Low-Intensity Laser Therapy is an Effective Treatment for Recurrent Herpes Simplex Infection. Results from a Randomized Double-Blind Placebo-Controlled Study

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Recurrent infection with herpes simplex virus is a common disease. Recently, alternative therapies have been introduced. Among those, low-intensity laser therapy mainly used for the acceleration of wound healing and in pain therapy has previously been shown to be of benefit in herpes zoster infections. In this study we evaluated the influence of low-intensity laser therapy (wavelength 690 nm, intensity: 80 mW per cm^2, dose: 48 J per cm^2) in 50 patients with recurrent perioral herpes simplex infection (at least once per month for more than 6 mo) in a randomized, double-blind placebo-controlled trial design. Patients in the laser group received daily irradiations for 2 wk, whereas patients in the placebo group were sham-irradiated. After completion of the laser/sham treatment, patients were asked to return to the Department of Dermatology, University of Vienna Medical School at the time of recurrence. All except two patients completed the study and were monitored for 52 wk. The median recurrence-free interval in the laser-treated group was 37.5 wk (range: 2–52 wk) and in the placebo group 3 wk (range: 1–20 wk). This difference was found to be statistically significant ($p < 0.0001$; Wilcoxon's Rank Sum Test). In conclusion, we demonstrated that a total of 10 irradiations with low-intensity laser therapy significantly lowers the incidence of local recurrence of herpes simplex infection. Since this athermic phototherapeutic modality represents a safe, noninvasive treatment, it might be considered as an alternative to established therapeutic regimens in this indication. ***Key words: biostimulation/immunology/low level laser/virus. J Invest Dermatol 113:221–223, 1999***

Perioral infection with herpes simplex virus (HSV) is a common disease with an estimated 16%–45% of the population having been infected, mainly in early childhood (Vestey and Norval, 1992). There is no seasonal variation in the incidence of infection. After infection of nerve endings, viruses are transported to the nuclei of the sensory ganglia where they multiply (Whitley and Kimberlin, 1998). Between 28 and 60% of individuals with latent herpes simplex suffer from recrudescence with a frequency of 2–20 per y (Norval and el Ghorr, 1996; Whitley and Kimberlin, 1998). Reactivations can be triggered by physical or emotional stress, fever, exposure to ultraviolet light, and immune suppression. The onset of recurrence is preceded by pain, burning, or itching which generally persists for about 6 h and is followed by the appearance of vesicles. Lesions progress to pustules or ulcers and usually heal within 8–10 d. Immune responses to herpes simplex infection involve Langerhans cells, lymphocyte-mediated delayed-type hypersensitivity and cytotoxicity, macrophages, and natural killer cells (Whitley and Kimberlin, 1998). There is evidence that a temporary depression in immunologic responses might occur shortly before or during recrudescence (Vestey and Norval, 1992). Development of drug-resistant HSV strains is of increasing significance, especially in immunocompromised patients such as organ transplant recipients and AIDS patients (Whitley and Kimberlin, 1998).

Low-intensity laser therapy represents an athermic phototherapy utilizing light sources emitting low energies (in the milliwatt range) of usually red or near infrared monochromatic light and is mainly used for the acceleration of wound healing (Al-Watban and Zhang, 1996; Schindl *et al*, 1997a, b; Halevy *et al*, 1997; Yu *et al*, 1997a) and in pain therapy (Walker, 1983; Emmanoulidis and Diamantopoulos, 1986; Moore *et al*, 1988). Additionally, it has been shown that this type of phototherapy might have an effect on several immunologic reactions (Ohta *et al*, 1987; Yu *et al*, 1997b; Schindl *et al*, 1997c). These findings have influenced a number of uncontrolled clinical studies about the effect of low-intensity laser therapy on herpes simplex infection (Haichenberger-Wildner and Michels, 1981; Landthaler *et al*, 1983).

Our study evaluates the efficacy of low-intensity laser therapy in the treatment of recurrent herpes simplex infection in a randomized, double-blind placebo-controlled trial design.

MATERIALS AND METHODS

Patients Fifty consecutive patients who presented or were referred to the Department of Dermatology, University of Vienna Medical School due to recurrent herpes simplex infections of the perioral region were included in this study. All patients had had at least one course of treatment with orally applied acyclovir (800 mg per d) for 4 wk, which had been completed at least 3 mo before enrolment. Recurrent herpes simplex infection was defined as at least one herpes attack per month for more than 6 mo independent of any known triggering mechanism such as fever, sun exposure, or menstruation. Patients were randomized into a laser group and a placebo group (n = 25 for both groups) after signing informed

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Table I. Demographic characteristics of study population with recurrent perioral herpes simplex infection (at least one recurrence within the last 6 mo)

	Laser group (n = 24)	Placebo group (n = 24)
Age (mean ± SD)	31.3 ± 12.1	36.6 ± 14.8
Sex (M/F)	5/19	6/18
Site of infection		
Upper lip	12	13
Lower lip	5	2
Both	7	9

consent. Current antiviral or immunosuppressive therapy, homeopathy or acupuncture as well as HIV infection were exclusion criteria. Patients' characteristics are given in **Table I**.

Intervention All patients in both groups were treated by the same physician in the recurrence-free period. Patients in the laser group received low-intensity laser therapy by means of an 80 mW, 690 nm continuous wave diode laser (Helbo Lasers, Gallspach, Austria). Irradiations (exposure time, 10 min; area, 1 cm^2; intensity, 80 mW per cm^2; dose, 48 J per cm^2) once daily for 2 wk at the site of original chronic herpes infection. In those patients with herpes infections located on both the upper and lower lip both sites were irradiated. The placebo irradiation was performed in the same manner as in the verum group except that the laser was not turned on. Patients in both groups were wearing nontransparent protection glasses during the procedure. Any pre-existing medication was left unchanged during the trial. After completing the irradiation procedure patients were told to present at the department at the time of recurrence. The total observation period was 52 wk. The evaluator was not aware of the study protocol.

Statistical analysis The median periods of remission intervals of the laser-treated group and the placebo group were compared using Wilcoxon's Rank Sum Test. $p < 0.05$ were regarded as statistically significant.

RESULTS

Two of 50 enrolled subjects did not complete the study: one patient of the placebo group discontinued because of time problems and one patient of the laser group had to undergo an appendectomy. All remaining 48 patients were monitored for 52 wk. One of these patients was still in remission at the end of the observation period but was not followed up. No side-effects of any kind were noted.

The treatment outcome is shown in **Fig 1**. The median recurrence-free interval in the laser-treated group was 37.5 wk (range, 2–52 wk; 95% confidence interval, 24–42 wk) compared with 3 wk (range, 1–20 wk; 95% confidence interval, 2–4 wk) in the placebo group. This difference was found to be statistically significant ($p < 0.0001$). No influence of the anatomic site of infection on the treatment outcome could be documented.

DISCUSSION

In this study we demonstrated the efficacy of low-intensity laser therapy in the treatment of recurrent herpes simplex infection in a randomized, double-blind placebo-controlled trial design. These results confirm earlier findings from retrospective, uncontrolled studies (Haichenberger-Wildner and Michels, 1981; Landthaler *et al*, 1983).

Although potent agents against herpesvirus infections have become available during the last decade, the increasing clinical use of acyclovir and famciclovir has been associated with the emergence of drug-resistant herpesvirus strains (Reusser, 1996). Moreover, the intermittent administration of acyclovir does not alter the frequency of recurrences (Whitley and Kimberlin, 1998). Owing to these facts and because of the increasing patient demand for nonchemical therapies various alternative treatment modalities have been introduced, among which the combination of neutral red with laser exposure as a photodynamic treatment modality deserves to be mentioned from the photobiologic viewpoint (Felber *et al*, 1973).

Whereas ultraviolet radiation, in general, alters various cutaneous

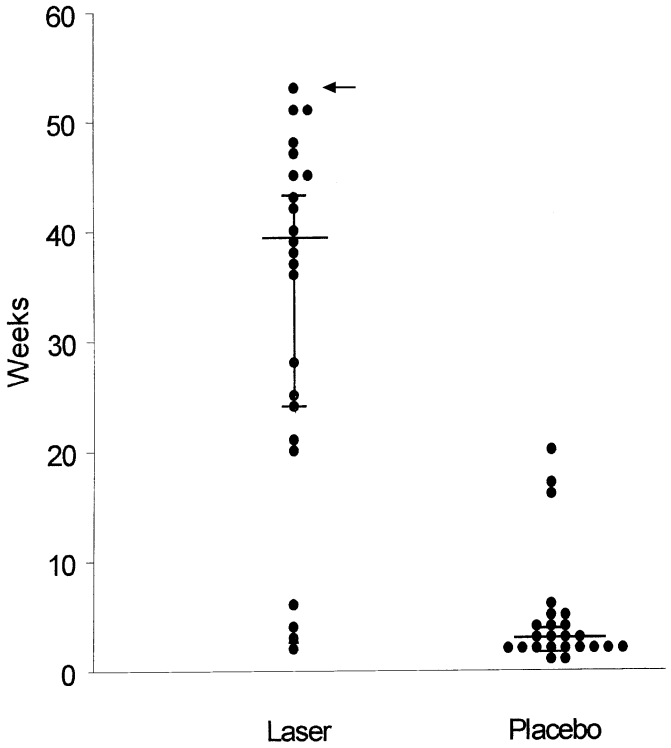

Figure 1. Low intensity laser therapy lowers the incidence of local recurrence of perioral herpes simplex infection. Remission intervals after 10 sessions of 690 nm low-intensity laser therapy (median 37.5 wk, range 2.0–< 52 wk) and placebo treatment (median 3.0 wk, range 1.0–20.0 wk) in patients with recurrent perioral herpes simplex infection. The difference between the groups (n = 24) was statistically significant ($p < 0.0001$, Wilcoxon's Rank Sum Test). *Bars* indicate the respective medians and 95% confidence intervals. *Arrow* indicates censored value (patient with remission interval longer than 52 wk).

cell functions, little is known about immune-modulating effects of (low-intensity) red and near infrared light on the skin. Low-intensity laser therapy has been introduced mainly for the induction of wound healing and pain therapy in the 1970s (Mester *et al*, 1971). Since then, a number of reports investigated a putative influence of this athermic phototherapy on the immune system and its constituents (Ohta *et al*, 1987; Yu *et al*, 1997b; Schindl *et al*, 1997c). These experiments, however, yielded conflicting results which can be explained in part by the different irradiation parameters used and the well-established fluence-dependence of (laser) light effects (Inoue *et al*, 1989a; Funk *et al*, 1992).

Danno and Sugie (1996) demonstrated that a weak thermal effect induced by near infrared exposure reversibly suppressed the density of Langerhans cells and the ability of the skin to induce contact hypersensitivity reactions. Inoue *et al* (1989b) described suppressed tuberculin reactions in guinea pigs and a possible systemic inhibitory effect on delayed hypersensitivity reactions after a single low power laser irradiation at a fluence of 3.6 J per cm^2. In contrast to ultraviolet radiation which is known to have an inductive effect on herpes simplex infection (Norval and el Ghorr, 1996), the results of this study, together with findings from other authors dealing with the effect of low-intensity laser therapy for the treatment of herpes simplex (Körner *et al*, 1989; Perrin *et al*, 1997) and herpes zoster (Moore *et al*, 1988; Moore and Calderhead, 1991; Matsumura *et al*, 1993) show an immune-stimulating effect. Körner *et al* (1989) used a Nd:YAG laser operated at fluences between 5 and 183 J per cm^2 and found no direct virus-inactivating effect on HSV-1 cultures but a 50% reduction in virus yield in cultures incubated with irradiated leukocytes. This observation could provide a possible explanation of the mechanism of the treatment effect and is backed by results from other investigators reporting on the activation and proliferation of lymphocytes (Inoue *et al*, 1989a; Yu *et al*, 1997b;

Schindl *et al*, 1997c; Manteifel *et al*, 1997) and macrophages (Bolton *et al*, 1990) as well as the synthesis and expression of cytokines (Funk *et al*, 1992; Yu *et al*, 1996) following low intensities of red and near-infrared laser light. Utilizing a krypton-laser (wavelength 647 nm) at similar irradiation parameters as applied in our study (intensity, 50 mW per cm^2; fluence, 4.5 J per cm^2), Landthaler *et al* (1983) achieved a significant prolongation of remission intervals from 30 to 73 d in patients with recurrent herpes simplex infection. Interestingly, patients with labial herpes infection showed better results than those with genital infection.

A psychologic influence on herpes infection is well established (Luby and Klinge, 1985; Biondi and Zannino, 1997) and also has been described for low-intensity laser therapy (Zimmermann, 1990). Such an influence could clearly be ruled out in our study due to the selected randomized, double-blind placebo-controlled trial design.

In conclusion, we demonstrated that a total of 10 daily irradiations by means of a low-intensity laser device significantly lowers the incidence of local recurrence of perioral herpes simplex infection. This athermic phototherapeutic procedure represents a safe, relatively cost-effective, and noninvasive treatment modality. Therefore, it may be considered as a beneficial alternate treatment regimen for recurring herpes simplex infections. Future work will focus on the elucidation of the underlying mechanisms and the potential role of this therapy. Additionally, larger studies are needed to evaluate the influence of the type of HSV (HSV-1 *versus* HSV-2) and different irradiation protocols on the effects of laser therapy in recurrent perioral herpes simplex infection.

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