Acta Derm Venereol (Stockh) 1998; 78: 46–47

Acyclovir Cream Prevents Clinical and Thermographic Progression of Recrudescent Herpes Labialis beyond the Prodromal Stage

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Early treatment of recrudescent herpes labialis over the symptomatic area has been claimed to inhibit the clinical signs of recrudescent herpes labialis. Electronic infrared thermography can both recognise the prodromal phase and identify the area requiring drug therapy.

Our objective was to use infrared thermography to identify prodromal herpes and follow the response to topical acyclovir cream therapy over the thermographically active area.

Seventy instances of prodromal cold sores were confirmed thermographically. Zovirax cold sore cream (acyclovir) was applied 5 times per day for 5 days to the thermographically positive area. All returned after 72 h for a further thermographic and clinical examination of the initially active area.

All 70 patients illustrated a localised increase in temperature over the symptomatic area during the prodromal stage. The development of a clinical herpes lesion was prevented in 46% of the patients. In the lesions that did develop, an 80% reduction in clinical lesion size was observed in 82% of the subjects. The remaining 18% showed a reduction in healing time. *Key words: imaging; antiviral; infection.*

(Accepted June 30, 1997.)

Acta Derm Venereol (Stockh) 1998; 78: 46–47.

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The appearance and size of the subclinical prodromal phase of recrudescent herpes labialis (RHL) have been objectively measured by electronic infrared thermography (IRT) (1). The method has been used to study the preventative effect of acyclovir cream.

METHODS AND MATERIALS

Patient population

Seventy patients (47 female, 23 male; mean age 40 ± 6 years) were recruited from staff within the Royal Victoria Hospital Trust, Belfast. All were known cold sore sufferers and were specifically recruited because of the necessity of thermoimaging patients at the earliest stage of their prodromal RHL. They attended the School of Clinical Dentistry within 12 h of recognising the prodromal symptoms of tingling/burning. All presented at the subclinical stage of RHL and were on no anti–viral medication. Written consent was obtained and all underwent the same study protocol, which involved recording the clinical stage of RHL, the presence of prodromal symptoms, thermal acclimatisation in an environmentally controlled room for a period of 20 min and thermographic assessment of the symptomatic area and the contralateral asymptomatic area of skin/lip. Two images were recorded after acclimatisation using the AGEMA 900 Thermovision System (AGEMA Infrared Systems, Danderyd, Sweden), one at a focal distance 0.5 m to assess facial thermal asymmetry and a second at a fixed distance of 0.05 m for detailed examination of the thermographically positive area. Each patient was dispensed a 2-g tube of Zovirax cold sore cream (Wellcome Warner Consumer Health Care, Dartford, Kent, U.K.), which contains 5% acyclovir w/w, and directed to apply this topically 5 times per day for 5 days to the thermographically positive area. Patients were asked to return 72 h later and underwent the same study protocol to assess lesion termination/development. Patients who developed clinical lesions had virus culture for identification of HSV-1 as previously reported (1).

RESULTS

Seventy active episodes of RHL were thermographically assessed in 70 patients. All attended during the subclinical prodromal stage of the developing RHL, with a mean presentation time for the group of 7 h ± 5 h. All reported perceived prodromal symptoms of tingling at one of seven anatomical sites. The distribution was approximately 50% on both the upper lip and lower lip, respectively. Four presented with lesions directly below the nose. Seventeen episodes were located on the right part of the upper lip. Eight episodes were on the midline of the upper lip, with 7 on the left quadrant of the upper lip. The distribution of lower lip episodes was comparable with 8 on the lower right quadrant, 6 on the midline and 20 on the lower left quadrant.

On attendance during the prodromal phase all patients showed an increase in temperature with the mean localised change in temperature ($\Delta t^{\circ}C$) being $1.1^{\circ}C \pm 0.3^{\circ}C$ over a mean thermographically positive area of 126 $mm^2 \pm 34$ mm^2 (Fig. 1), as compared to the contralateral side. Of the 70 lesions all treated with acyclovir cream, 32 (46%) returned after 72 h of treatment with complete prevention of the developing lesion (Fig. 2), i.e. no clinical, thermographic or symptomatic evidence of RHL. Thirty-eight lesions (54%) progressed to produce a clinical manifestation of RHL. In 31 of these cases the $\Delta t^{\circ}C$ mean measured at the symptomatic site was $0.6^{\circ}C \pm 0.2^{\circ}C$.

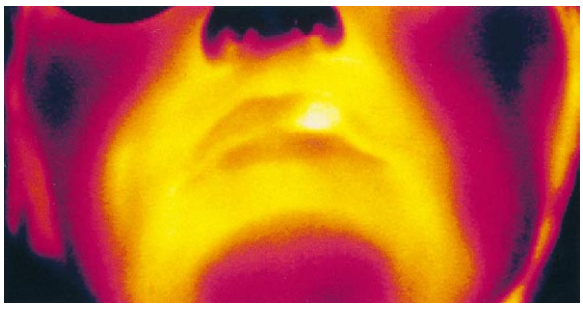

Fig. 1. Thermogram of subclinical prodromal herpes labialis. In this thermogram colour palette, increasing temperature is represented by lightening of colouration. Note localised increase in temperature over prodromal site, which disrupts the symmetrical pattern of facial features.

 ISSN 0001-5555

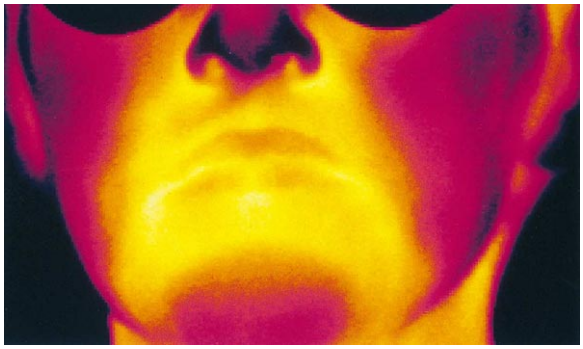

Fig. 2. Thermogram of prevented recrudescent herpes labialis lesion. Thermal symmetry is evident, indicating that drug therapy has eliminated the initial virus-associated subclinical inflammatory response.

The clinical area of these lesions was reduced by about 80%, with the mean area being $10\ mm^2 \pm 9.5\ mm^2$. The remaining 7 lesions (10%) in which patients related no improvement in the initial clinical course of their RHL after treatment exhibited a mean area of $31.5\ mm^2 \pm 6\ mm^2$.

No difference was observed in the $\Delta t^{\circ}C$ values for the three outcome groups, i.e. prevented, clinically improved and non-improved, and no relationship was observed between treatment outcome and the time elapsed before treatment began. They were 1.1 ± 0.3, 1.0 ± 2.5, and 1.1 ± 0.25, respectively, and the time before treatment values was 6–8 h $\pm$ 6.3, 7.1 h $\pm$ 6.4 and 7–8 h $\pm$ 6.1, respectively. Three patients reported adverse effects: one reported a dry flaking area, which affected the uninvolved skin to which the cream was applied, and 2 patients reported a stinging sensation on applying the cream.

DISCUSSION

Prevention of RHL has been observed previously during clinical trials (2, 3). In their study, Fiddian & Ivanyi (4) reported that early patient-initiated treatment with acyclovir cream prevented lesions in a proportion of patients. However, without an objective means of validating the prodromal stage, definitive conclusions concerning prevention have to be considered anecdotal. Furthermore, patients in that study (4) applied acyclovir cream over a much smaller area than is currently recommended. A key development has been to use IRT to accurately identify and quantify the subclinical inflammatory response (1). The reproducibility of IRT has been further supported by this investigation, which again has illustrated the constant $\Delta t^{\circ}C$ for a subclinical prodromal lesion and that the thermographically active area is about 4 to 5 times the symptomatic area.

The two key factors in this study were early patient recognition of disease and the application of IRT to visualise true subclinical prodromal RHL, allowing evaluation of the preventive action of topical acyclovir. This study therefore demonstrated, for the first time, validation of the therapeutic effect of acyclovir as a preventative cold sore treatment.

No relationship was found to exist between the temperature of the prodromal area and subsequent treatment outcome, as the $\Delta t^{\circ}C$ observed at the prodromal areas for each treatment outcome did not differ. This may indicate variable virulence of different strains of HSV-1 or unknown host factors involved in terminating the lesion at the prodromal stage.

Early treatment has been shown to influence the clinical outcome of RHL when treatment has been investigated at different stages of lesion development, i.e. prodromal, vesicular or ulcerative stages. However, we were studying the earliest stages of RHL and discerned no relationship between clinical outcome and time to treatment within a 12-h period from onset of symptoms. One factor that may affect clinical outcome is the amount of drug used. By directing treatment over the larger thermographically active area more drug was therefore applied. Application of the drug to the entire area of disease involvement was probably important. The preventive outcome in this study was higher than that previously reported in studies which applied the drug over a smaller area, and this then argues for the treatment to the larger thermographically positive area to be significant in the prevention of RHL lesions with acyclovir cream.

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