REVIEW ARTICLE

Lysine for Herpes Simplex Prophylaxis: A Review of the Evidence

Venthan J. Mailoo, BSc(Hons), MBBS; Sanketh Rampes

Abstract

Background: Herpes simplex virus (HSV) has been implicated in the etiology of recurrent aphthous ulcers, cold sores, and genital sores.

Primary Study Objective: To summarize the research evidence for use of L-lysine to prevent HSV disease recurrence, a use not widely recognized by doctors.

Methods/Design: Two scientists conducted a literature search of EMBASE, Medline, AMED, and CINAHL for the expanded terms *lysine* and *herpes simplex* or *HSV* in the title field and then independently screened the abstracts for clinically relevant articles. Disagreements on article inclusion were discussed before the literature was reviewed to see whether lysine is effective for preventing herpes simplex relapse.

Intervention: Oral L-lysine supplements were taken daily.

Primary Outcome Measures: Described individually for each trial reviewed.

Results: L-lysine supplementation appears to be ineffective for prophylaxis or treatment of herpes simplex lesions with doses of less than 1 g/d without low-arginine diets. Doses in excess of 3 g/d appear to improve patients' subjective experience of the disease.

Conclusion: Longer duration controlled studies of daily lysine doses exceeding 1.2 g/d are required to definitively test its role in herpes simplex prophylaxis. Patients with cardiovascular or gallbladder disease should be cautioned and warned of the theoretical risks of lysine supplementation.

Venthan J. Mailoo, BSc(Hons), MBBS, is anaesthetics senior house officer at Northampton General Hospital in Northhampton, United Kingdom. Sanketh Rampes is a medical student at Kings College London in London, United Kingdom.

Corresponding author: Venthan J. Mailoo, BSc(Hons), MBBS
E-mail address: VenthanMailoo@gmail.com

Cold sores are a common recurrent problem and genital sores less so, caused by variants of the herpes simplex virus (HSV) sometimes treated with aciclovir, famciclovir, or valaciclovir.[1] It has been postulated that HSV may also contribute to RAUs[2] and estimated that up to 90% of the adult population is infected with HSV, which lies dormant in nervous tissue until relapse is triggered by stress or immune dysfunction. Based on tissue culture studies, it is thought that lysine-arginine balance may affect HSV expression.[3] Arginine-rich proteins are required for reproduction of HSV, whereas lysine competitively inhibits their synthesis.[2] L-lysine (the biologically active isomer of lysine) has been used by the general public and alternative health practitioners. A daily dose of 50 mg/kg of body weight has previously been recommended for cold sores[4] but this is not often advised by doctors due to conflicting evidence.[5] Patients requiring preventative or frequent oral acyclovir may prefer to try dietary changes or lysine supplements. Doses of up to 3 g/day are thought to be harmless[5] as oral lysine toxicity has not occurred in humans.[6] Two scientists conducted a literature search of EMBASE, Medline, AMED, and CINAHL for the expanded terms *lysine* and *herpes simplex* or *HSV* in the title field and then independently screened the abstracts for clinically relevant articles. Any disagreement on article inclusion was discussed and then the literature was reviewed to see whether lysine affects herpes simplex relapse. The evidence base is summarized in Table 1.

Table 1. Summary of Previously Reviewed Literature

Study	N	Method	Results	Limitations
Milman et al[3,7,10,13,14] (1978)[a]	119	1 g L-lysine daily. Double-blind randomized placebo controlled for 48 d, 5-d courses of lysine for each relapse.[7]	No significant effect on the healing rate of lesions[3,7] or recurrence.[7]	The original sample was 198, but 79 dropped out.[7] Short study duration.
Griffith et al[8] (1978)	42	312 mg to 1.2 g L-lysine daily. Uncontrolled multicentered study for 2 mo to 3 y with low-arginine diet.	Subjective reduction in lesion frequency. Lysine reduced recovery time, clinical manifestations, and recurrence rate. No recurrences in patients taking 500 mg or more lysine per day. When lysine was discontinued, recurrence often occurred within 1-4 wk.[8]	Uncontrolled observational study. Variable doses. 3 of 45 cases were not followed up.[8] Small sample size.[9] No statistical analysis.
Milman et al[10] (1980)	65	1 g L-lysine daily. Double-blind, placebo-controlled cross-over for 12 wk in each arm. Recurrences were recorded on contemporaneous questionnaires.[10]	27.7% (18) recurrence-free in lysine group, 12.3% (8) in control group ($P < .05$). Lysine did not significantly affect the overall recurrence rate (91 during lysine treatment, 104 during placebo treatment), severity of lesions, or rate of healing.[10]	79 subjects were recruited but 14 dropped out.[7,10] Inadequate power.[3] Inclusion criterion was at least 3 episodes of recurrent herpes labialis within the previous year, but the trial lasted only 12 wk.[10]
Walsh et al[11] (1983)	1534	Variable dose. 4000 questionnaires were mailed to self-selected subjects purchasing lysine from health food shops; 1543 (38%) were returned.[11]	88% considered lysine effective for herpes. 60% of subjects with cold sores without medical therapy said their symptoms were severe before taking lysine versus 4% with lysine. 4% described their symptoms as intolerable before taking lysine versus <1% with lysine. Without lysine, 64% of patients with aphthous ulcers considered their symptoms severe and 25% intolerable compared with only 12% severe and 3% intolerable with lysine ($P < .001$).[11]	Low response rate. No account for selection bias, recall bias, or the placebo effect.
Miller & Foulke[12] (1984)	9	500 mg L-lysine daily. Uncontrolled with low arginine diet for 8 mo. No statistical analysis.[12]	Subjective reduction in lesion frequency, duration, and severity. Relapses associated with high arginine intake within the previous 36 h.[12]	Low dose (500 mg though the authors specified 4 g would be a therapeutic dose) uncontrolled observational study. Small sample size.[9,12]
McCune et al[3,7,9,17] (1984)[a]	41	1248 mg lysine vs placebo or 624 mg lysine vs placebo with 6 mo on each arm.[9] Double-blind placebo-controlled cross-over with high-lysine, low-arginine diet.[3]	Significantly fewer recurrences with 1248 mg (0.89 vs 1.56; $P < .05$). No difference in healing time.[3,7,9] 624 mg was ineffective.	The original sample was 47, but 1 moved and 5 were noncompliant.[7] The low-arginine diet may have lessened the impact of lysine supplementation in this trial.

Study	N	Method	Results	Limitations
DiGiovanna & Blank[3,7,14,19] (1984)[a]	20	1.2 g lysine daily. Double-blind, placebo-controlled for 4-5 mo.	No significant differences between treatment or placebo.[3,7]	3 placebo patients with continuous lesions dropped out of the study.[3] This may have reduced the power of the study.
Thein & Hurt[13] (1984)	29	1 g lysine daily. Double-blind, randomized, placebo controlled cross-over for 6 mo with a low-arginine diet. Herpes symptoms recorded in contemporaneous journals.[13]	Significantly fewer recurrences with serum lysine >165 nmol/mL, but not <165 nmol/mL ($P < .05$). No significant difference for the first 6 mo of the trial, but significantly fewer lesions per patient (1.8 vs 2.9) in the experimental group during the second 6 mo ($P < .05$).[13]	The lack of difference between the groups during the first 6 mo may have been due to poor matching (the group first put on placebo had fewer lesions at baseline than the group first put on lysine).[13] The low arginine diet may have lessened the impact of lysine supplementation in this trial.
Simon et al[14] (1985)	31	Double-blind placebo controlled. 1 g lysine daily for 3 m (n = 16), followed by 750 mg/d for 3 mo (n = 8). Placebo group n = 15 for 3 mo followed by n = 10 for 3 mo. Recurrence rates were predicted based on the subjects' episodes during the preceding 12 mo and then compared actual recurrence rates.[14]	On 1 g/d, 17 recurrences in the lysine group (n = 16), 26 recurrences in the placebo group (n = 15). The control group experienced a 25% reduction in recurrences during each 3-mo period. The lysine group experienced a 40% reduction ($P < .05$) during the first 3 mo (1 g/d; $P < .05$). No significant difference on 750 mg/d.[14]	Simon et al[14] attributed recurrence reduction in the placebo group to the placebo effect, though it could be the natural disease course. Recall bias. 13 subjects dropped out of the study.[7] No statistical comparison made between lysine and placebo groups.
Griffith et al[3,7,9,15,17,18] (1987)[a]	59	3 g L-lysine daily. Randomized double-blind placebo-controlled for 6 mo.[3,7,9]	"Milder" symptoms reported in 74% of the lysine group and 28% of the placebo group. Greater reduction of recurrences (predicted from the previous year) in the lysine than placebo group ($P < .01$). No significant difference in healing time.[7,9]	Small sample size[15] of 114 subjects were recruited but only 34 experimental and 25 control patients completed the study. 7 were excluded due to acyclovir use.[9]

[a]As cited in studies denoted by reference numbers.

Of the articles in Table 1 only, Thein and Hurt[16] was selected for inclusion in a Cochrane Skin Group review of randomized controlled trials, and this was deemed to be "very low" quality evidence due to imprecision and bias.

Summary of 2 Trials Not Included in Previous Literature Reviews

Wright[2] conducted a study of 28 patients with RAUs and 14 patients with herpes labialis using a 500 mg/day prophylactic dose and 4-g treatment dose, followed up by telephone interview after 6 months. All but 1 patient with herpes labialis and 1 with RAUs reported that lysine was effective. Patients were nonconcordant with prophylactic lysine, in some cases due to forgetfulness and in other cases due to believing they had been cured. Starting the treatment dose at onset of herpes labialis, prodrome was effective for only reducing the duration of lesions in 25% of patients. Two RAU patients required 1 g of lysine daily for prevention. One patient found no benefit from lysine but the other 25 patients found 500 mg/day to be 100% effective for prophylaxis.

Ozden et al[17] tested the relationship between HSV status and RAUs and the effects of L-lysine supplementation on the latter. Saliva and serum samples were collected from 30 RAU subjects and 17 healthy subjects without histories of oral mucosal disease before and after treatment. Saliva was tested for HSV-1 DNA by real-time polymerase chain reaction. Serum was tested for HSV-1 immunoglobulin G (IgG) by enzyme-linked immunosorbent assay. The RAU patients were randomly divided into placebo (n = 14) and lysine (n = 16) groups. Experimental subjects took 1260 mg of lysine daily for 2 months, increased to 2520 mg/day if prodromal symptoms occurred. Number of episodes, ulcer duration, number of ulcers per attack, severity of symptoms, and subjects' subjective perception of degree of success of therapy on a scale from 1 to 10 were recorded. A total of 100% of RAU and 76.5% of healthy subjects tested positive for HSV-1 IgG antibody. HSV-1 DNA was present in 1 of 17 healthy controls (5.9%) and in 4 of 30 RAU patients. Two months of lysine supplementation did not significantly affect these biological markers. Ulcers did not occur in 18.7% of the lysine group and 28.5% of the placebo group during the trial. Ulcer recurrence was decreased in 62.5% of the lysine group and 14.2% of the placebo group ($\chi^2 = 7.97$, $P < .05$). One placebo patient experienced increased ulcer recurrence. Decreased numbers of lesions per attack were reported by 56.2% of the lysine group ($\chi^2 = 8.37$, $P < .05$) and 1 placebo patient (7.1%). Average perceived success was 7.5 ± 1.4 in the lysine group and 3.8 ± 2.0 in the placebo group ($t = 5.85$, $P < .001$). There were no significant between-group differences for lesion duration or severity. This study was limited by its short duration.

Potential Risks and Adverse Effects or Long-term Lysine Use

Arginine deficiency may occur with kidney or small bowel pathology, sepsis, sickle cell disease, burns, trauma, or surgery. It is essential for growth, wound healing, endothelial function, and nitric oxide production. Lysine should, therefore, be used with caution in patients with cardiovascular disease, impotence, gallstones, asthma, or immune dysfunction.[18]

Discussion

Of the 12 studies analyzed in this paper, only 8 were placebo controlled, 7 of which were double-blind, 7 randomized, and 3 of which used cross-over methodology to minimize time effects. Ten trials tested prophylactic lysine to prevent cold-sores or mouth ulcers. Two studies[2,12] reported 500 mg/day to be effective for reducing lesion frequency, but neither of these were controlled or statistically tested. In contrast, 2 double-blind controlled trials showed no significant prophylaxis with 624 mg/day[3,7,9,17] or 750 mg/day.[14] Two double-blind placebo controlled trials showed clinically significant reductions in recurrence rates with 1 g/day[14] and 1248 mg/day,[3,7,9,17] in contrast to 2 that showed no significant difference with 1.2 g/day[3,7,14,19] and 1260 mg/day.[17] One randomized trial with 34 experimental patients taking 3 g of lysine daily and 25 control patients taking placebo demonstrated a statistically significant difference in reduction of recurrence rate.[3,7,9,15,17,18]

Two randomized controlled trials showed no significant therapeutic effect from lysine supplements to treat active herpes simplex sores. One of these was with 1 g/day for 5 days,[3,7,10,13,14] whereas the other was with 2520 mg/day.[17] Only 25% of patients in an uncontrolled trial of a 4 g lysine daily treatment dose reported reduced duration of lesions.[2] This literature review revealed no convincing evidence for the use of lysine to treat herpes simplex sores.

Meta-analyses and randomized controlled trials are considered the best standard of evidence on which to base health care interventions. Only randomized controlled trials were considered for the Cochrane Skin Group review of treatments for herpes simplex.[16] Randomized controlled trials are expensive and, therefore, likely to be funded by only state health systems if significant cost-savings or improvements in quality of life are likely to result, or by the private sector if profit is likely to result. Lysine supplementation is not expected to significantly improve public health or generate sufficient profit to attract the funding required for randomized controlled trials. There is therefore a bias in research toward pharmaceutical as opposed to nutritional management of herpes simplex. This bias may extend to other diseases that are affected by nutritional imbalance, and it transfers power from patients to pharmaceutical companies.

Conclusions

L-lysine supplementation appears to be ineffective for prophylaxis or treatment of herpes simplex lesions with doses of less than 1 g/day without low-arginine diets. Findings from 1 small double-blind, randomized, placebo-controlled trial suggest that doses in excess of 3 g/day may reduce recurrence rates and improve patients' self-reported symptoms. Longer-duration, randomized controlled studies of lysine doses exceeding 1.2 g/day are required to definitively test its role in herpes simplex prophylaxis and determine the minimum reliably effective daily dose. This literature review uncovered no convincing evidence that lysine can be used to treat active herpes simplex lesions. In the absence of such research, on the balance of possible risk to benefit, clinicians could consider advising patients that there is a theoretical role of lysine supplementation in the prevention of herpes simplex sores but the research evidence is insufficient to back this. Patients with cardiovascular or gallbladder disease should be cautioned and warned of the theoretical risks.

References

1. Johnston C, Wald A. Herpes simplex infection. BMJ Best Practice Web site. http://bestpractice.bmj.com/best-practice/monograph/53.html. Accessed August 29, 2015.
2. Wright EF. Clinical effectiveness of lysine in treating recurrent aphthous ulcers and herpes labialis. *Gen Dent*. 1994;42:40-42.
3. Gaby AR. Natural remedies for Herpes simplex. *Altern Med Rev*. 2006;11:93-101.
4. No author listed. Lysine and cold sores. *Med Update*. 2004;29(12):7.
5. Robb-Nicholson C. By the way, doctor. I keep hearing that aspirin can help prevent colon cancer, but I have no idea how much I should take. Can you help? I've had adenomatous polyps in the past. *Harv Womens Health Watch*. 2010;18(4):8.
6. Braverman ER, Pfeiffer CC, Blum K, Smayda R. *The Healing Nutrients Within: Facts, Findings, and New Research on Amino Acids*. 3rd ed. Laguna Beach, CA: Basic Health Publications; 2009.
7. Tomblin FA, Lucas KH. Lysine for management of herpes labialis. *Am J Health Syst Pharm*. 2001;58:298-300, 304.
8. Griffith RS, Norins AL, Kagan C. A multicentered study of lysine therapy in Herpes simplex infection. *Dermatologica*. 1978;156:257-267.
9. Roberts JJ, Solanki NS, Kurmis R, Lammerink S, Wong KL, Greenwood JE. Prophylaxis against Herpes Simplex Virus reactivation in patients with facial burns: A potential role for L-lysine. *J Burn Care Res*. 2013;34:e368-369.
10. Milman N, Scheibel J, Jessen O. Lysine prophylaxis in recurrent herpes simplex labialis: A double-blind, controlled crossover study. *Acta Derm Venereol*. 1980;60:85-87.
11. Walsh DE, Griffith RS, Behforooz A. Subjective response to lysine in the therapy of herpes simplex. *J Antimicrob Chemother*. 1983;12:489-496.
12. Miller CS, Foulke CN. Use of lysine in treating recurrent oral herpes simplex infections. *Gen Dent*. 1984;32:490-493.
13. Thein DJ, Hurt WC. Lysine as a prophylactic agent in the treatment of recurrent herpes simplex labialis. *Oral Surg Oral Med Oral Pathol*. 1984;58(6):659-666.
14. Simon CA, Van Melle GD, Ramelet AA. Failure of lysine in frequently recurrent herpes simplex infection. *Arch Dermatol*. 1985;121:167-168.
15. Beauman JG. Genital herpes: A review. *Am Fam Phys*. 2005;72(8):1527-1534.
16. Chi C-C, Wang S-H, Delamere FM, Wojnarowska F, Peters MC, Kanjirath PP. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev*. August 2015;8:CD010095.
17. Ozden FO, Turanli AY, Acikgoz G, Eroglu C. Clinical success of lysine in association with serumal and salivary presence of HSV-1 in patients with recurrent aphthous ulceration. *J Exp Integr Med*. 2011;1(3):191-196.
18. Bumpstead L. Long-term use of supplemental lysine: Is it safe? *J Austral Trad Med Soc*. 2013;19:228.

Appendix 1. Key Points

1. Cold sores are a common problem caused by herpes simplex virus (HSV) variants.
2. Lysine-arginine balance is thought to affect HSV expression.
3. Oral lysine has been investigated in the prevention of HSV recurrence. Trials have yielded mixed results.
4. Doses less than 1 g appear ineffective in prophylaxis or treatment of HSV lesions, whereas doses in excess of 3 g appear to improve patient's subjective experience of the disease.
5. Longer trials using daily L-lysine doses exceeding 1.2 g are required to definitively determine its role in HSV prophylaxis.