A pilot study of treatment of herpes labialis with 1072 nm narrow waveband light

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Summary

A randomized prospective double-blind study was performed to compare the efficacy of a single 5 min 1072 nm narrow waveband light application against topical aciclovir applied five times daily in the treatment of herpes labialis. Treatment was initiated within 36 h of the onset of symptoms and the end point was defined as the day that the crust was discarded leaving an uninterrupted underlying skin at the site of the cold sore. The results demonstrated that a single 5 min light treatment significantly reduced cold sore healing time by 4 days; 1072 nm light healed cold sores in 4.3 ± 1.8 days (mean ± SD) as compared with aciclovir applied five times daily, 8.5 ± 3.0 days ($P < 0.0001$).

Background

Although infrared light is recognized as a treatment of musculo-skeletal disorders and indolent wounds, the evidence that it has therapeutic effect remains anecdotal. Indeed, until very recently the results of clinical trials exploring proposed therapeutic effects of infrared light had not been documented with meaningful statistical significance.[1–6] In 1999, however, Schindl and Neumann demonstrated that low intensity laser therapy is an effective nonthermic treatment for recurrent herpes simplex infection.[7]

In the laboratory various photobiological effects of infrared light have been explored, albeit dictated by the random commercial availability of predominately laser light sources.[8–13] These well-documented experiments have demonstrated unequivocally that selected wavelengths of infrared light have nonthermal photobiological effect. We were unable to find any evidence to suggest that these laboratory results had been correlated with the known anecdotal clinical therapeutic effects of infrared light.

We hypothesized that within the infrared spectrum there might be one or more narrow wavebands of light with therapeutic photobiological effect. As long ago as 1981 Anderson and Parrish[14] introduced the possibility of treating large tissue volumes with certain long wavelength photosensitisers within the optical window of skin, between 600 and 1300 nm. We reasoned that tissue penetration would be influenced by light transmitted by water, which represents the major component of the human body. Examination of the transmission spectrum of the water molecule demonstrated a peak transmission of light with a wavelength of 1072 nm (Fig. 1).

For this study we decided to use a narrow waveband of light centred at 1072 nm using quantities of light which would not have thermal effect. (Terms: 1072 NWBL = light with a centre wavelength of 1072 nm and a bandwidth of ± 20 nm).

Cold sores appeared to be the obvious choice when searching for a clinical model to observe the effects of light therapy. They are known to be activated by exposure to ultraviolet light[15] and recurrence rates are known to be reduced by exposure to low intensity laser therapy. Approximately 20% of the world's population suffer from cold sores, providing within the community a potentially large number of patient volunteers to be recruited into clinical trials.

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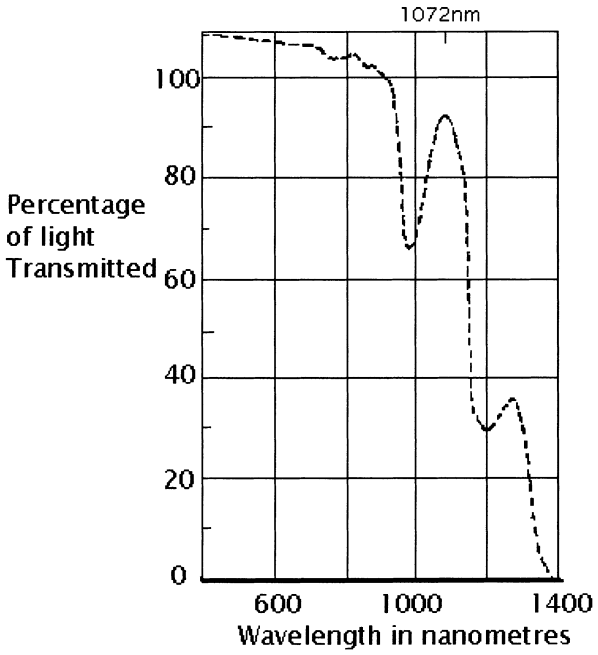

Figure 1 Light transmission spectrum of water between wavelengths 400 nm and 1400 nm.

Patients and methods

Protocol

Patient volunteers were recruited by advertisement within the local press after ethics permission had been obtained. Informed consent was obtained from all volunteer patients.

The interventions compared were a single 5 min treatment of 1072 NWBL vs. five times daily topical aciclovir applied until the cold sore was reported to be cured. Despite medical publications[16,17] to the contrary, topical aciclovir appears to be accepted by the general population as treatment of choice for cold sores. The duration of the cold sore must have been 36 h or less in all volunteers. The time of onset of the cold sore was defined as either the time of onset of symptoms or first appearance of the lesion, whichever was the soonest.

The initial parameters measured were cold sore size and the duration of the cold sore prior to intervention. Cold sore size was documented by photograph and the largest diameter measured by ruler.

The key outcome variable was the time at which the cold sore was cured, defined as the time when the crust had fallen off the cold sore leaving uninterrupted skin at the site. This was verified by the patient on a written response questionnaire and validated visually by an independent observer blind to treatment.

The possibility that using a light treatment device would have a placebo effect was explored by subdividing those patients receiving topical aciclovir into two groups: group 1 receiving only aciclovir and group 2 receiving aciclovir and placebo light. In a similar way any therapeutic effect of the placebo cream, advantageous or otherwise, was explored by treating half of the 1072 NWBL group with placebo cream.

The protocol was approved by North Tees General Hospital Ethics Committee.

Randomization method

The individuals were allocated to receive one of four treatments without restriction according to a standard computer-generated randomization table. Each treatment type was allocated an alphabetical letter which was assigned randomly to the patient number. Patient numbers were allocated sequentially. Each treatment arm was housed in a separate lettered container.

It was deemed unethical to withhold treatment from subjects, hence there is not a placebo control group in the study (i.e. either placebo light only or placebo cream only).

The 4 groups ran concurrently and were delivered the following treatments: group 1, topical aciclovir five times daily; group 2, topical aciclovir five times daily plus placebo light once for 5 min; group 3, 1072 NWBL once for 5 min; group 4, 1072 NWBL once for 5 min plus placebo cream five times daily.

Method of masking

The pharmaceutical creams were labelled with the patient number alone in Hartlepool General Hospital pharmacy. The pots in which the creams were dispensed were identical in external appearance and the quantity, consistency, colour and odour of the placebo cream appeared identical to topical aciclovir.

As the light is invisible to the human eye the external appearance of the light applicators and their external functions were identical. There was no mechanism by which either the patient or the researchers could discriminate between groups 2 and 4, and a separate staff member who independently followed-up the patients was blind to all four treatment arms. The code was located at Hartlepool General Hospital in a sealed envelope and was broken only at the conclusion of the trial after data analysis. The code was inaccessible to both the individuals carrying out the intervention and the outcome assessor who visually confirmed that the cold sore was healed. The

Table 1 Comparison of the four treatment groups.

	Patients treated between 18 and 36 h of onset of cold sore, % of total, (*n*)	Mean cold sore diameter [mm ± SD (*n*)]	Nurse observed cold sore cured [mean days ± SD (*n*)]	Patient reported cold sore cured [mean days ± SD (*n*)]
Light @1072 nm single 5 min application	8, 73% (11)	2.5 ± 1.1 (11)	7.0 ± 3.2 (11)	4.6 ±2.2 (11)
Light @1072 nm single application plus placebo cream five times daily	10, 71% (14)	3.3 ±1.9 (14)	8.7 ± 3.9 (9)	4.0 ± 1.4 (14)
Aciclovir cream five times daily	10, 71% (14)	3.3 ± 1.7 (14)	12.1 ± 4.3 (12)	8.8 ± 3.5 (14)
Aciclovir cream five times daily plus a single application of placebo light	11, 92% (12)	2.7 ± 1.0 (12)	10.6 ± 4.5 (12)	8.1 ± 2.5 (12)
P value	Lowest $P = 0.32$	$P = 0.45$	$P = 0.025$	$P < 0.0001$

data was analysed independently by The University of Teesside Medical Research Department prior to decoding.

Apparatus

The light source used a multimode laser diode array centred at 1072 nm with a bandwidth of ± 20 nm. The optical power was maintained between 5 and 10 mw/cm^2 peak power at the skin surface, switched at 600 hz with a 20% duty cycle. Internal monitoring of the light output ensured that treatment parameters remained constant. The treatment area was constant at 6 cm^2. The device, a class I laser product, operated from a 5 V double insulated supply with less than 20 μA earth leakage and contained an internal timer which facilitated a constant treatment time of 5 mins.

Statistics

Conventional one-way analysis of variance was used to compare cold sore size and days to heal among the four treatment groups. The two-sample *t*-test was used to compare the pooled aciclovir and 1072 NWBL groups.

For the proportion of patients treated between 18 and 36 h of onset, the four treatment groups were compared by applying the Fisher exact test to each pair of groups. This incurred three tests rather than six because the numbers from two of the groups were identical (Table 1). A single Fisher exact test was used to compare the pooled aciclovir and 1072 NWBL groups.

The statistical analysis was carried out using Minitab version 12.

Results

The data was analysed on an intention-to-treat basis.

Sixty volunteers were recruited into the trial. Eight patients were lost to follow-up and one patient with acne was excluded (Fig. 2). In the 1072 NWBL treatment group, 18 females and seven males were recruited and in the aciclovir treatment group, 22 females and four males were recruited. The mean age of

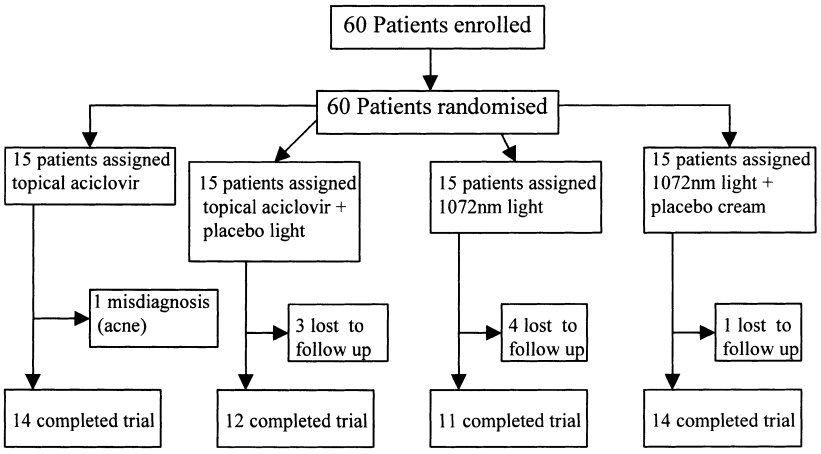

Figure 2 Trial profile.

Table 2 Pooled groups, active light vs. topical aciclovir.

	Patients treated between 18 and 36 h of onset of cold sore, % of total, (*n*)	Mean cold sore diameter [mm ± SD (*n*)]	Nurse observed cold sore cured [mean days ± SD (*n*)]	Patient reported cold sore cured [mean days ± SD (*n*)]
Active light, single 5 min treatment	18, 78% (25)	2.91 ± 1.53 (25)	7.8 ± 3.5 (20)	4.3 ± 1.8 (25)
Topical aciclovir five times daily	21, 87% (26)	3.0 ± 1.23 (26)	11.3 ± 4.3 (24)	8.5 ± 3.0 (26)
P value 95% confidence interval of the difference	$P = 0.46$	$P = 0.82$	$P = 0.005$ 1.1–6.0	$P < 0.0001$ 2.6–5.7

the 1072 NWBL treatment group was 41.8 years (range, 24–66 years) and the mean age of the aciclovir treated group was 40.3 years (range, 23–54 years).

Table 1 column 1 shows that the time interval between onset of symptoms and initiating treatment (less than 18 h or 18–36 h) was not significant between the groups ($P = 0.32$). Column 2 shows that the baseline parameter of cold sore size at the onset of treatment was not significantly different between the groups ($P = 0.45$).

Self reported time to cure

Table 1 column 4 shows the self-reported time to cure for each treatment arm. The two 1072 NWBL groups are reported as cured in about half the time than the two aciclovir groups, approximately 4 days vs. 8 days ($P < 0.0001$).

Table 2 is a comparison of the pooled 1072 NWBL groups vs. the pooled aciclovir groups. The results in column 4 compare the self-reported time to cure of the pooled groups and are also represented as a histogram in Fig. 3. The 1072 NWBL group is reported as healed in 4.3 days vs. 8.5 days in the aciclovir group ($P < 0.0001$).

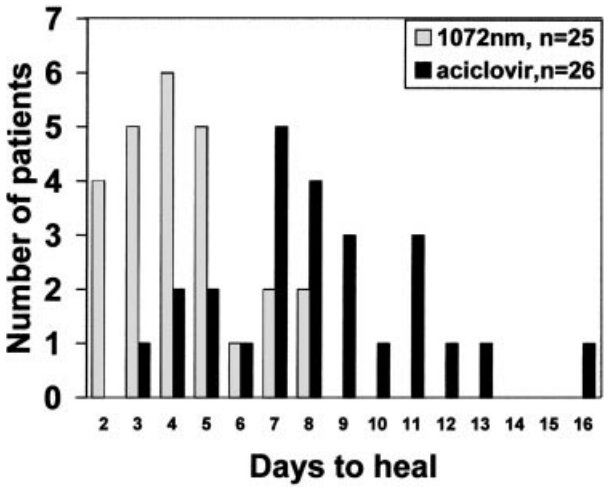

Figure 3 1072 nm light vs. aciclovir in the treatment of herpes labialis.

Once again there is no significant difference in the baseline parameters of cold sore size and the time of onset of treatment between the 1072 NWBL and aciclovir treated groups.

Nurse observed cold sore cured

The time at which the healed cold sore was available to be observed by the outcome assessor nurse was subject to a variable delay (Tables 1 and 2, column 3) affected by communication, transport and convenience.

However, the delays should have balanced out between the groups and there was no reason to suspect that any one group was seen sooner or later than the others. The results show a very similar pattern to those described for the self-reported time to cure, aciclovir 11.3 + 4.3 days, 1072 nm light 7.8 + 3.5 days, albeit with reduced statistical significance ($P = 0.005$).

Discussion

This study demonstrates statistically significant evidence from a randomized controlled trial that patients treated with 1072 NWBL within 36 h of onset of herpes labialis reported that their cold sores healed in half the time (4 days) compared with patients treated with conventional medication (8 days) in the form of aciclovir cream. To our knowledge this is the first time that a narrow waveband of light has been demonstrated to cause shortened cold sore healing time with a meaningful statistical significance. The difference in healing time was not influenced by the size of the cold sore. For both the 1072 NWBL and aciclovir treatment groups there was a placebo control for comparison and

all outcomes were recorded blind to the treatment received by the subject.

Previous research has shown that similar types of phototherapy using athermic quantities of low energy red or near infrared monochromatic light have been used for the acceleration of wound healing[18, 19] and in pain therapy.[20, 21] In addition it has been reported that this type of phototherapy might have an effect on several immunological reactions[22, 23] and is an effective treatment in preventing recurrent herpes simplex infection. *In vitro* investigations have not found any evidence to suggest that infrared irradiation inactivates the herpes simplex virus within infected cells.[24]

The mechanism by which infrared light has photobiological effect at molecular level, either demonstrated clinically, or by laboratory experiment, remains unexplained. We might imagine a hypothesis whereby cell membranes are the main beneficiary of light energy within the vicinity of 1072 nm. A more efficient cell membrane would increase resistance of the cell to virus entry, exposing the virus to an enhanced local immune response. Wound healing and repair might equally be enhanced.

In the light of our findings we would like to think that an increased awareness of the potential of infrared light to treat disease will stimulate further studies. Co-ordinated research would enable a map to be plotted of the therapeutic potential of light across the infrared spectrum. Of particular interest might be light within the optical window of skin (600–1300 nm) which would, in theory, have potential applications in the treatment of systemic disease processes. In the meantime we think that the knowledge that 1072 NWBL has therapeutic effect deserves further study, with respect to both dermatological and systemic disease.

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