

Treatment and prevention of herpes labialis

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ABSTRACT

OBJECTIVE To review the evidence regarding the treatment and prevention of herpes labialis.

QUALITY OF EVIDENCE The evidence relating to treatment and prevention of herpes labialis is derived from randomized controlled trials (level I evidence).

MAIN MESSAGE Treatment with an indifferent cream (zinc oxide or zinc sulfate), an anesthetic cream, or an antiviral cream has a small favourable effect on the duration of symptoms, if applied promptly. This is also the case with oral antiviral medication. If antiviral medicine (cream or oral) is started before exposure to the triggering factor (sunlight), it will provide some protection. Research on sunscreens has shown mixed results: some protection has been reported under experimental conditions that could not be replicated under natural conditions. In the long term, the number of relapses of herpes labialis can be limited with oral antiviral medication.

CONCLUSION Only prompt topical or oral therapy will alleviate symptoms of herpes labialis. Both topical and oral treatment can contribute to the prevention of herpes labialis.

RÉSUMÉ

OBJECTIF Revoir les données concernant le traitement et la prévention de l'herpès labial.

QUALITÉ DES PREUVES Les preuves concernant le traitement et la prévention de l'herpès labial proviennent d'essais cliniques randomisés (preuves de niveau I).

PRINCIPAL MESSAGE Le traitement avec une crème non spécifique (oxyde ou sulfate de zinc), anesthésiante ou antivirale a un effet légèrement favorable sur la durée des symptômes à condition que la crème soit appliquée précocement. On obtient le même effet avec une médication antivirale orale. Si le traitement antiviral (en crème ou per os) est institué avant l'exposition au facteur déclenchant (lumière solaire), il confèrera une certaine protection. La recherche sur les écrans solaires a donné des résultats contradictoires: dans des conditions expérimentales, on a rapporté une certaine protection mais cela n'a pu être confirmé dans des conditions naturelles. À long terme, le nombre de récurrences de l'herpès labial peut être réduit par les antiviraux oraux.

CONCLUSION Seuls un traitement topique ou une médication orale précoces peuvent soulager les symptômes de l'herpès labial. Les traitements topiques ou oraux peuvent contribuer à la prévention de l'herpès labial.

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Herpes labialis (cold sore, fever blister) is a commonly occurring ailment. Its average incidence is 1.6 per 1000 patients per year and its prevalence is 2.5 per 1000 patients per year.¹ Approximately one-third of all infected patients suffer relapses.² Herpes labialis is a rash of the skin and mucous membranes (in particular, the lips) and is characterized by erythema and blisters that are preceded and accompanied by burning pain. It is a harmless but often annoying ailment in immunocompetent patients and it usually heals spontaneously within 10 days. Herpes labialis is contagious for individuals who have not been previously infected by the virus and for those with weakened immune systems (eg, those with HIV infection or undergoing chemotherapy³). In addition, herpes labialis infection can result in genital herpes through orogenital contact.⁴

Herpes labialis is caused by herpes simplex virus type 1 (HSV-1). Infection with type 2 virus can also lead to (primary) herpes labialis, but this type rarely causes a relapse of the ailment.⁵ The primary infection with HSV-1 usually occurs before the age of 20 years. Antibodies against the virus can be found in about 80% of all adolescents. Probably because of the improved socioeconomic circumstances in industrial countries, individuals are older when first infected than was the case some decades ago. As a result of this epidemiologic shift, it is becoming more common for the primary infection to manifest as genital herpes because of orogenital contact.^{4,6,7}

After primary infection, the virus recedes via the sensory nerve into the respective ganglion (usually the trigeminal ganglion), where it lies latent throughout the individual's lifetime. Stimuli such as fever, menstruation, sunlight, and upper respiratory infections can reactivate the virus, after which it returns to the epithelial cells via the sensory nerve.⁸ In contrast to the primary infection, during which all oral mucosa can be affected, relapsing infections are limited to the mucosa of the hard palate or, in older children and adults, the lips.⁹ The number of relapses decreases after the age of 35 years.¹⁰

To diagnose herpes labialis in general practice, physicians are limited to taking patients' histories and performing physical examinations. A primary infection with HSV-1 is often asymptomatic. However, when symptoms do occur, young children often present with herpetic stomatitis, characterized by fever and the formation of small blisters and ulcers (2 to 10 mm) in the front of and around the mouth, on the tongue, and on the lips.¹¹ Adults often present with sore throat and cervical lymph node swelling, strongly resembling infectious mononucleosis. Relapses are characterized by burning skin rash on the lips and around the mouth (papules, vesicles, and crusts). In about 25% of relapse cases the infection heals before any blisters can form.

This article aims to review the treatment of immunocompetent patients with herpes labialis and the available preventive therapies.

Quality of evidence

Literature searches for randomized controlled trials (RCTs), meta-analyses, and reviews were conducted in April 2008: both the Cochrane Central Register of Controlled Trials (key word *herpes labialis*) and MEDLINE (MeSH terms *herpes labialis*, *therapeutics*, and *prevention and control*) were searched. To be included in this review, assessed treatments had to be feasible in outpatient health care. All studies of immunocompromised patients were excluded. Without language restrictions we found 81 MEDLINE hits (44 RCTs, 37 reviews). Four of the RCTs were not written in English. Based on the titles and abstracts, only 1 German RCT added any information to the English publications. We included this RCT in our review.

Effects of treatment

Indifferent cream. In a study of 46 herpes labialis patients, time until recovery was shortened (5.0 vs 6.5 days) in those individuals who received prompt treatment with zinc oxide and glycine cream (applied every 2 hours during the day, starting as soon as possible after the first symptoms appeared and continuing until the complaints disappeared).¹² The effects of zinc sulfate (1%) gel, applied in a similar fashion, were studied in 79 patients.¹³ After 5 days, 50% of the patients in the treatment group were symptom-free, compared with 35% in the placebo group.

Anesthetic cream. In a small, randomized, placebo-controlled crossover study (7 patients), lidocaine and prilocaine cream (25 mg of each per 1 g) reduced the mean duration of subjective symptoms (2.1 vs 5.1 days) and the duration of eruptions (2.6 vs 7.3 days).¹⁴

Antiviral cream. The effects of acyclovir cream (5 times daily for 5 days) were investigated in 10 studies (number of patients per study varied from 30¹⁵ to 673¹⁶).¹⁵⁻²⁴ Treatment in each study was started as soon as the first prodromal symptoms appeared. None of the studies reported a decrease in the duration or severity of pain according to complaints. There was, however, a reduction in the time to recovery in 8 of the studies, varying from 0.5 (4.3 vs 4.8¹⁶) to 2.5 (5.7 vs 8.3¹⁵) days. Penciclovir cream showed similar effects in 2 other studies (534²⁵ and 2209²⁶ patients). One of those studies also

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

reported a reduction in the duration of pain (3.5 vs 4.1 days).²⁶ Penciclovir cream, however, has to be applied every 2 hours during the day, which makes it less practical than acyclovir cream.

Oral antiviral medication. Five studies assessed the effects of oral antiviral medicines on herpes labialis. One of the studies (149 patients) showed that oral acyclovir (200 mg 5 times daily for 5 days) had no effect on the duration of pain or the time to recovery.²⁷ Another study (174 patients) reported a reduction in the duration of the symptoms (8.1 vs 12.5 days) when a higher dose (400 mg 5 times daily for 5 days) was used.²⁸ The effect of valacyclovir, administered in either a 1-day (2000 mg twice daily) or a 2-day (2000 mg twice on the first day and 1000 mg twice on the second day) regimen, was investigated in 2 other studies (1524 and 1627 patients, respectively).²⁹ The 1-day regimen resulted in a 1-day reduction in the duration of symptoms (4.0 vs 5.0 days). A smaller effect was reported for the 2-day regimen (4.5 vs 5.0 days). Two treatment regimens with famciclovir (single 1500-mg dose or 750 mg twice daily for 1 day) were studied in 701 patients.³⁰ The patients in the famciclovir groups had a shorter median time until the first lesions healed than did the placebo group (single dose: 4.4 days; 750 mg twice daily: 4.0 days; placebo: 6.2 days). In all of these studies, treatment was initiated when the first prodromal symptoms appeared.

Heat application. A recently marketed device in the shape of a lipstick (Hotkiss, Herpotherm) can be used on the area where prodromal symptoms of herpes labialis are felt. Once applied, it heats up to 50°C within a few seconds. This high temperature supposedly blocks replication of the virus and the resultant formation of blisters. Randomized research on the effectiveness of this treatment has not yet been published.

Effects of short-term preventive therapies

Sunscreen. The prophylactic effect of sunscreens was studied in a crossover trial in which 38 patients were exposed to experimental ultraviolet (UV) light. None of the test subjects using a sunscreen developed herpes labialis compared with 71% of those using a placebo.³¹ In a study of 51 patients, which was performed under natural conditions, use of a sunscreen lotion with a high protective factor did not result in a lower incidence of herpes labialis.³²

Antiviral cream. Acyclovir cream (applied 5 minutes after experimental UV exposure) was not effective with respect to the frequency and seriousness of herpes labialis in a study of 196 patients known to have sun-caused relapses.³³ This antiviral cream (5 times daily for 3 to 7 days, starting at least 12 hours before sun exposure) did, however, have a prophylactic effect on 196 skiers

in a study performed under natural conditions.³⁴ In the acyclovir group, 21% of the skiers developed lesions compared with 40% in the placebo group. Not only the antiviral, but also the UV light-absorbing characteristic of acyclovir, could have caused this effect.³⁵

Oral antiviral medication. The effect of systemically administered acyclovir (400 mg twice daily for a maximum of 7 days, starting 12 days before sun exposure) was investigated in 147 skiers: 7% of the individuals in the acyclovir group and 26% in the placebo group developed fever blisters.³⁶ Under experimental conditions, oral acyclovir (200 mg 5 times daily, starting 7 days before or 5 minutes after UV exposure) did not prevent the formation of immediate herpes lesions (within 48 hours of exposure) in a placebo controlled trial with 196 patients. It did, however, inhibit delayed lesions (2 to 7 days after exposure).³³ Oral acyclovir (800 mg twice daily for 3 to 7 days, starting 12 to 24 hours before sun exposure) showed no prophylactic effect in a later study of 239 patients.³⁷

Effects of long-term preventive therapies

Antiviral cream. Despite the possible impracticality of the intervention, 2 small crossover trials (16³⁸ and 23³⁹ patients) were carried out to study the long-term effects of prophylactic application of acyclovir. The antiviral cream was applied either twice³⁸ or 4 times³⁹ a day for 16 weeks. Small differences in the average number of days with symptoms (acyclovir group: 12.2 days; placebo group: 17.4 days) and with lesions (acyclovir group: 9.5 days; placebo group: 12.4 days) were only seen with the 4-times-daily regimen.³⁹

Oral antiviral medication. A crossover trial investigated 11 patients given 200 mg of acyclovir 4 times daily for 12 weeks.⁴⁰ Two of the patients in the treatment group and 9 in the placebo group had relapses. In a similar study, 22 patients were administered 400 mg of acyclovir twice daily for 4 months. This prophylactic regimen also reduced the number of relapses (average 0.85 vs 1.80 episodes per patient).⁴¹ A pooled analysis of 2 studies (98 patients in total) showed that once-daily administration of 500 mg of valacyclovir for 4 months increased the time interval until the next relapse from 9.6 to 13.1 weeks. During the 4-month period, 60% of the patients receiving the drug were relapse-free compared with 38% in the placebo group.⁴²

Side effects

Indifferent cream. The side effects of zinc oxide and glycerin cream included a burning sensation and itching, which occurred more often in the treatment group than in the placebo group. The difference, however, was not statistically significant.¹² The adverse effects of the zinc sulfate gel were generally dryness and a feeling of tightness,

but these sensations did not arise more frequently in the treatment group than in the placebo group.¹³ No side effects have been reported for sunscreen use.

Antiviral cream. The reported side effects of acyclovir and penciclovir creams did not differ from those cited for the placebo groups in either type or frequency.¹⁵⁻²⁶

Oral antiviral medication. The most frequently reported side effects of oral antiviral medication were headache and nausea, irrespective of dosage and duration of treatment.^{29,30,41,42}

Conclusion

Herpes labialis is a frequently occurring, self-limiting ailment. Many patients do not consult their general practitioners, but use over-the-counter medication. Treatment with indifferent (zinc oxide and zinc sulfate), anesthetic, or antiviral cream has a small favourable effect on the duration of the symptoms, if applied promptly. This is also the case with oral antiviral medication. If antiviral medicine (topical or oral) is started before exposure to the triggering factor (sunlight), it will provide some protection. Research results are, however, contradictory. Research on sunscreens has also shown mixed results, with some protection reported under experimental conditions that could not be replicated under natural conditions. In the long-term, the number of relapses of herpes labialis can be limited with oral antiviral medication. ✨

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Contributors

Drs Opstelten, Knuistingh Neven, and Eekhof contributed to the concept of the article, the literature search, the review of selected articles, and preparing the manuscript for submission.

Competing interests

None declared

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EDITOR'S KEY POINTS

- Herpes labialis is a common self-limited ailment. Approximately one-third of all infected patients suffer relapses. Many patients do not consult their general practitioners and instead use over-the-counter medications. This article reviews the treatment of and available preventive therapies for herpes labialis in immunocompetent patients.
- Prompt treatment with oral antiviral medication or indifferent, anesthetic, or antiviral cream can shorten the duration of eruptions and, in some cases, pain symptoms. Prophylactic treatment with antiviral medication or sunscreen might help prevent relapses, but research shows mixed results. In the long term, the number of relapses can be limited with oral antiviral medication.
- Few side effects were reported for any treatment; some patients experienced burning and itching sensations with topical treatments and some experienced headache and nausea with oral treatments.

POINTS DE REPÈRE DU RÉDACTEUR

- L'herpès labial est une affection fréquente sans grande conséquence. Environ un tiers de tous les patients infectés auront des récurrences. Plusieurs patients ne consultent pas leur médecin, utilisant plutôt des médicaments en vente libre. Cet article rappelle le traitement ainsi que les mesures de prévention de l'herpès labial chez des patients immunocompétents.
- Un traitement précoce avec un antiviral oral ou avec une crème non spécifique, anesthésiante ou antivirale peut réduire la durée de l'éruption et, parfois, celle de la douleur. Un traitement prophylactique avec un antiviral ou un écran solaire pourrait aider à prévenir les récurrences, mais les résultats de la recherche sont contradictoires. À long terme, une médication antivirale orale peut réduire le nombre de récurrences.
- Peu d'effets indésirables ont été rapportés en rapport avec ces traitements; certains patients ont ressenti des brûlements et démangeaisons avec le traitement topique et d'autres, des céphalées et nausées avec la médication orale.

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