

A randomised double-blind study comparing the effect of 1072-nm light against placebo for the treatment of herpes labialis

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Summary

Background. Previous research demonstrated that 1072-nm narrowband laser light is effective in the treatment of cold sores.

Aim. To evaluate the efficacy of an over-the-counter cold-sore treatment device (Virulite CS) incorporating 1072-nm light-emitting diodes.

Methods. A randomised, prospective, double-blind, self-reported study was performed to compare the efficacy of at least six 3-min treatments of 1072-nm narrowband light against placebo, in the treatment of herpes labialis.

Results. The 1072-nm light-emitting diode device reduced cold-sore healing time to 6.3 days compared with 9.4 days for placebo ($P = 0.048$). The time the cold sore took to form a crust was also reduced from 2.00 days for those treated with 1072-nm light, compared with 2.88 days for placebo ($P = 0.059$).

Conclusions. The significant difference between the mean healing times in the two groups demonstrates that the Virulite CS device is an effective means of treating herpes labialis.

Introduction

Previous research has demonstrated that 1072-nm narrowband light via a laser diode array reduced healing time of cold sores by almost 50% compared with topical aciclovir.¹ The purpose of this research was to determine if a commercially available, over-the-counter, 1072-nm light-emitting-diode light source is efficacious in the treatment of cold sores. Not only are light-emitting diodes significantly cheaper than laser diodes, but they are thermally and electronically more robust.

Patients and methods

Patients and criteria

Volunteers were recruited from general practice surgeries with the use of an ethically approved poster and from

the general public. Recruitment began in August 2004, and follow-up continued until January 2005. The research protocol was approved by the South Tees ethics committee (REC reference number L04-18). Volunteers were deemed eligible if they fulfilled the following criteria: (i) a history of recurrent orofacial herpes² (at least three episodes within the past year), (ii) the cold sore had been present for 36 h or less, (iii) patients were readily and reliably contactable via telephone and/or e-mail, (iv) patients would be staying within the northeast of England for 3 weeks after entering the trial, and (v) patients were willing not to use anything for their cold sore except the supplied device.

Cold sores affecting only the lips were included in the trial; cold sores affecting the nose, face and chin were excluded. Volunteers on any antiviral treatment, systemic steroids, having any major systemic illness, radiotherapy, chemotherapy, or with a diagnosis of any malignancy (except basal cell carcinoma outside the perioral region) were excluded.

The volunteers were asked to contact the researcher within 24 h of developing the cold sore. This enabled the nurse to see the volunteer within 36 h of the onset of the cold sore to initiate treatment. A medical

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assessor photographed the cold sore at initial presentation, facilitating confirmation of the diagnosis. The interventions compared were a minimum of one 3-min treatment of the 1072-nm active light (Virulite CS) three times daily for 2 days vs. one 3-min treatment of a placebo device (no light) three times daily for 2 days.

The volunteers were contacted by telephone every 2–3 days, and asked to report the time a crust formed on the cold sore. Healing was taken to be the day and time the crust fell off, leaving uninterrupted skin at the site of the cold sore. Healing time of the cold sore was determined by measuring the time between the initial presentation to the research assistant and the time when the volunteer reported that there was re-epithelialization. The time for the cold sore to form a crust, as reported by the volunteer, was also recorded.

Sample size

From earlier trials of the Virulite CS, the reduction in mean healing time was estimated as 3 days, and the standard deviation was estimated as 3 days for active and for placebo. With these values the sample size required for an 80% chance of achieving a significant difference in mean healing time with $P = 0.05$ was $n = 16$ in each arm of the trial.

Randomization method

Each eligible volunteer was allocated to receive one of two treatments without restriction according to a standard computer-generated randomization table (Fig. 1). Patient numbers were allocated sequentially and the two groups ran concurrently. Volunteers received either a Virulite CS device or a placebo Virulite CS device.

Method of masking

The external appearance of the placebo and active Virulite CS devices were identical and there was no means by which the researcher or the volunteer could distinguish between them, as 1072-nm light is invisible to the human eye.

The code was inaccessible to both the volunteers and research assistants, and was kept in a sealed envelope. The code was broken after the data were examined for exclusions. The data were examined independently by a medical statistician employed by the National Health Service.

Apparatus

The Virulite CS device is approved by the Council of Europe (CE mark) and available to the general public. It

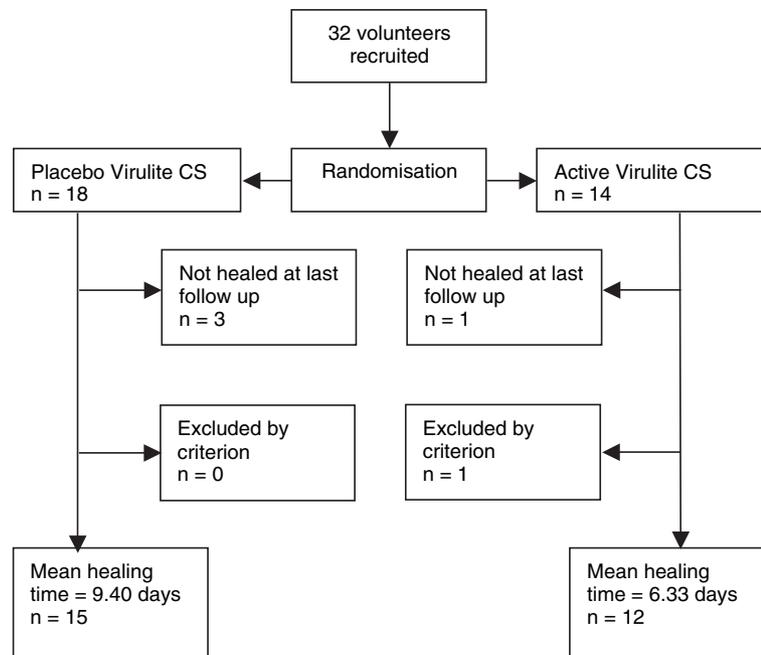


Figure 1 Trial profile.

is a handheld battery-operated device (PP3; 9 V), with a clear treatment window that is held against the skin surface at the site of the cold-sore infection. The device emits pulsed 1072-nm narrowband light from two light-emitting diodes, and has an internal microprocessor that 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 μ s. Placebo devices used dummy light-emitting diodes with a microprocessor modified to control the visible flashing lights, treatment time and audio signal.

Results

In total, 32 volunteers were recruited. The results were analysed according to protocol. The end-point for analysis was the healing (re-epithelialization) time as identified by the volunteer. Two volunteers reported crusting but were then lost to further follow-up, thus their crusting times were included.

The data for healing time and time to crusting were examined with respect to the conditions on which the *t*-test is valid.³ Inspection of the histograms of the active and placebo data indicated pronounced skewness of all data, thus the data was transformed using natural logarithms.^{4,5} The Bartlett test indicated that equality of variance had been preserved. A two-tailed *t*-test was applied to the transformed data. The statistical analysis was carried out using Epi Info (version 3.3.2) and Microsoft Excel 2000.

The healing time and time to crusting are presented in Table 1. The mean time to crust formation was 2.00 days for the active group and 2.88 days for the placebo group, almost achieving statistical significance ($P = 0.059$). The mean self-reported healing time was 6.33 days for the active group and 9.40 days for the placebo group, which was statistically significant ($P = 0.048$). The confidence interval for the difference between the means was 0.2–5.9. In Table 1, the median and interquartile range dictated by the skewness of the data are shown. Four volunteers were lost to

follow-up and one volunteer was excluded for failing the qualifying criteria.

Although feedback from volunteers was encouraged, comments tended to relate to whether they felt that the cold sores were as bad or not as bad as usual and to their perceived rate of recovery. No specific side-effects were reported.

Discussion

The significant difference between the mean healing times in the two groups demonstrates that the Virulite CS device is an effective means of treating herpes labialis. The reduction in healing time was mirrored by a reduction in crusting time in the treated group, both being approximately two-thirds that of the placebo. The two-thirds reduction in healing time is also mirrored in the interquartile range.

Compared with pharmaceutical preparations, optoelectronic devices have an extremely long shelf life. A Virulite CS device could be used several hundred times to treat recurrent herpes labialis over a number of years, which would significantly reduce the cost of cold-sore treatment,^{6–8} both to the NHS and to the individual. In addition to the cost benefit in recurrent herpes labialis, there is improved efficacy; the device reduces healing time by 33%, which is better than the 10–12% reduction achieved with topical aciclovir.⁹ Compared with the initial pilot study,¹ which used a laser-diode array, the efficacy of the over-the-counter, light-emitting-diode Virulite CS device tested in this study is reduced, showing a 33% reduction in cold-sore healing time compared with almost 50% with a laser diode. This might be explained by the difficulty that the research assistant had in assessing volunteers on the day that self-reported healing took place. In the original pilot study,¹ confirmation of healing was by face-to-face consultation with visual and photographic documentation. The volunteers received no reimbursement for attending follow-up appointments, and this may have been a factor in those lost to follow-up.^{10–12}

The mechanism by which a nonthermal quantity of near-infrared light has a photobiological effect remains

Group	Healing time (days)	Time to crust (days)	Median (days)	IQR (days)
Active	6.3 \pm 2.99* ($n = 12$)	2.00 \pm 1.21* ($n = 12$)	6	4–9
Placebo	9.4 \pm 4.58* ($n = 15$) $P = 0.048$	2.8 \pm 1.31* ($n = 16$) $P = 0.059$	8	6–12

Table 1 Healing time in the two groups.

*Values are mean \pm SD. IQR, interquartile range.

unexplained. Evidence is accumulating to suggest that 1072-nm light might enhance the local immune response to effect a reduction in cold-sore healing time. *In vitro* investigations have not found any evidence to suggest that infrared radiation inactivates the herpes virus within infected cells.¹³ Several workers have documented that near-infrared light might have an effect on immunological reactions,^{14,15} and is an effective treatment in preventing herpes simplex infection. More recently, Bradford *et al.*¹⁶ demonstrated that 1072-nm light not only improved lymphocyte viability in culture but also conveyed a level of cytoprotection against the toxic effects of ultraviolet light, which is a known precipitant of cold sores,^{17–19} and is known to adversely affect immune-cell function.^{20–22} This *in vitro* study importantly identified a quantitative change in the biochemical mediator nitric oxide as a result of a 1072-nm light photobiological reaction.

With the knowledge that 1072-nm light has efficacy in the treatment of cold sores and has a positive effect on immune cells, further studies directed towards the investigation of this treatment in recurrent herpes simplex labialis will be of interest.

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