

Evaluation of the efficacy of low-level light therapy using 1072 nm infrared light for the treatment of herpes simplex labialis

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Summary

Background. Recent research has shown that low-level light therapy (LLLT) using 1072 nm infrared light is effective in reducing the duration of herpes simplex labialis (HSL) episodes and enhancing the healing process.

Methods. This was a prospective, randomized, placebo-controlled, clinical trial to evaluate the efficacy of a 1072 nm light-emitting diode device for the treatment of HSL. In total, 87 patients with recurrent HSL were recruited and randomly divided into two groups. Subjects received a 3-min treatment with either 1072 nm infrared light therapy or placebo (sham) light therapy three times/day for 2 days. The devices used for both groups were identical in appearance and could not be differentiated by volunteers or researchers, and 1072 nm light is invisible to the human eye. The primary endpoint was healing time, which was taken as the time for the HSL lesions to resolve fully and for the underlying skin to become completely re-epithelialized, and the secondary endpoint was lesion crusting.

Results. The median time to healing for the active group was 129 h, compared with 177 h for the control group, which was significant ($P = 0.01$). There was no difference between the two groups for median time to lesion crusting ($P = 0.66$).

Conclusions. Compared with placebo treatment, the treatment of HSL lesions with 1072 nm infrared light significantly reduced healing time.

Introduction

Herpes simplex labialis (HSL), commonly known as 'cold sores' or 'fever blisters', is a highly prevalent viral infection of the skin that manifests as grouped vesicles, erythema and related discomfort, and is typically caused by herpes simplex virus (HSV) type I.¹⁻³ The most common site of infection is the lip and perioral area, although the lesions can also occur on the perinasal and periorbital area and on other parts of the face when the infection is severe. Recurrent HSL infections of the perioral area occur in up to one-fifth

of young adults, and the virus is reported to persist in up to 40% of the population in the USA.^{1,2} Transmission is through personal contact with a virus-shedding individual. The disease is predominantly acquired in early childhood, and the virus remains dormant in nerve tissue, then reactivates at intervals. Recurrences may be induced by intrinsic and extrinsic factors, such as high fever, trauma, immune suppression, emotional stress and ultraviolet light.^{3,4}

The conventional treatment of choice for HSL is topical and/or systemic aciclovir. Its derivatives famciclovir or valaciclovir are also used.⁵ Although these antiviral agents are effective in treating HSL when used systemically, they carry the risk of nephrotoxicity by crystallization within the tubules of the nephrons if hydration is not sufficiently provided.⁶ This can be problematic in some elderly patients who cannot drink sufficient water by themselves without a caregiver, especially for those who have reduced kidney function because of other conditions such as hypertension or

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diabetes mellitus. Aciclovir is an effective treatment for HSL; however, it has a short half-life, which necessitates frequent application of the topical agent or administration of the systemic agent. Famciclovir and valaciclovir have a longer half-life but are much more expensive, and currently, there are no topical forms of these medications.⁷ Furthermore, because the antiviral agents work more effectively when treatment is initiated as soon as possible after the onset of HSL, delayed treatment can prolong the lesions and associated discomfort. Thus there is a need for new effective treatments that are simpler and easier to use.

It has been reported that low-level light therapy (LLLT) using 1072 nm infrared light from laser diodes reduced the healing time of HSL episodes by about 50% compared with topical aciclovir,⁸ and a follow-up study showed that a commercially available, over-the-counter device, using light-emitting diodes (LEDs) emitting 1072 nm infrared light, was effective for the treatment of HSL, although the study groups were small.⁹ In addition, an *ex vivo* study showed that irradiation with 1072 nm infrared light enhanced the cell viability of peripheral blood mononuclear cells (PBMCs) and increased the levels of inducible nitric oxide synthase (iNOS) suggesting a possible cytoprotective effect; however, the significance of raised iNOS levels is still unclear.

In this study, we evaluated the efficacy of 1072 nm LLLT using an LED device for the treatment of HSL compared to a placebo device.

Methods

The study was approved by South Tees Ethics Committee, and all patients provided informed consent.

Patients

Volunteers were recruited via general-practice surgeries and from the general public by the use of an ethically approved poster. All volunteers were given a patient information sheet and an opportunity to clarify any concerns they had. Recruitment began in January 2007 and follow-up continued until May 2008.

Volunteers had to have a history of recurrent orofacial herpes, with at least three episodes within the past year; be staying within the northeast of England for 3 weeks after entering the trial; be readily and reliably contactable via telephone and/or e-mail and to contact the clinic as soon as they had an outbreak of HSL; and be willing not to use anything to treat their HSL outbreak except the supplied hand-held

1072 nm LED device. Volunteers on any antiviral treatment or systemic steroids, having any major systemic illness, radiotherapy or chemotherapy, or with a diagnosis of any malignancy (except basal cell carcinoma other than in the perioral region) were excluded.

Each eligible subject was allocated to receive one of two treatments, active or placebo without restriction, according to a standard computer generated randomization table. Patient numbers were allocated sequentially, and the two groups ran concurrently. The code was broken after the data were examined for exclusions. The data were examined independently by a medical statistician.

A formal sample size requirement analysis was not carried out prior to the start of the study. The final sample size was arrived at purely on the basis of what was practical within the duration of the study. In total, 87 volunteers were recruited: 41 participants in the study group (7 men, 34 women; mean \pm SD age 40.2 \pm 12.9 years, range 20–65), and 47 participants in the control group (9 men, 37 women; mean \pm SD age 42.8 \pm 11.2 years, range 20–65).

Study design

The interventions compared were treatment with the 1072 nm light (the active Virulite CS device) or placebo, with the treatment carried out for 3 min three times daily for 2 days.

HSL episodes affecting the lips only were included, whereas any HSL episodes affecting the nose, face and chin were excluded. For each HSL episode, the lesion had to be present for \leq 36 h. Consequently, all volunteers were asked to contact the researcher within 24 h of developing an HSL lesion, to enable the nurse to see the volunteer within 36 h of the onset of the outbreak and begin treatment. A medical assessor photographed the HSL lesion at the initial presentation, facilitating confirmation of the diagnosis. After initial evaluation by the researchers to confirm the diagnosis of HSL, the subject received either an active or placebo (sham) device, and was instructed to use it as prescribed. The external appearances of both active and placebo device were identical, and it was not possible for either the volunteer or the researcher to distinguish between them (1072 nm light is invisible to the human eye). The active device used in the trial (Virulite CS; Pacer Therapeutics Ltd, Pangbourne, Berkshire, UK) is a Conformité Européenne (CE)-approved, hand-held LED device, emitting pulsed 1072 \pm 12 nm infrared light. The device has a shrouded treatment

aperture that is placed over the HSL lesion, while an internal microprocessor ensures consistent light intensity and duration, with a timer and automatic treatment cut-off after a 3-min treatment cycle. The end of treatment is denoted by an audible signal. The active devices were pulsed at 600 Hz, with a pulse width of 300 ms. Placebo devices used dummy LEDs with a microprocessor modified to control the 'power on' light, treatment time and audio signal.

Endpoints

Because HSL commonly progresses from erythema and vesicle formation to crusting and finally healing by re-epithelialization, the primary end-point was set as the re-epithelialization of the lesion, defined as when the crust(s) fell off, leaving uninterrupted, regenerated skin. The secondary end-point was set as the crusting of the lesions. The volunteers were seen every 2–3 days, and asked to report the time a crust formed on the lesions and the time the HSL lesions achieved re-epithelialization. The data recorded by the patients were collected and analysed. When recording and creating the data for statistical analysis, we defined 'healing time' as the time between the initial presentation and the time when the volunteer reported that there was re-epithelialization, and 'crusting time' as the time between the initial presentation and the time the lesions crusted.

Statistical analysis

The statistical analysis was performed using Epi Info (version 3.3.2; Centers for Disease Control; <http://www.cdc.gov/epiinfo/html/downloads.htm>) and Excel (2000; Microsoft Corp., Redmond, WA, USA). Because the data were not normally distributed, the Wilcoxon rank sum test was used. The 95% CI for the reduction in median healing time was approximated by assuming normality, i.e. the standard error of the median was estimated as 1.25 times the standard error of the mean, and the sampling distribution of median healing time was assumed to be normal.

Result

Of the 87 volunteers enrolled, 80 completed the trial (Fig. 1). Figure 2 shows the distribution of healing times (in days) for the active and placebo groups.

The median time to re-epithelialization (healing time; primary end-point) was 129 h for the patients

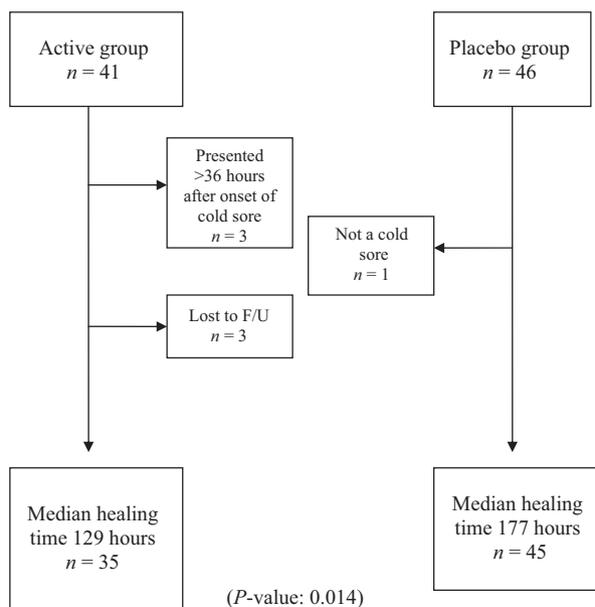


Figure 1 Trial profile.

who used the active device, and 177 h for those who used the placebo device, which was significant ($P = 0.01$; Table 1). Use of the 1072 nm infrared light device reduced the median healing time by 48 h (95% CI 10.7–85.3).

The median time to crusting (crusting time; secondary endpoint) was 48.0 h for both groups ($P = 0.66$; Table 1).

Discussion

HSL infection is generally considered problematic and bothersome by most patients, as it causes not only pain and discomfort, but also an unsightly appearance for a considerable period, which may affect work and social activities.^{1,2} Despite the availability of an effective treatment in aciclovir, its requirement for multiple daily applications (five times/day) and the cosmetically undesirable appearance after application can reduce compliance. Furthermore, in some regions, or indeed under some circumstances such as during working hours, immediate therapeutic intervention may not be possible, thus delaying treatment. Because the antiviral agents work more effectively when they are used as soon as possible from the onset of HSL, treatment delay can prolong the lesion and associated symptoms. Because of the problems of topical medication, some patients prefer oral aciclovir, but this must be taken up to five times per day for 5 days. Other aciclovir derivatives (e.g. famciclovir) are much more expensive

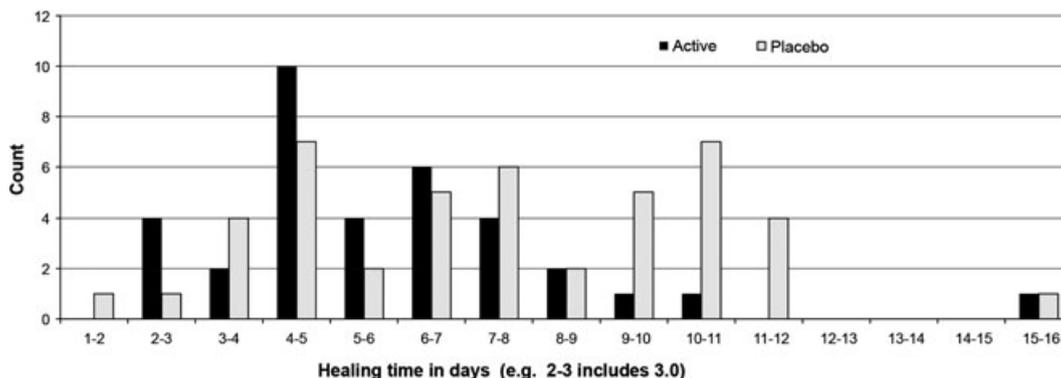


Figure 2 Distribution of healing times (days); active vs. placebo groups.

than aciclovir.³⁻⁵ In addition, the increasing use of aciclovir and famciclovir is thought to be associated with the emergence of drug-resistant herpesvirus strains.¹⁰

The problems with conventional treatments have encouraged researchers to seek other treatment options for HSL. Light and laser therapies have attracted attention as a promising new treatment method for this condition.^{8,9,11-18} For example, the use of photodynamic therapy (PDT) using photosensitive agents (e.g. neutral red, methylene blue) was investigated back in the 1970s, although it did not gain general acceptance at that time because of controversy about its efficacy and unfavourable adverse effect profile

caused by phototoxic reactions.¹¹⁻¹³ More recent studies have investigated PDT for herpesvirus infection using 5-aminolaevulinic acid as the photosensitizer.¹⁴

A number of recent studies that evaluated the effect of light/laser treatment for HSV infection indicated a photobiomodulation effect, rather than a photodynamic reaction, as the possible mechanism of action that may be effective for improving this viral condition.^{8,9,15-18} Photobiomodulation is a process by which the incident photons are absorbed by chromophores (for example, in the respiratory chain of the mitochondria for longer-wavelength visible light and in cellular membranes for near-infrared light, to modulate various cell functions), and is believed to result in enhancement of local immune-cell functions and collagen synthesis, leading to acceleration of the wound-healing process.¹⁹ Schindl *et al.* reported that LLLT with a 690 nm diode laser (10 min daily for 2 weeks) prolonged the recurrence-free period (37.5 weeks with LLLT vs. 3 weeks with sham treatment).¹⁸ Carvalho *et al.* used laser therapy with a 780 nm gallium-aluminium-arsenide (GaAlAs) laser (1 session/week for a total of 10 treatment sessions), noting that it reduced the size and inflammatory oedema of recurrent HSL lesions.¹⁵

In the present study, we investigated the efficacy of 1072 nm infrared LLLT for HSL. We found that the median healing time of HSL lesions was reduced by 48 h. This result confirms our previous studies, where we evaluated the efficacy of this specific wavelength for HSL with a smaller number of subjects.^{8,9}

Current available therapies prevent the development of visible lesions by interfering with replication of the virus, clearly the most desirable outcome. However, studies with aciclovir have shown a limited effect if used late in the lesional stages of the infection, in some instances shortening the duration of the lesion

Table 1 Comparison of healing and crusting times, active vs. placebo.

	Treatment		Difference*	Pt
	Placebo	Active		
Healing time				
Patients, <i>n</i>	45	35		
Median (h)	177.0	129.0	48	0.01
IQR (h)	121.5	84.0		
Mean (h)	180.2	142.6	37.6	
SD (h)	72.5	63.2		
SE of median	13.5	13.4		
SE of difference between medians			19.0	
CI for difference between medians			85.3-10.7	
Crusting time				
Number	33	29		
Median	48.0	48.0	0.0	0.66
IQR (h)	33.0	31.5		
Mean (h)	59.6	49.7	9.9	
SD (h)	40.8	23.8		

IQR, interquartile range. *Placebo minus active. †Wilcoxon rank-sum test.

by only 1 day compared with placebo.^{20,21} Conversely, 1072 nm light seems to be effective in reducing healing time even when treatment is started in the later stages of the infection. This is desirable for patients whose episodes occur without a prodrome, or who start treatment in the papule stage of the infection.

The mechanism of action by which 1072 nm infrared light effects the healing time of HSL is not yet fully known. An *in vitro* study by Bradford *et al.* found that 1072 nm infrared LLLT elicited a significant protective effect on human lymphocytes.²² In their study, the cell viability of peripheral blood mononuclear cells (PBMCs) after exposure to ultraviolet (UV) light was significantly increased when cells were pretreated with 1072 nm light before the UV exposure (preconditioning). Quantitative immunoblotting showed that there was a significant 4.9-fold increase in the level of iNOS in the pretreated group compared with the control group. Nitric oxide (NO) in low concentrations is known to be a potent inhibitor of apoptosis in various cell types.²³ The authors suggested that the increase in iNOS might be the underlying mechanism of protective preconditioning by 1072 nm light therapy in human lymphocytes.²² Considering this, we can hypothesize that 1072 nm infrared light therapy may enhance the cell viability of lymphocytes that act against HSV infection. However, iNOS is also known to generate high concentrations of NO partly to kill bacteria, therefore suggesting that the significance of raised levels of iNOS after irradiation with 1072 nm is still unclear.

Another possibility is that 1072 nm LLLT may have the established classic effects of LLLT, whereby the photons absorbed by the mitochondria increase the production of adenosine triphosphate, reactive oxygen species and NO, which facilitates gene transcription of the given cells (e.g. leucocytes, endothelial cells, fibroblasts) through signalling pathways involving nuclear factor κ light-chain-enhancer of activated B cells and activator protein-1.²³ As a result, these cells are activated, enhancing production of their responsible proteins or performance of their given roles (e.g. lymphocytes produce antibodies, fibroblasts produce collagen and extracellular matrix, mast cells degranulate, and macrophages increase phagocytic activities).²⁴ Because light at 1072 nm falls within the red and near-infrared waveband of 600–1100 nm, which has been described as the optical window by other authors, it is highly likely that 1072 nm exerts its cellular effect via the established mechanism of action of other near-infrared wavelengths.^{24,25} Further studies to elucidate the exact mechanisms of action of 1072 nm have been completed by one of the present

authors (SYL). The results showed that 1072 nm LLLT seems to enhance the natural immune response against skin infection with methicillin-resistant *Staphylococcus aureus* by increasing the primary cytokines that are activated promptly after bacterial intrusion. A measurable increase in vascular endothelial growth factor (VEGF) was seen,²⁶ and there was a significant increase in tumour necrosis factor- α , interleukin (IL)-1b and IL-6. These primary cytokines act as the first responders to infection, and are activated immediately after the infection is detected by local immune cells such as Langerhans cells.²⁷ IL-6 is also an important mediator of the acute phase response, secreted by macrophages to specific microbial molecules that are detected by receptors of the host cells, including Toll-like receptor.²⁸ Activation of these primary cytokines stimulates other immune cells to initiate antibacterial actions such as production of antibodies and phagocytosis of pathogens, and also to produce secondary cytokines and growth factors.²⁹ VEGF is the key protein that stimulates the production and growth of new blood vessels when blood circulation is not sufficient to supply enough oxygen. VEGF is known to increase in wound healing after injury or in local infections to provide more oxygen, nutrients and immune cells that are needed for the antibacterial actions and wound-healing processes. VEGF also acts as a chemoattractant for macrophages and granulocytes, and as a vasodilator with the involvement of nitric oxide.^{30–32}

Conclusion

We found that treatment with LLLT at a wavelength of 1072 nm resulted in a significant reduction in the healing time of HSL lesions. This result, along with the fact that 1072 nm increased the production of iNOS from human lymphocytes, suggests that this wavelength seems to produce the classic LLLT effects, with the additional discovery of its action on immune cells and immunomodulation, which may be beneficial for some inflammatory diseases, including HSL and other common infections such as localized wound infections and wound management.

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