The use of local concentrated heat versus topical acyclovir for a herpes labialis outbreak: results of a pilot study under real life conditions

Background: Frequent outbreak of herpes labialis can affect quality of life by prodromes like burning, itching, and swelling. Topical applied preparations aim to shorten the duration of symptoms, inhibit the virus replication and/or accelerate the healing process. Local concentrated heat (LCH) can reduce burning, itching, or swelling of the skin by influence of mechano-heat sensitive afferent neurons.

Patients and methods: To examine the effectiveness of two different topical applications (LCH versus topical acyclovir [TACV]) under real life conditions, we conducted a prospective, observational, reference-controlled cohort pilot study with 103 patients. Occurrence of prodromal burning, itching, swelling, and quality of life were assessed.

Results: The LCH observation group (OG) showed a significantly faster improvement in all symptoms after 1-day of application than the TACV OG. The burden and duration of disease was lower and shorter in the LCH OG than in the TACV OG.

Conclusions: The prodromal symptoms in recurrent herpes labialis were attenuated more effectively by LCH than by TACV.

Keywords: herpes labialis, local concentrated heat, acyclovir

Introduction

Herpes labialis or cold sores are primarily caused by infections of herpes simplex virus type 1 (HSV-1), which has a seroprevalence of >90% within the adult population in Europe. HSV-1 is a member of the virus subfamily of α-Herpesviridae. The virions consist of nucleocapsid, tegument, and a lipid envelope originated from the host cell with embedded virus encoded glycoproteins at the surface. In addition to a total of 30 viral proteins the virions contain also cellular proteins (e.g., heat shock protein [HSP] and actin). The viral replication cycle has several phases. After the virions are absorbed in the target cell they bind to structures of the cellular surface (e.g., carbohydrate polymers and protein receptors) via glycoproteins and the envelope merges with the cell membrane. After the liberation of the nucleocapsid into the cytoplasm and its migration to the nuclear pores via microtubules, the viral genomic deoxyribonucleic acid (DNA) infiltrates the nucleus and circulates. Through cascading expression of different gene groups the virus genome finally replicates together with other virus components into cell vesicles. Merging with the cell membrane the fully developed virus particle is released. Aberrant, non-infectious virus particles are distinguished from fully developed, infectious virions. Virions have the ability to remain in a state of latency in specific target cells. Different internal (e.g., stress and immunosuppression) or external (e.g., ultraviolet [UV] light and hormones) factors can trigger the reactivation
of the latent virus genome and thus the development of infectious virions.\textsuperscript{12} After primary infection with HSV-1 \textit{(gingivostomatitis herpetica)}, which often shows no or only mild symptoms, a latency phase with no symptoms follows that can vary in duration. The abovementioned trigger factors can cause recurrent reactivation.\textsuperscript{2,6–8} Frequency and severity of the clinical symptoms vary individually. Reactivation is characterized by a typical succession of painful burning, erythema, and blistering.\textsuperscript{9} A commonly used therapeutic intervention is the topic application of acyclovir starting in the prodromal phase.\textsuperscript{10} Acyclovir as an antimetabolite inhibits the replication of HSV mainly by blocking the viral thymidine kinase.\textsuperscript{11} Since acyclovir reaches relevant bioavailability only within the skin through epicutaneous application, it has no direct influence on neurogenic prodromal symptoms such as pain, burning, and pruritus.\textsuperscript{12}

### Materials and methods

#### Study design

This non-interventional pilot study (NIS) was conducted between April and November 2012 in collaboration with eleven pharmacies in Germany. The study had been approved by the ethics committee of the University of Greifswald, registered at German authorities and at “German Register for Clinical Studies” (DRKS identifier: 00004777). The NIS was designed as a prospective, reference controlled, observational cohort study with 103 patients to describe the symptomatic outcomes after use of local concentrated heat (LCH) or a topical acyclovir (TACV) treatment. For application of LCH, a CE-certified medical device of class 2A (Herpotherm\textsuperscript{®}, Riemser Pharma GmbH, Greifswald, Germany) with a guaranteed duration-heat-constant was used, which is intended for non-invasive administration onto the skin.\textsuperscript{13} The LCH device produces a microchip controlled concentrated thermal impulse of 50°C–53°C on a 38.5 mm\textsuperscript{2} covered plate for 4 seconds. The NIS was patient-initiated, and involved the self-application under real life conditions.

Patients in need for treatment who bought either a TACV or a LCH device were asked by the pharmacist to participate in the study. The majority (63\%) of the patients had used TACV in the past, only 3\% of the patients had been aware of LCH as an alternative therapy. After the pharmacist informed the patient about the aim of the study, the patient was asked to sign the informed consent form. There was no selection of subjects to one or another observation group (OG). TACV and LCH were applied according to the instructions in the summary of product characteristics (SPC). TACV: 5 times per day for 5 days; LCH maximum of 5 times per day until symptoms disappeared.

### Pharmacist’s questionnaire

Information regarding the demographics of the patients, visibility of vesicles, possible current and previous therapies, and the rate of recurrences per year were obtained for both OGs. Finally, each patient was explicitly informed about the “SPC/instruction for use” for their respective treatment option: when to start, how to proceed, and how to enter the data into the patient’s questionnaire.

### Patient’s questionnaire

Herpes labialis is most often treated with over-the-counter (OTC) drugs.\textsuperscript{9} As the outbreaks are not predictable, patients personally decide when to start the treatment, based on typical first symptoms of a herpes labialis recurrence period, such as itching, pricking, or a feeling of tension at the lips. From the beginning of prodromal symptoms (burning, itching, and/or swelling of the lips) and during 7 days of treatment patients were asked to determine

#### Table 1 Patients and treatment characteristics during former recurrence episodes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LCH (N=51)</th>
<th>TACV (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13</td>
<td>25.5</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>74.5</td>
</tr>
<tr>
<td>Prodromes visible at the time of recruitment</td>
<td>23</td>
<td>45.1</td>
</tr>
<tr>
<td>Number of herpes labialis episodes per year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>10</td>
<td>19.6</td>
</tr>
<tr>
<td>3–4</td>
<td>17</td>
<td>33.3</td>
</tr>
<tr>
<td>5–6</td>
<td>17</td>
<td>33.3</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>13.7</td>
</tr>
<tr>
<td>Former treatment modalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domestic remedies</td>
<td>9</td>
<td>17.6</td>
</tr>
<tr>
<td>Topical Acyclovir</td>
<td>36</td>
<td>70.6</td>
</tr>
<tr>
<td>Topical Penciclovir</td>
<td>10</td>
<td>19.6</td>
</tr>
<tr>
<td>Local concentrated heat</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>RX-drugs</td>
<td>7</td>
<td>13.7</td>
</tr>
<tr>
<td>Average number of prodromes during former recurrences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>13.7</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>27.5</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>25.5</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>19.6</td>
</tr>
<tr>
<td>&gt;4</td>
<td>7</td>
<td>13.7</td>
</tr>
</tbody>
</table>

**Abbreviations:** LCH, local concentrated heat; TACV, topical acyclovir; RX-drugs, prescription drugs; N, number.
if any prodromes or crusts were present. To record the daily development of swelling, pruritus, and burning we used a patient diary with a Numeric Analog Scale (NAS; 0 = no sensation; 9 = worst sensation imaginable). Quality of Life (QoL) was also assessed daily using a NAS. To ensure therapy adherence with “SPC/instruction for use”, patients were asked to enter the number of treatments per day. After 7 days of observation, patients were asked to evaluate the success as well as the tolerability of their chosen therapy using a 5 point Likert scale. All adverse events were reported.

**Incentives**

Patients could choose between vouchers for books, fuel, or pharmacy products as a thank you for their participation in the study. Patients received the voucher only when they brought back the completed patient’s questionnaire to the pharmacy after the observation period of 7 days.

**Data management and statistical analyses**

All patients that provided data during the therapy period were included in statistical analyses. A database (Microsoft Excel for MAC V14.3.2, IBM Corporation, Armonk, NY, USA)
was used for single data entry. The structure of the database was adapted to the questionnaire. Descriptive statistics were produced including frequencies (or percentages) for categorical variables, as well as means, standard deviations, medians, minimums, and maximums for continuous variables. Single descriptors and frequencies of various factors were tabulated. SAS® Version 9.2 (SAS Institute Inc., Cary, NC, USA) and Origin 6.1 G (Origin Lab Corporation, Northampton, MA, USA) were used to conduct all analyses. Associations between factors were determined using Fisher’s exact tests, and the Wilcoxon–Mann–Whitney test was used to compare mean scores of patients’ outcomes of the LCH with

Figure 1 NAS progression as mean ± standard deviation of (A) burning, (B) itching, (C) swelling, and (D) QoL.

Notes: LCH: N=51; TACV: N=52; 0= no sensation; 9= worst sensation imaginable.

Abbreviations: LCH, local concentrated heat; NAS, numeric analog scale; QoL, quality of life; TACV, topical acyclovir.
Concentrated heat versus topical acyclovir for herpes outbreak

TACV therapies. The statistical tests was 2-tailed and a probability of $P<0.05$ was considered statistically significant.

**Results**

**Characteristics of the study population**

A total of 103 patients were enrolled in this study. Fifty-one patients were exposed to LCH while fifty-two were treated with TACV. The mean age of the patients was 40±15 years (range 18–72 years). The LCH therapy OG consisted of 13 males and 38 females. Sixteen males and 36 females were treated with TACV. Overall, 72% of the patients were female. A total of 41 patients (80%) treated with LCH and 35 patients (67%) treated with TACV had more than two recurrences per year. Eighty-six percent of patients in the LCH OG (44 of 51) and 79% of the TACV OG (41 of 52) developed two or more classical lesions during former recurrences. Fifty-four out of 103 patients developed lesions immediately before the start of treatment. Table 1 shows the sex, number of herpes labialis episodes per year, former treatment modalities, and the average number of prodromes during former recurrences.

**Burning, itching, swelling, and QoL**

Treatment via both TACV and LCH reduced burning, itching, swelling, and led to less deterioration in QoL over the observation period. There was a significantly faster improvement for these symptoms and QoL (assessed by NAS) of herpes labialis in the LCH OG than in the TACV OG (Figures 1A–D, 2, and Table 2). This was noticeable after one day of treatment (day 2; $P<0.05$). Patients in the LCH OG reported a spontaneous improvement in burning, itching, swelling, and QoL after 1-day of treatment. Patients in the TACV OG reported an improvement in all observed symptoms after 2 days. In general, the perception of burning, itching, and swelling corresponded with the QoL curve in both OGs. Mean NAS score of itching, swelling, burning, and impairment of QoL was reduced by 50% at least 2 days earlier in the LCH OG than in the TACV OG (Figure 1A–D).

**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning</td>
<td>0.210</td>
<td>0.046</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.0003</td>
<td>0.005</td>
<td>0.133</td>
</tr>
<tr>
<td>Itching</td>
<td>0.943</td>
<td>0.044</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.016</td>
<td>0.056</td>
</tr>
<tr>
<td>Swelling</td>
<td>0.608</td>
<td>0.032</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.007</td>
<td>0.113</td>
</tr>
<tr>
<td>QoL</td>
<td>0.702</td>
<td>0.091</td>
<td>0.0225</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Abbreviation:* QoL, quality of life.
Development of prodromes

The burden and duration of all symptoms was lower and shorter in the LCH than in the TACV OG (Figure 3). The mean time for prodromes to be present was 2.3 days for the LCH OG and 4.5 days for patients treated with TACV.

Assessment of success and tolerance

Success in application was reported as “very good” by 53% of patients from the LCH OG but in only 12% of the TACV OG (Figure 4A). Self-reported success of the herpes labialis treatment by patients was associated with the type of application (P<0.0001, Fisher’s exact tests). Tolerance was comparable in both OGs (Figure 4B).

Adverse events

During this study, only one case in the LCH OG reported any skin irritation. No serious adverse events were reported.

Discussion

To date, there are no other studies that investigated the influence of topical herpes labialis treatment via patient reported outcomes under real life conditions. However, this study clearly has its limitations. To start with, it must be stated that at no time a clinical assessment of the condition took place, whether it was based on medical examination or on microbiological and/or infection-serological findings. Therefore, it cannot completely be ruled out that false diagnoses have been included in the study. Furthermore, no statement on potential therapy resistances can be made. Thus, the homogeneity of the study population cannot be assured. Additionally, it must be considered that the presentation of LCH (previously unknown to most of the patients) as a therapy option within the study setting, could have indirectly influenced the choice of therapy. However, equal prices eliminated the possibility of preferences due to pecuniary reasons.

The improvement of burning, itching, and swelling as a measure for QoL are key outcome parameters. Both OG in the present study found that treatment had a positive influence on QoL. The perception of burning, itching, and swelling correlated clearly with the QoL in both OGs. The use of LCH led to an immediate improvement of these prodromal symptoms. These effects have also been observed in another cohort study investigating the effect of LCH after insect stings.

Application of LCH (approx. 53°C for 4 seconds) causes thermal conduction into the skin. This is determined mainly by the thermal diffusivity of skin, which is 0.40 cm²/s × 10³. Other physical parameters, such as heat convection and heat radiation have only marginal significance and can be neglected according to current knowledge. It can be assumed that using the present setting of LCH the vital epidermis reaches a temperature of 47°C–48°C for a time period of approximately 2–3 seconds. This thermal effect is called “heating” and has a biological response of functional but fully reversible alterations. In deeper layers, a lower isotherm level can be assumed that leads to reactive hyperemia in the sense of a neurosensory initiated hyperperfusion.
Efficacy of LHC can be explained by activation of the transient receptor potential vanilloid subfamily member 1 (TRPV-1). LHC activates TRPV-1 and thus causes calcium influx into the target cell. TRPV-1 in the skin is expressed in small to medium diameter sensoric neurons (C- and A-δ-fibers) as well as in other cells as keratinocytes, fibroblasts, endothelial cells, and mastocytes. Its physiological functionality is assumed to be connected with thermal sensory perception and neuro-immunological reaction pattern. The long-term analgesic and antipruritic effect can be explained by the inhibition of neurogenic inflammatory processes as well as mainly by the alterations in axonal integrity.

Another hypothesis for the efficacy of LHC concentrates on HSPs. The expression of HSPs is intensified under stress conditions (eg, heat), thus HSPs induce convolution of secondary structures of proteins in order to prevent denaturation. In cells infected with HSV-1 intensified expression of HSP70 and HSP72 could be detected even without heat stress. The range of induced HSPs under heat stress varies depending on cell type. For keratinocytes, HPS27 is considered to play a major role. Intensified expression of HSP27 inhibits the release of pro-inflammatory mediators by modulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, which has immunomodulating effects. Specific investigations on HSV-1 infected keratinocytes under heat stress showed that HPS27 can modulate the release of pro-inflammatory cytokines.

**Figure 4** Patient reported (A) tolerance and (B) success of each cohort.

*Notes:* LCH: N=51; TACV: N=52.

*Abbreviations:* LCH, local concentrated heat; TACV, topical acyclovir.
conditions have not been carried out so far. The relevance of HSP in terms of any antiviral effects of LCH is not based on adequate reasoning and very unlikely.

A direct thermal inactivation of HSV-1 could not yet be proven.\textsuperscript{33–35} An alternative hypothesis is based on the assumption of heat sensitive inhibition of the viral reproduction. However, data exists that contradicts this hypothesis showing that within the temperature range under review an induction of viral reproduction can be expected.\textsuperscript{36} Speculations about heat sensitive inhibition of DNAse activity\textsuperscript{37} or about heat sensitive inhibition of infectivity\textsuperscript{38} have been disproved. For an induction of an intensified synthesis of nitric oxide (NO), which, depending on concentration, can cause antiviral effects via oxidative mechanisms,\textsuperscript{39,40} the duration of application is far too short.\textsuperscript{21,41} It is known that there is a bi-phase vasogenic response: metabolic interactions via induction of inducible NO synthase can be expected at the earliest after approximately 10 minutes.\textsuperscript{22,42}

Overall, the presented data clearly indicate that LCH reduces the prodromal symptoms pruritus and burning that are the main factors for worsening QoL. Possibly, the efficacy of LCH can be explained by the activation of TRPV-1 (similar to Capsaicin),\textsuperscript{43} which, in the medium term, inhibits the functionality of small to medium diameter sensoric neurons. Although direct impact on the replication of the virus cannot be ruled out completely, it could not be proven so far, either in vitro or in vivo.

Acknowledgments
This study was completely sponsored by Riemser Pharma GmbH. The authors are very grateful to the staff of the pharmacies involved. We also acknowledge the excellent statistical analysis of Mr. Julius Mungo and Mrs. Anja Berensmeier.

Disclosure
CM was a former employee of Riemser Pharma GmbH while LCB and FV are currently employees. JW received lecturing fees, used to be co-operating partner in scientific projects and investigator in clinical studies sponsored by Riemser Arzneimittel AG and Riemser Pharma GmbH. The authors report no other conflicts of interest in this work.

References


