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**Is Phototherapy an Effective Treatment for Herpes Simplex Labialis?**

Sarah Landis

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences-Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**Objective:** The objective of this evidence based medicine review is to determine if laser phototherapy is an effective treatment for herpes simplex labialis.

**Study Design:** Review of one case study published in 2009, and two randomized controlled trials published in 2010 and 2013. All studies were published in English.

**Data Source:** One case study and two randomized controlled trials were retrieved from PubMed database to write this EBM review

**Outcomes measured:** Decreases in healing time or size based on patient reporting, scoring systems, or photo documentation.

**Results:** The study conducted by Marotti *et al* determined that the use of laser phototherapy decreases healing time and size of the herpes simplex labialis lesions. In the study by De Carvalho et al, there was a significant difference in monthly average size of the lesions between the groups ( $p=0.013$ ). The study performed by Dougal *et al* showed a significant difference in healing time between the groups ( $p=0.01$ ).

**Conclusions:** Laser phototherapy is an effective and well tolerated treatment for herpes simplex labialis outbreaks.

**Key Words:** Phototherapy, Herpes Simplex Labialis

## **Introduction**

Herpes simplex labialis, colloquially referred to as the “cold sore” is a viral infection most commonly of the trigeminal nerve ganglion. The virus produces uncomfortable, embarrassing, and unsightly vesicular lesions that can recur throughout the lifetime of the patient, particularly during times of stress or immune system compromise. It affects an estimated 20-40% of the U.S. population.<sup>1</sup>

Herpes simplex labialis (most commonly HSV-1) is acquired most commonly through oral contact, often during childhood.<sup>2</sup> It can also be passed to the genitals during oral sexual contact.<sup>2</sup> During the primary infection, replication occurs in the epithelium of the lips, face, and oral mucosa.<sup>3</sup> From this replication, viral progeny invade the basal epithelium and peripheral nerves.<sup>2</sup> Virions additionally migrate to the trigeminal nerve ganglion, where they integrate into the host and enter into a latent phase.<sup>3</sup> The virus can then become reactivated throughout the host’s life, especially in times of stress or immune system compromise. During reactivation, the virus migrates peripherally down axons where it forms vesicular lesions on the lips or oral mucosa.<sup>3</sup>

It is difficult to quantify the healthcare associated costs and office visits of herpes simplex labialis, as lesion etiology can be either HSV-1 or HSV-2, although most commonly HSV-1. Either etiology is potentially possible, since cold sores could be HSV-2 contracted from oral sexual contact. Therefore, the classification of viral etiology by location and therefore associated costs and office visits can be challenging to distinguish. Additionally, the reported estimated costs for HSV are typically combined for cold sore and genital herpes.

Signs of herpes simplex labialis outbreaks include a burning, tingling, or itching on the lip or oral mucosa just prior to eruption. Painful vesicles then form on an erythematous and indurated base. The vesicles rupture, leaving an open ulceration on the lip. These outbreaks cause patients to seek medical

care for treatment of vesicular lesions, pain, and to hasten healing time. Treatment of infections typically includes systemic and/or oral anti-virals are used, such as famciclovir, acyclovir, valaciclovir, or penciclovir. However, there is always a concern for the development of drug resistance.

Although the former are traditional treatments for herpes simplex labialis, laser phototherapy may be a new turning point in the treatment of cold sores. This thesis uses two randomized control trials and a case report to compare the effectiveness of laser phototherapy to other traditional methods of treatment for herpes simplex labialis.

### **Objective**

The objective of this EBM review is to determine if laser phototherapy an effective treatment for herpes simplex labialis.

### **Methods**

The studies used in this thesis are two randomized controlled trials (RCTs) and one case study. Search strategy methods were based on the population of interest, interventions, comparisons between the control and experimental groups, and the outcomes of the studies. The population of interest was patients with herpes simplex labialis greater than or equal to 18 years old. The interventions included phototherapy treatment using various wavelengths of light. The experimental group received laser phototherapy for treatment, whereas the control group received an alternative, such as a traditional medical treatment (anti-viral) or no treatment. The outcomes measured were decreasing the healing time and/or size of herpes simplex labialis lesions.

The study conducted by Marotti *et al* was a case report that followed 4 patients referred from the School of Dentistry of the University of Sao Paulo between the ages 21-52 with herpes simplex labialis.<sup>1</sup> Inclusion criteria required patients to be in the vesicular stage when treatment began, and exclusion

criteria determined that participants could not be past the vesicular stage of an outbreak.<sup>1</sup> Treatment for each patient included rupture of the vesicles, application of 0.01% methylblue solution to the lesion(s) for 5 minutes, followed by a phototherapy session using a 660 nm laser for over 2 minutes at 4 points for a total of 4 treatments.<sup>1</sup> The 4 laser treatments occurred at initial presentation, after 24 hours, 72 hours, and 1 week later.<sup>1</sup> There was no control group for this study.<sup>1</sup> To evaluate the efficacy of the study as well as patient healing progress, visible improvement was documented with photographs of the patients' lips.<sup>1</sup> Photographs were taken before intervention, after the application of methyl blue solution, immediately after phototherapy treatments and/or 24 hours post laser treatment, and 1 week post laser treatment.<sup>1</sup> One of the participants had a photograph showing improvement 6 hours status post laser phototherapy.<sup>1</sup>

The study conducted by de Carvalho *et al* was a RTC from March 2003 to July 2004 that included 71 patients referred from the School of Dentistry of the University of Sao Paulo with an average age of 28.8 years. Inclusion criteria required patients to have recurrent outbreaks, with at least 3 in the past year, and exclusion criteria required that participants were not experiencing a first-time outbreak, had a previous laser phototherapy treatment, or previously used systemic acyclovir as treatment.<sup>5</sup> The experimental group included 41 patients and was treated with 1 session of phototherapy per week for 10 weeks using a GaAlAs laser at 750 nm, 60 mW, with a beam size of 0.4 cm<sup>3</sup>.<sup>5</sup> The duration of laser exposure was either 2 or 3 seconds, depending on the stage of the lesion.<sup>5</sup> Lesions were treated for 3 seconds if the participant was experiencing a prodrome, or had vesicles or crusts.<sup>5</sup> Lesions were treated for 2 seconds for any other stage.<sup>5</sup> The laser was exposed to 30 different points on the participants' lips: slightly above the vermillion border, through middle of the lip, and at the transition to the labial mucosa.<sup>5</sup> Patients in the control group included 30 patients who were treated with topical

5% acyclovir five times per day.<sup>5</sup> The lesions were measured based on size using a scoring system: 0 = absent, 1 = small (0.1-2.0 mm), 2 = medium (2.1-5.0 mm), and 3 = large (>5.0 mm).<sup>5</sup>

The study performed by Dougal *et al* was a RTC from January 2007-May 2008 that included 87 patients over the age of 18 years old who were recruited from general practice surgeries and the general public.<sup>4</sup> Inclusion criteria involved patients with only recurrent oro-facial herpes simplex labialis (lip lesions only) who had 3 or greater outbreaks within the last year.<sup>4</sup> Exclusion criteria involved other locations of herpes simplex, usage of anti-retroviral treatment or systemic steroids, a major systemic illness, radiotherapy or chemotherapy, or diagnosis of malignancy.<sup>4</sup> Patients contacted the study researchers within 24 hours of an outbreak. A nurse or research team volunteer would see the patient within 36 hours of reporting an outbreak and approve initiation of treatment with the hand-held 1072 nm laser device or placebo.<sup>4</sup> The participants were treated with phototherapy using a hand-held light source of even intensity for 3 minutes per treatment that was prescribed for home use by the patient three times per day for 2 days.<sup>4</sup> The experimental group with 41 participants was exposed to the active LED 1072 nm infrared light source 3 times per day for 2 days.<sup>4</sup> The control group with 47 participants was exposed to an identical appearing LED light source without the infrared laser component (a “dummy LED”) 3 times per day for 2 days.<sup>4</sup> The variable examined in this study was healing time, defined by the time that it took for the herpes simplex labialis lesions to fully resolve with the underlying skin to “completely re-epithelialize.”<sup>4</sup> Participants were seen every 2-3 days, at which point they reported a healing time, recorded in hours.<sup>4</sup>

The articles obtained for this EMB review were searched for in PubMed. I chose these particular articles because each one was able to help to answer my clinical question, involved patient orientated outcomes, and could be practiced within the scope of the PA practice. Key words used to search and

obtain articles included “phototherapy” and “herpes simplex labialis.” All of the articles were published in English between 2009 and 2013 in peer-reviewed journals. Inclusion criteria involved patients with recurrent herpes simplex labialis outbreaks who were greater than or equal to 18 years old. Patients were excluded from my search who had genital herpes, a first time labial outbreak, or studies that used other methods in conjunction with phototherapy treatments. Data from de Carvalho *et al* and Marotti *et al* studies were reported as continuous and could not be converted to dichotomous data. The study conducted by Dougal *et al* was reported as continuous data and was converted into dichotomous data that reported the ABI, RBI, and NNT. The statistical data was reported in p-values.

**Table 1: Demographics and Characteristics of Included Studies**

Study	Type	# Patients	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
de Carvalho (2010) <sup>5</sup>	Randomized Control Trial	71	Avg. 28.8	Recurrent herpes simplex labialis; >18 yo	1 <sup>st</sup> time outbreak, previous laser phototherapy treatment, or systemic acyclovir treatment	0	2 or 3 second phototherapy sessions 1x/wk x 10 wks using a GaAlAs laser at 780nm, 60mW, 0.4 cm <sup>3</sup>
Dougal (2013) <sup>4</sup>	Randomized Control Trial	87	>18	Recurrent oro-facial herpes simplex (lip lesions only) with at least 3 episodes in the last year; >18 yo	Locations of HSV other than oro-facial area, anti-retroviral tx or systemic steroids, major systemic illness, radiotherapy or chemotherapy, diagnosis of malignancy	7	3 minute phototherapy sessions TID x 2 days with a hand-held device containing a LED 1072 nm infrared laser
Marotti (2009) <sup>1</sup>	Case Report	4	21-52	Patients in the vesicular stage of a herpes simplex labialis outbreak; >18 yo	Patients past the vesicular stage of an outbreak	0	Manual rupturing of vesicles, methyl blue solution application, followed by 4 sessions of phototherapy (initial presentation, 24 hrs, 72 hrs, & 1 wk) using a 660 nm laser. Session duration=2 mins.

### Outcomes Measured

The goal of the study by Marotti *et al* was to evaluate the patient healing process (healing time + size) based on visible improvement by documentation with photographs of the patients' lips.<sup>1</sup>

Photographs were taken both after the application of methyl blue solution and after phototherapy treatment for this assessment.<sup>1</sup>

de Carvalho *et al* compared size of the herpes simplex labialis lesions status post laser phototherapy versus the control group using topical 5% acyclovir.<sup>5</sup> The lesions were measured based on size using a scoring system: 0 = absent, 1 = small (0.1-2.0 mm), 2= medium (2.1-5.0 mm), and 3 = large (>5.0 mm).<sup>5</sup>

The study performed by Dougal *et al* compared healing time between each group. Healing time was defined by the time that it took for the herpes simplex labialis lesions to fully resolve with the underlying skin to “completely re-epithelialize.”<sup>4</sup> Healing time was recorded in hours.<sup>4</sup>

### Results

The study by Marotti *et al* demonstrated that patients with herpes simplex labialis who were treated with laser phototherapy experienced a faster healing process, with decreased healing times and size. The treatment was well tolerated without adverse effects and lesions healed for all participants by 1 week post-treatment. None of the patients withdrew from this study.<sup>1</sup>

**Table 2: 1 Week Status-Post Laser Phototherapy Treatment**

Variable Measured	Case 1	Case 2	Case 3	Case 4
Decreased healing time and size after 1 week	Completely healed	Completely healed	Completely healed	Completely healed

In the study conducted by de Carvalho *et al*, there was a statistically significant difference in the monthly average size of the herpes simplex labialis lesions between the experimental and control groups (p-value = 0.013).<sup>5</sup> The monthly average lesion size for the experimental group was 0.122, as compared to the control group lesion size which was 0.223.<sup>5</sup> The treatment was well tolerated without adverse effects.<sup>5</sup> None of the participants withdrew from the study.<sup>5</sup>

**Table 3: Comparison of Monthly Average Lesion Size**

Experimental group monthly average lesion size	Control group monthly average lesion size	p-value
0.122	0.223	p=0.013

In the study by Dougal *et al*, there was a significant difference (p-value = 0.01; 95% CI 10.7-85.3) in healing time between the experimental (129 hours) and control groups (177 hours).<sup>4</sup> The use of the active LED infrared light source decreased healing time by 48 hours.<sup>4</sup> By days 6-7, 74.2% of the of the experimental group participants experienced healed lesions, as compared to 44.0% of the control group.<sup>4</sup> The relative benefit increase was 68.6%, which shows an increase in the rates of positive outcomes.<sup>4</sup> The absolute benefit increase was 30.2%, which shows that there was a beneficial effect for patients using laser phototherapy as treatment.<sup>4</sup> The number needed to treat was 4, which indicates that 4 patients need to be treated in order to prevent an adverse outcome.<sup>4</sup> The treatment was well tolerated without adverse effects.<sup>4</sup> 7 patients withdrew from this study.<sup>4</sup>

**Table 4: Healing Time Comparison**

	Experimental Group	Control Group	p-value	CER	EER	ABI	NNT	RBI
Healing Time (hours)	129	177	p=0.01	0.44	0.742	30.2%	4	68.6%

**Discussion**

The effectiveness of laser phototherapy for treatment of herpes simplex labialis regarding size reduction and/or decreased healing time of the lesions was examined in this EBM review by evaluating two RTCs and one case study. All three peer-reviewed studies demonstrate significant improvement in lip lesions, which suggests patient oriented outcomes and clinical significance as a potential future cold sore treatment.

The usage of laser phototherapy is part of a new approach in treating herpes simplex labialis outbreaks. The mechanism of action focuses on the photo-bio-modulation effect, which is believed to help improve immune function and consequently, the healing process (reduced size and/or time).<sup>5</sup> The photo-bio-modulation effect works to enhance immune function and collagen synthesis as chromophores of the mitochondria absorb photons, producing ATP and NO, thereby improving and increasing the healing process. This leads signaling pathways to produce leukocytes, endothelial cells, fibroblasts, antibodies, ECM, mast cell degranulation, and increased macrophage activity.<sup>4,5</sup>

Another proposed mechanism regarding the 1072 LED infrared laser shows that it may protect lymphocytes that act as an immune response against herpes simplex labialis outbreaks by increasing iNOS (nitric oxide synthase) after laser treatment.<sup>5</sup> iNOS produces nitrous oxide (NO), which can be an apoptosis inhibitor, thereby preserving lymphocytes needed for a protective immune response.<sup>5</sup> A third proposed mechanism of the 1072 infrared LED laser may stimulate cytokine activation and cascade to increase the presence of VEGF, TNF-alpha, and IL-6, which all act positively in the immune response against a herpes simplex labialis outbreak.<sup>5</sup>

The study by Marotti *et al* demonstrates that the usage of laser phototherapy is effective in the treatment of herpes simplex labialis lesions by decreasing the healing time.<sup>1</sup> By 24 hours post treatment, all participants had visible improvement of the lesion, and by one week post treatment, the lesions were

almost undetectable.<sup>1</sup> This finding shows that laser phototherapy has faster results than traditional treatments for lesions, which demonstrates patient oriented outcomes.

The study by de Carvalho *et al*, demonstrated that there was a statistical significance between the experimental group receiving phototherapy from the GaAlAs laser versus the control group using 5% acyclovir ( $p=0.013$ ).<sup>5</sup> The monthly average lesions size was reduced to nearly half after using the laser phototherapy treatments.<sup>5</sup> This study provides data that supports the usage of laser phototherapy over the use of a topical anti-viral medication to reduce lesions size over the same period of time.<sup>5</sup> The decrease in size is important to patients, since experiencing smaller lesions is less embarrassing and more comfortable for patients overall.

The study by Dougal *et al* demonstrated that healing time in hours was decreased with the usage of LED phototherapy as compared to a placebo, with statistical significance ( $p=0.01$ ).<sup>4</sup> The time improvement between the two groups was 48 hours, which demonstrates clinical significance and patient oriented outcomes in using phototherapy as cold sore treatment.<sup>4</sup> A full 2 day improvement is an attractive quality to patients considering this form of laser phototherapy treatment.<sup>4</sup>

Although the studies used in this EBM review provide support for the treatment of herpes simplex labialis, there are some discrepancies in study design. The study conducted by Marotti *et al* had some inconsistencies regarding reporting of the photographed results. The participants' photographed results were not all taken at the same point, or extra photographs were taken for some participants over others.<sup>1</sup> For example, case 1 was photographed 6 hours status post treatment, whereas the other cases did not.<sup>1</sup> Also, case 2 had pictures taken *before and after* methyl blue treatment, whereas the other cases only had photographs taken after methyl blue was applied.<sup>1</sup> To enhance the validity of the results,

patients should have been photographed consistently throughout the course of the study and at the exact same time periods.

Additionally, the study by Dougal *et al* proposed a suggestion that may not be conclusive or valid based on the study design. The authors state that the use of the LED laser is effective at all stages of the cold sore lesion breakout, where as the usage of acyclovir can only begin in the early stages of lesions (i.e. with prodrome or within 72 hours of the lesion appearance).<sup>4</sup> However, this claim is difficult to make since the participants of the study were required to report within 24 hours of lesion appearance and had to be seen by a nurse within 36 hours.<sup>4</sup> This shows that participants of the study could only have a lesion for a maximum of 72 hours, which is also the maximum time that allows for acyclovir to be effective.<sup>4</sup> Since 72 hours was the maximum time participants could have had a cold sore to participate, it is difficult to claim that the laser is effective in all stages of the breakout.

The limitations of using laser phototherapy may hinder its indication for treating herpes simplex labialis in the future. Availability or access to laser phototherapy, guaranteed insurance coverage, and training operators of the machines are all limitations to using this form of treatment. These could be large limitations just for the treatment of a self-limiting lesion that doesn't typically require medically necessary treatment in most patients. Most patients seek treatment in primary care offices for lesion annoyance, discomfort, or cosmetic reasons. However, insurance may deny such a costly treatment for a non-emergent, self-limiting problem that can be treated with inexpensive, prescription topical or systemic antivirals or over the counter topicals such as Abreeva.

A consideration for future studies in laser phototherapy treatments is testing with different wavelengths with the same type of laser or different lasers with the same wavelength. Another future study could evaluate different stages of the cold sore to determine the most effective time to treat lesions

using laser phototherapy. Any of the proposed studies could have an effect on the healing time or size of the lesions, which could change the healing process.

## **Conclusion**

Although there are multiple systemic, topical, and homeopathic treatments available for herpes simplex labialis outbreaks, laser phototherapy may eventually become the new standard of care for cold sore treatment. The classic usage of anti-viral medical therapy for treatments can also lead to viral resistance, systemic drug reactions, and non-compliance of drug application due to cosmetic appearance or frequency. The studies used in this EBM review have demonstrated the effectiveness of laser phototherapy for treatment of herpes simplex labialis. The improved healing time and/or size decrease is important to patients, as herpes simplex labialis lesions are uncomfortable and unsightly for patients. There are limitations to this type of treatment, and perhaps future progressions in medicine and insurance coverage will help to make this type of treatment attainable for the standard of care. Laser phototherapy may also be used in the future as a prophylaxis for those prone to outbreaks. Overall, it is a promising intervention for cold sore treatment and should continue to be studied for the future.

## References

1. Marotti J, Aranha ACC, Eduardo CDP, Ribeiro MS. Photodynamic therapy can be effective as a treatment for herpes simplex labialis. *Photomedicine and laser surgery*. 2009;27(2):357-363.
2. Herpes Simplex Virus. World Health Organization Website. <http://www.who.int/mediacentre/factsheets/fs400/en/>. Published January 2016. Accessed October 9, 2016.
3. Dental care for the patient with an oral herpetic lesion. American Academy of Oral Medicine Website. [http://www.aaom.com/index.php?option=com\\_content&view=article&id=161:clinical-practice-statement--dental-care-for-the-patient-with-an-oral-herpetic-lesion&catid=24:clinical-practice-statement&Itemid=180](http://www.aaom.com/index.php?option=com_content&view=article&id=161:clinical-practice-statement--dental-care-for-the-patient-with-an-oral-herpetic-lesion&catid=24:clinical-practice-statement&Itemid=180). Published November 25, 2014. Updated January 2, 2016. Accessed October 9, 2016.
4. de Carvalho RR, de Paula Eduardo F, Ramalho KM, et al. Effect of laser phototherapy on recurring herpes labialis prevention: An in vivo study. *Lasers in medical science*. 2010;25(3):397-402.
5. Dougal G, Lee S. Evaluation of the efficacy of low-level light therapy using 1072 nm infrared light for the treatment of herpes simplex labialis. *Clin Exp Dermatol*. 2013;38(7):713-718.