hence, there is no cure for the virus, and patients must battle this vicious cycle for the rest of their lives.

HSV-1 is very common in the United States, as 60% of people are infected.⁶ 150 million people suffer from cold sores every year, and there are 380 million outbreaks worldwide.² There is estimated to be about 500,000 primary infections per year in the United States; primary infections are defined as the first HSV-1 outbreak a patient experiences.² This outbreak tends to be the most severe, and patients may experience fever, swollen glands, and bleeding gums in addition to painful lesions.⁹ The outbreaks thereafter are not associated as commonly with systemic symptoms.

Because so many patients are infected with herpes simplex virus type 1 and there is no cure for the virus, it is imperative to have effective treatments to reduce recurrence and severity of outbreaks. Currently, there are topical and oral agents available to patients. Some topical agents include over-the-counter abreva (Docosanol) and prescription denevir (Penicyclovir). These agents are thought to act by “inhibiting the fusion of the human host cell with the viral envelope of the herpes virus, thereby preventing viral entry into cells and therefore replication.”¹ Oral agents include valtrex (Valacyclovir), famvir (Famcyclovir), and acyclovir. These agents work to “inhibit herpes viral DNA replication by competitive inhibition of viral DNA polymerase and by incorporation into and termination of the growing viral DNA chain.”⁸ A newer agent called Sitavig (acyclovir) is a muco-adhesive buccal tablet that has the same mechanism of action as the oral agents; however, it is placed on the upper gum and dissolves

directly into the oral mucosa, thereby reaching the site of the cold sore directly and reducing systemic distribution.⁷

Although these treatments have proven to be medically effective, they are not necessarily cost-effective. The average patient has two to six outbreaks per year, so they are constantly purchasing and seeking prescription refills for these medications.² In the United States, more than \$1 billion is spent every year on antiviral medication to treat HSV-1.² Furthermore, some of these therapies are only effective if used during the prodrome phase before the lesion appears, and many patients may not begin therapy quickly enough.⁶ Oral agents also pose the threat of nephrotoxicity if adequate hydration is not provided.³ Topical agents require constant reapplication, which is inconvenient and not aesthetically pleasing for patients. For these reasons, along with the fact that patients are affected emotionally by unsightly lesions, a new, effective, and affordable therapy option is needed. Low-level light therapy (LLLT) is a promising solution to battling this lifelong virus.

The pathophysiology of LLLT as a treatment option for herpes labialis is not yet fully understood, but many proposals have been discussed, and it appears it may have multiple mechanisms of action. Munoz et al states that LLLT “acts in the final stage of HSV-1 replication by limiting viral spread from cell to cell, and laser therapy acts also on the host immune response to unblock the suppression of pro-inflammatory mediators induced by accumulation of progeny virus in infected epithelial cells.”⁶ Dougal et al supports this hypothesis by stating that LLLT “seems to enhance the natural immune response against skin infection by increasing primary cytokines that are activated promptly after bacterial or viral intrusion.”³ In addition, an increase in vascular endothelial growth factor (VEGF) was also noted in previous studies in Dougal et al;³ VEGF stimulates production of new blood vessels, which increases blood flow and oxygen to the

wounded sites, thereby accelerating the repair process.³ Dougal et al also proposes that LLLT may have a protective effect on human lymphocytes via an increase in nitric oxide, making lymphocytes more viable when acting against HSV-1 infections.³

OBJECTIVE

The objective of this selective evidence-based medicine review is to determine whether or not low-level light therapy accelerates healing time of oral herpes simplex lesions.

METHODS

These studies included people age 20-65 with a history of recurrent orofacial herpes infections and whom have had at least three outbreaks within the past year.^{3,4} Only lesions affecting the lips were included.^{3,4} The patients were required to live nearby for three weeks after entering the trial, as well as be readily contactable via telephone and/or email.^{3,4} Patients were excluded from the study if they did not agree to use only the proposed therapy, had been on any antivirals or systemic steroids recently, had any major systemic illness, had ever received radiotherapy or chemotherapy, or had any diagnosis of malignancy.^{3,4} Patients were also excluded if their lesion had been present for over 36 hours before initiating treatment.

The interventions studied were direct application of 1072-nm light to the lesion via a Virulite CS device, as well as 670-nm diode laser treatment.^{3,4,6} These techniques were compared to placebo light therapy with dummy LEDs in an identical device, acyclovir tablets, antiviral cream, and other palliative therapies.^{3,4,6} The studies measured the length of time it took for lesions to heal completely, which was further defined as the time it took for underlying skin to become completely re-epithelialized.^{3,4} Dougal et al and Hargate also measured the time it took for a crust to form over the HSV-1 lesion.^{3,4} Munoz et al continued with a prospective study to see how often patients had recurrences over one year after undergoing laser treatment versus

other modern-day treatment options (acyclovir tablets, antiviral cream, etc.).⁶ All studies were randomized; Dougal et al and Hargate were double-blind control trials, and Munoz et al was semi-blind, which will be further explained in “Outcomes Measured.”^{3,4,6}

All articles are published in peer-reviewed journals from 2006-2013 and are published in English. They were discovered on PubMed using key words “herpes labialis” and “light therapy.” The articles being reviewed were selected because they include patient-oriented evidence that matters (POEMs), and these articles are relevant to the clinical question I have proposed. Inclusion criteria for selecting these articles includes randomized control trials that evaluate the use of low-level light therapy as an effective treatment for oral herpes lesions. Articles that were published more than 15 years ago were excluded. Statistics reported include P-value, confidence interval (CI), and mean and median difference in healing time between interventions.^{3,4,6} Table 1 represents the demographics and interventions of the studies selected.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Dougal et al (2013) ³	RCT	87	20-65	At least three cold sore outbreaks within the past year; pts were required to be living near the trial for three weeks after entering, as well as be readily contactable via telephone and/or email; only cold sores affecting the lips were included.	Cold sore present >36 hours; pts did not agree to use only the proposed therapy, had been on any antivirals or systemic steroids recently, had any major systemic illness, radiotherapy or chemotherapy, or had any diagnosis of malignancy; cold sores	7	1072-nm light via Virulite CS device applied directly to the lesion for three minutes, three times a day for two days

					affecting the nose, face, chin		
Hargate (2006) ⁴	RCT	32	N/A	Same as above.	Same as above.	5	Same as above.
Munoz et al (2012) ⁶	RCT	232	N/A	Pts affected by herpes simplex type I virus who attended the clinic "Leonardo Fernandez" in Cienfuegos, Cuba during the period from January 2001 to January 2003.	Blisters outside of the actual lip areas	0	670-nm diode laser treatment- Prodromal and vesicle stage: 40mW, 1.6J, 2.04 J/cm ² , 51 mW/cm ² , spot size 0.79 cm ² x40 seconds; Crust stage and secondarily infected lesions: 40mW, 4.8J x two minutes; All patients also received radiation over C2-C3 vertebrae, where the latent virus tends to reside in the trigeminal nerve.

OUTCOMES MEASURED

The outcomes measured in Dougal et al and Hargate include healing time of lesions, which is defined as the time from initial presentation to complete skin re-epithelialization, as well as the time it took for the lesion to crust over.^{3,4} Patients were told to contact the researcher within 24 hours of developing an HSV-1 lesion; this allowed enough time for the patient to be seen by the researcher to confirm the lesion, have a photograph taken, and initiate therapy before the 36-hour mark.^{3,4}

Once the lesion was confirmed, patients received either the active (Virulite CS) or placebo device and were instructed to use it accordingly. Both devices were identical. Additionally, 1072-nm light is invisible to the human eye, so patients could not tell whether they were being treated with 1027-nm light versus dummy LED lights.⁴ Volunteers were instructed to

apply the lit device to their lesion three times daily for two days, with each application lasting three minutes; both the active and placebo devices emitted an identical sound to denote the end of each three-minute treatment cycle.^{3,4} Volunteers were then seen or contacted by telephone every two to three days and were asked to report the time it took for crust to form, as well as when the crust fell off and the underlying skin was uninterrupted and regenerated.^{3,4}

Munoz et al measured how many patients achieved complete re-epithelization after seven days, and they also monitored patients over a one-year period to measure the number of recurrent outbreaks.⁶ Patients were randomized to the 670-nm laser treatment group or the control group, which offered treatment with oral and topical acyclovir and other palliative treatments, including anesthetic cream.⁶ Patients in the control group were also advised to avoid hot and spicy foods.⁶ To maintain a semi-blind study, there were three dentists involved as researchers; the first dentist confirmed the lesions, the second provided the indicated treatment, and the third dentist was responsible for evaluating the results of treatment.⁶ Patients in the laser group were seen and treated daily until they were clinically and subjectively asymptomatic; the energy and duration of therapy they received was dependent on the state of the lesion.⁶

In the prodromal and vesicle stages, 1.6 Joules of 670-nm light was applied for 40 seconds daily.⁶ Once patients entered the crusting stage of healing or if the lesions became secondarily infected, 4.8J for two minutes daily was given.⁶ Volunteers also received 1.2J of radiation over the C2-C3 vertebrae for 30 seconds at each visit, as the virus is thought to reside in these nerve ganglia when it enters the latent phase.⁶

RESULTS

All three articles reported continuous data that could not be converted into dichotomous data. Dougal et al reported median time to two endpoints to demonstrate the progression of

healing.³ The primary endpoint was defined as complete underlying skin re-epithelization (also known as healing time), while the secondary endpoint involved median time to crust formation over the lesion.³ All volunteers were randomly assigned to the active or placebo group. The active group initially included 41 volunteers whom would receive the 1072-nm LLLT, but three were excluded because they presented 36 hours after the onset of the cold sore, and three were lost to follow-up.³ The placebo group contained 46 patients at first, but one was excluded because the lesion was not a cold sore.³ The median healing time for the active group, in which volunteers received the 1072-nm light therapy, was 129 hours.³ The placebo group had a median healing time of 177 hours.³ This difference of 48 hours demonstrates a statistically significant reduction in healing time with a p-value of 0.014 and a 95% confidence interval of 10.7-85.3.³ The median time to crust formation was 48 hours for both groups, which is not significant (p=0.66).³

Hargate measured similar endpoints; however, they reported the mean time to achieve each endpoint rather than median time.⁴ The active group included 14 patients, but one patient had not healed at last follow-up, and one was excluded by criterion.⁴ The placebo group contained 18 patients at first, but three had not healed at last follow-up.⁴ Mean complete healing time for the active group was 6.33 days versus 9.40 days for the placebo.⁴ This is a statistically significant reduction with a p-value of 0.048.⁴ The confidence interval for the difference in mean healing time is 0.2-5.9.⁴ Mean time to crust formation for the active group was 2.00 days versus 2.88 days for the placebo group; this almost achieves statistical significance with a p-value of 0.059.⁴ Table 2 compares the statistically significant findings of these two studies.

Munoz et al studied 670-nm light therapy versus acyclovir tablets, acyclovir cream, and other palliative treatments (control therapy).⁶ There were 232 patients chosen for the study, and

they were randomly placed in the laser group or control group by a computer program (116 in each group).⁶ After seven days of treatment, zero patients in the laser group presented with visible signs of HSV-1 lesions, whereas many patients in the control group were still in the process of healing.⁶ Of the control group, 77 patients still had vesicles, 29 had crust formation, and 10 had secondary infections after seven days of acyclovir and palliative therapy.⁶ In addition, there were 84 episodes of recurrent outbreaks in the laser group versus 114 recurrences in the control group over a one-year period.⁶ This is broken down further by frequency of recurrence, demonstrated in Table 3.

Hargate and Munoz et al reported that none of the patients involved in the studies reported any negative side effects from the LLLT they received, and it was well-tolerated overall.^{4,6}

Table 2. Mean/Median Healing Time with 1072-nm LLLT Versus Placebo

	Dougal et al (Median healing time) ³	Hargate (Mean healing time) ⁴
Active group (1072-nm LLLT)	129 hours (=5.375 days) N=35	6.33 +/- 2.99 days N=12
Placebo group (dummy LED light)	177 hours (=7.375 days) N=45	9.40 +/- 4.58 days N=15
95% Confidence interval	10.5-85.3	0.2-5.9
P-Value (<0.05= statistically significant)	0.014	0.048

Table 3. Recurrence Frequency Compared for Patients of Both Groups in Munoz et al⁶

	Once a month	Every 2-3 months	Every 4-5 months	Every 6 months	Once a year	First time ever	No recurrence
Laser group	0	0	37	22	25	0	32
Control group	6	21	46	27	14	0	2

DISCUSSION

The results from all three studies suggest a promising new treatment for herpes simplex virus type 1 oral lesions. It appears the pathophysiology behind the use of LLLT to treat HSV-1

is becoming more understood; the next step is obtaining FDA approval and making the device available to patients.

The articles reviewed did not discuss whether these devices would be available by prescription only or over-the-counter. Insurance currently covers a percentage of the cost of prescription antiviral pills and creams, so it is acceptable to believe insurance companies would eventually cover another treatment option that is less expensive in the long-run and more effective for patients. This will require more research and proven benefits of LLLT, but the results are promising. The Virulite CS device is already approved by the Council of Europe and is available to the general public, so availability in the United States likely will not be an issue once LLLT becomes a widely accepted therapeutic option for HSV-1.⁴

Low-level light therapy has been used in other skin-related treatments, including hair loss, wrinkles, acne scars, and burns.⁵ The proposed increase in VEGF via LLLT provides more blood flow and oxygen to the scalp, thereby increasing hair growth.⁵ In addition, LLLT activates stem cells, electron transport, adenosine triphosphate, nitric oxide release, and other diverse signaling pathways to increase tissue repair and healing.⁵ LLLT can also treat vitiligo by inhibiting autoimmunity that causes hypopigmentation while also increasing pigmentation by increasing melanocytic proliferation.⁵ It has also been proposed that LLLT can be used to decrease the pain of diabetic peripheral neuropathy, as it increases cytokines and growth factors, leading to vasodilation and improved circulation.³ These proposals are promising to many areas of medicine, as LLLT has minimal, if any, adverse effects, is well-tolerated, and is efficacious.

All three articles suggest that LLLT accelerates healing time of HSV-1, but there are some limitations in each study. Dougal et al and Hargate received their results by patients reporting the status of their lesions every two to three days.^{3,4} Patients' feedback is subjective,

and they may not have completely understood the endpoints being measured or taken note of the exact time their lesions crusted over or were completely healed. Also, the patients were allowed to administer the indicated treatment to themselves at home, so there is no way of knowing if they used their device exactly as instructed. The sample sizes in each were also small, so replicating these studies with a larger group will provide more conclusive results and allow for a narrower confidence interval. The concealment and blinding of these studies appears to be well-executed. Munoz et al seemed to focus more on the recurrence rates of HSV-1 lesions rather than actual healing time of the lesions, so their results for healing time were cut off after the seven-day mark and therefore are incomplete.⁶

CONCLUSION

The result of this review suggests that low-level light therapy does indeed accelerate healing time of oral herpes simplex lesions by two to three days.^{3,4} It appears to have the added benefit of reducing recurrence of outbreaks as well, which is very encouraging for patients affected by the stubborn virus.⁶ The Virulite device is battery-operated, so it is a one-time purchase with a long shelf-life, thereby reducing cost for those whom will battle HSV-1 lifelong.⁴ It is well-tolerated and simple to use, and the most encouraging factor of all is that LLLT seems to be more efficacious than current treatment modalities.⁶ In future studies, it would be beneficial to follow subjects for years as they continue to use LLLT to treat their cold sores, paying extra attention to any adverse reactions reported. Currently, it appears that LLLT provides great benefit without any risk, which is exceptional. If future studies confirm this, it will expand research of using LLLT to treat a variety of patients in numerous areas of medicine.

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