

# Therapeutic Options for Herpes Labialis: Experimental and Natural Therapies

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*Herpes labialis, a common condition characterized by recurrent vesicular eruptions primarily on the lips and perioral skin, causes pain and discomfort for millions of adults each year. Over the past several years, the major focus of herpes research has been on the treatment of genital herpes. However, several studies have been conducted to evaluate the efficacy of therapies specifically for herpes labialis. Last year in Cutis®, we reviewed oral and topical therapies for herpes labialis. In this final part of the series, we review experimental and natural treatments that are available for herpes labialis and its associated symptoms.*

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**H**erpes labialis is a common condition characterized by recurrent vesicular eruptions, primarily on the lips and perioral skin. Herpes labialis is most commonly caused by herpes simplex virus type 1 (HSV-1), and, in patients with multiple recurrences, the condition can greatly affect quality of life by causing pain, embarrassment, and psychosocial distress. Oral HSV is the most easily acquired herpesvirus. Approximately 50% of Americans are seropositive for HSV-1 by the time they reach adolescence.<sup>1</sup> By 50 years of age, 80% to 90% carry the virus.<sup>1</sup> We review experimental and natural treatments that are available for herpes labialis and its associated symptoms.

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## Iontophoresis

Iontophoresis, a technique used to enhance the flux of ionic compounds across a membrane by the application of an electrical current to enhance the absorption of acyclovir cream, has been investigated in the topical treatment of recurrent herpes labialis.<sup>2</sup> In a study conducted by Spruance et al, 200 patients who were either experiencing prodromal symptoms or were in the early stages of developing a cold sore randomly received iontophoretic treatment with acyclovir cream or a placebo cream.<sup>2</sup> Each patient received a single topical application of acyclovir or placebo cream and 10 minutes of stimulation at the site of application. In acyclovir-treated patients who were already forming lesions, healing time was reduced by 24%; in patients treated during the prodromal phase, healing time was reduced by 41%. Investigators concluded that the efficacy of topical iontophoretic administration of acyclovir compares favorably with other available topical treatments while offering the convenience of a single dose.<sup>2</sup>

## Herbal Preparations

Herbal preparations for the treatment of herpes labialis have been a topic of interest and debate for several years. Saller et al<sup>3</sup> compared the efficacy of a combined topical preparation of sage and rhubarb extracts, a single-agent preparation of sage extract, and an acyclovir cream in a double-blind, comparative, randomized trial. Dried rhubarb extract (23 mg/g) is a standardized aqueous ethanolic extract, with 4.0% to 6.0% hydroxyanthracene derivatives and dried sage extract (23 mg/g) in an aqueous solution. The study consisted of 145 patients (sage-rhubarb cream, n=64; sage cream, n=40; and acyclovir cream, n=41), of whom 141 could be evaluated in the intent-to-treat analysis.<sup>3</sup>

The mean time to healing in all cured patients was 6.7 days with the sage-rhubarb cream, 7.6 days with the sage cream, and 6.5 days with the acyclovir cream.<sup>3</sup> On the first follow-up visit, the acyclovir-treated group had a decrease in swelling;

at the second follow-up visit, the sage-rhubarb cream group showed a decrease in pain. The investigators concluded that the combined topical sage-rhubarb preparation was as effective as topical acyclovir cream and more efficacious than the sage-alone cream in the treatment of herpes labialis.<sup>3</sup>

### L-lysine

L-lysine, an essential amino acid, has been reported to reduce outbreaks of cold sores, but this also has been a topic of debate. L-lysine has an inhibitory effect on the multiplication of HSV in cell cultures. Milman et al<sup>4</sup> evaluated the prophylactic effect of L-lysine monohydrochloride 1000 mg daily on recurrent herpes labialis in 65 patients in a double-blind, placebo-controlled, crossover study. After 12 weeks of lysine treatment, the patients shifted to placebo treatment for a similar period. On the whole, lysine prophylaxis had no effect on the recurrence rate of herpes labialis. However, significantly more patients were recurrence-free during treatment with lysine than with placebo ( $P=.05$ ), suggesting that certain patients may benefit from prophylactic lysine administration. In the herpes lesions described, lysine had no effect on the rate of healing or on the appearance of the lesions at their worst.<sup>4</sup>

DiGiovanna and Blank<sup>5</sup> carried out a double-blind placebo-controlled trial of oral lysine hydrochloride therapy (400 mg, 3 times daily) in 21 healthy patients with a history of frequently recurring herpes simplex. Using measures of episode frequency, duration, and severity, the investigators were unable to detect any substantial benefit of lysine therapy either as a treatment of episodes in progress or as a prophylactic drug for the prevention of recurrences. The investigators concluded that, in most patients, it is unlikely that lysine improves frequently recurrent herpes simplex infections.<sup>5</sup>

Thein and Hurt<sup>6</sup> examined the efficacy of long-term prophylactic lysine supplementation. Twenty-six volunteers with a history of frequently recurring herpetic lesions completed a 12-month, double-blind, crossover study. The experimental group received daily oral supplements of L-lysine 1000 mg. Serum samples were analyzed at scheduled intervals. In most instances, members of the lysine group reported fewer lesions than the control group. Similarly, patients who were no longer receiving lysine supplementation generally showed an increase in lesion frequency. Quantitative hematologic measurements revealed the most clinically useful relationship. Data from this sample population indicated that when a patient's serum

lysine concentration exceeded 165 nmol/mL, there was a corresponding decrease in recurrence rate. Conversely, the frequency rate increased as concentration levels fell below 165 nmol/mL. The authors concluded that prophylactic lysine use may be helpful in managing selected cases of recurrent herpes labialis if serum lysine levels can be maintained at adequate concentrations.<sup>6</sup>

### Butylated Hydroxytoluene

Butylated hydroxytoluene, a food preservative manufactured in the laboratory, may have antiviral properties. Butylated hydroxytoluene is thought to interfere with the association of envelope lipids and the hydrophobic regions of envelope proteins of the virus, thereby dissociating proteins from the envelope. The effect of topical therapy with 15% butylated hydroxytoluene in mineral oil on the course of recurrent herpes labialis was examined in 30 patients in a double-blind, placebo-controlled pilot study in which treatment was initiated by the physician.<sup>7</sup> Sixteen patients received butylated hydroxytoluene, and 14 received the placebo mineral oil vehicle. The time from lesion onset to dry crust formation was slightly shorter among butylated hydroxytoluene recipients than among placebo recipients (2.0 and 2.4 days, respectively;  $P=.01$ ). The duration of the vesicle-ulcer stages also was shorter (1.2 and 2.0 days, respectively), and lesion virus excretion appeared to be less in the patients who received butylated hydroxytoluene than in the controls, but both these differences were not significant. There was no clinical or laboratory evidence of toxicity.<sup>7</sup>

### Idoxuridine

Idoxuridine is a topical nucleoside antiviral agent. In a double-blind, randomized, patient-initiated treatment study reported by Spruance et al,<sup>8</sup> 301 immunocompetent patients experiencing a recurrence of herpes labialis were treated with either topical 15% idoxuridine in dimethyl sulfoxide, 80% dimethyl sulfoxide control solution, or 2% dimethyl sulfoxide control solution. Idoxuridine did not prevent the development of lesions but significantly accelerated lesion resolution compared with the combined control groups. For the total population, the mean duration of pain was reduced by 35% (1.3 days;  $P=.01$ ) and the mean healing time to loss of crust by 21% (1.7 days;  $P=.004$ ). Analysis of the study group revealed that the beneficial activity of the treatment was greatest among the patients who began treatment in the prodrome or erythema lesion stage. For these patients, the mean duration of pain was reduced by

42% (1.8 days;  $P=.08$ ), and the mean healing time to loss of crust was reduced by 38% (3.3 days;  $P<.001$ ). When only patients with herpes lesions, including vesicle, ulcer, or crust formation, were considered, there was a greater drug effect on the duration of pain (reduced by 2.6 days, 49%;  $P=.03$ ), and the mean healing time to normal skin was significantly shortened (reduced by 2.3 days, 23%;  $P=.004$ ).<sup>8</sup>

### **Betadine® (Iodine) Cold Sore Paint**

Simmons<sup>9</sup> reported an open-label, randomized, parallel-group efficacy study designed to compare Betadine cold sore paint and idoxuridine topical ointment in the prevention of HSV shedding from cold sores. Seventy-two patients aged 18 to 61 years (mean, 32.2 years) with symptoms indicating recent onset of herpes labialis were entered into the study. Patients were randomized to receive Betadine cold sore paint, idoxuridine topical ointment, or no treatment. To detect infectious virus, swabs were taken for virus culture before and 2 hours after treatment. The no-treatment control group was included to monitor the efficiency of the swabbing technique. The primary measure of efficacy was the proportion of patients in each group returning a swab positive for HSV prior to treatment application and negative for HSV 2 hours after treatment application. All 72 patients completed the study. HSV clearance rates were 0.636 for the Betadine treatment group and 0.092 for the idoxuridine treatment group ( $P=.00056$ ). It was concluded that recovery from infectious HSV from the lips of patients who applied Betadine cold sore paint to

their lesions was significantly lower than from patients who applied idoxuridine topical ointment.<sup>9</sup>

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