

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 cm², dose: 48 J per cm²) 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 Dermato-

logy, 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 Ghor, 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

Manuscript received December 22, 1998; revised March 29, 1999; accepted for publication May 11, 1999.

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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 cm²; fluence, 4.5 J per cm²), 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.

REFERENCES

- Al-Watban FAH, Zhang XY: Comparison of the effects of laser therapy on wound healing using different laser wavelengths. *Laser Ther* 8:127-135, 1996
- Biondi M, Zannino LG: Psychological stress, neuroimmunomodulation, and susceptibility to infectious diseases in animals and man: a review. *Psychother Psychosom* 66:3-26, 1997
- Bolton P, Young SR, Dyson M: Macrophage responsiveness to light therapy: a dose response study. *Laser Ther* 2:101-106, 1990
- Danno K, Sugie N: Effects of near-infrared radiation on the epidermal proliferation and cutaneous immune function in mice. *Photodermatol Photoimmunol Photomed* 12:233-236, 1996
- Emmanouilidis O, Diamantopoulos C: CW IR low-power laser application significantly accelerates chronic pain relief rehabilitation of professional athletes. A double blind study. *Lasers Surg Med* 6:173, 1986
- Felber TD, Smith EB, Knox JM, Wallis G, Melnick JL: Photodynamic inactivation of herpes simplex. *JAMA* 223:289-292, 1973
- Funk JO, Kruse A, Kirchner H: Cytokine production after helium-neon laser irradiation in cultures of human peripheral blood mononuclear cells. *J Photochem Photobiol B* 16:347-355, 1992
- Haichenberger-Wildner I, Michels H: Laserstrahlen bei Herpeserkrankungen. *Med Cosmetol* 11:142-144, 1981
- Halevy S, Lubart R, Reuveni H, Grossman N: 780nm low power laser therapy for wound healing-in vivo and in vitro studies. *Laser Ther* 9:159-164, 1997
- Inoue K, Nishioka J, Hukuda S: Altered lymphocyte proliferation by low dosage laser irradiation. *Clin Exp Rheumatol* 7:521-523, 1989a
- Inoue K, Nishioka J, Hukuda S: Suppressed tuberculin reaction in guinea pigs following laser irradiation. *Lasers Surg Med* 9:271-275, 1989b
- Körner R, Bahmer F, Wigand R: The effect of infrared laser rays on herpes simplex virus and the functions of immunocompetent cells. *Hautarzt* 40:350-354, 1989
- Landthaler M, Haina D, Waidelich W: Behandlung von Zoster, postzosterischen Schmerzen und Herpes simplex recidivans in loco mit Laser-Licht. *Fortschritte Med* 101:1039-1041, 1983
- Luby ED, Klinge V: Genital herpes. A pervasive psychosocial disorder. *Arch Dermatol* 121:494-497, 1985
- Manteifel V, Bakeevo L, Kern T: Define structural changes in chondriome of human lymphocytes after irradiation with He-Ne laser: appearance of giant mitochondria. *J Photochem Photobiol B: Biol* 38:25-30, 1997
- Matsumura C, Ishikawa F, Imai M, Kemmotsu O: Useful effect of application of helium-neon LLLT on an early stage case of herpes zoster: a case report. *Laser Ther* 5:43-46, 1993
- Mester E, Spiry T, Szende B, Tota JG: Effect of laser rays on wound healing. *Am J Surg* 122:532-535, 1971
- Moore KC, Calderhead RG: The clinical application of low incident power density 830nm GaAlAs diode laser radiation in the therapy of chronic intractable pain: a historical and optoelectronic rationale and clinical review. *Int J Optoelectronics* 6:503-520, 1991
- Moore KC, Hira N, Kumar PS, Jayakumar CS, Oshiro T: A double blind crossover trial of low level laser therapy in the treatment of post herpetic neuralgia. *Laser Ther* 1:7-9, 1988
- Norval M, el Ghorri AA: UV radiation and mouse models of herpes simplex virus infection. *Photochem Photobiol* 64:242-245, 1996
- Ohta A, Abergel RP, Uitto J: Laser modulation of human immune system: inhibition of lymphocyte proliferation by a gallium-arsenide laser at low energy. *Lasers Surg Med* 7:199-201, 1987
- Perrin D, Jolivald JR, Triki H, *et al*: Effect of laser irradiation on latency of herpes simplex virus in a mouse model. *Pathol Biol Paris* 45:24-27, 1997
- Reusser P: Herpesvirus resistance to antiviral drugs: a review of the mechanisms, clinical importance and therapeutic options. *J Hosp Infect* 33:235-248, 1996
- Schindl A, Schindl M, Schindl L: Successful phototherapy with low intensity laser irradiation of a chronic radiation ulcer in a patient with lupus erythematosus and diabetes mellitus. *Br J Dermatol* 137:840-841, 1997a
- Schindl A, Schindl M, Schindl L: Successful treatment of persistent radiation ulcer by low power laser therapy. *J Am Acad Dermatol* 37:646-648, 1997b
- Schindl L, Schindl M, Polo L, Jori G, Perl S, Schindl A: Effects of low power laser-irradiation on differential blood count and body temperature in endotoxin-preimmunized rabbits. *Life Sci* 60:1669-1677, 1997c
- Vestey JP, Norval M: Mucocutaneous infections with herpes simplex virus and their management. *Clin Exp Dermatol* 17:221-234, 1992
- Walker JB: Relief from chronic pain by low power laser irradiation. *Neurosci Lett* 43:339-344, 1983
- Whitley RJ, Kimberlin DW: Herpes simplex viruses. *Clin Infect Dis* 26:541-555, 1998
- Yu H, Chang K, Yu C, Chen J, Chen G: Low-energy helium neon laser irradiation stimulates IL-1 and IL-8 release from cultured human keratinocytes. *J Invest Dermatol* 107:593-596, 1996
- Yu W, Naim JO, Lanzafame RJ: Effects of photostimulation on wound healing in diabetic mice. *Lasers Surg Med* 20:56-63, 1997a
- Yu W, Chi L, Naim JO, Lanzafame RJ: Improvement of host response to sepsis by photobiomodulation. *Lasers Surg Med* 21:262-268, 1997b
- Zimmermann M: Studies on the therapeutic efficacy of a HeNe laser. *Dtsch Z Mund Kieferheilkd Gesichtschir* 14:313-319, 1990