L-Lysine Hydrochloride: An Alternative Prophylactic Therapy Reducing the Recurrence Rate of Herpes Labialis

Kirsten Harlow

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Abstract

Background: 57.7% of the US population between the ages of 14-49 years is seropositive to antibodies for the herpes simplex virus type 1 (HSV1). It has been concluded in studies that lysine, an essential amino acid, inhibits the multiplication of HSV1 in cell cultures when there is high concentration of lysine in the culture medium. Conversely, arginine, a natural amino acid is required for viral replication. At the cellular level, lysine acts as a herpes virus inhibitor by antagonizing arginine. An effective treatment in the prevention of recurrent HSV1 outbreaks has the potential to impact daily living. Could lysine become an effective prophylactic treatment that reduces the recurrence rate of herpes labialis outbreaks?

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, Web of Science, Google Scholar using the keywords: lysine, L-lysine, oral herpes simplex, herpetic stomatitis, herpes simplex, HSV-1, herpesvirus 1, herpes labialis, prevention, and prophylactic. Relevant articles were assessed for quality using GRADE. A search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to the use of L-lysine for prophylactic treatment of herpes labialis.

Results: Two randomized, double blind, placebo-controlled trials met inclusion criteria and were included in this systematic review. The first study with 26 participants demonstrated a strong association between high serum lysine levels and a decrease in lesion frequency suggesting that prophylactic lysine may be useful in managing select cases of recurrent herpes labialis. The second trial with 65 participants demonstrated no statistically significant reduction in the number of herpes labialis recurrences during the trial; however, the results suggest that certain patients may benefit from prophylactic lysine therapy with a reduction in herpes labialis and this requires further investigation.

Conclusion: The effects of L-lysine prophylactic therapy in suppression of herpes labialis is clear but not for all individuals. Supplemental L-lysine taken at recommended dosages provides a prophylactic therapy benefit to patients whose body responds to the supplementation with an increase in serum lysine levels. Treatment effect seems to vary per person depending on serum lysine levels. The questions remaining are what is the optimal lysine serum level to provide protection for a majority of persons from herpetic outbreaks and is it consistently attainable with individual variables such as patient response to supplementation? L-lysine prophylactic therapy is a cost efficient safe therapy to be considered by patients who are open to trying alternative treatments for herpes labialis.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Keywords
Lysine, herpes labialis, prophylactic, herpes simplex, human

Subject Categories
Medicine and Health Sciences

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Reducing the Recurrence Rate of Herpes Labialis

Kirsten F. Harlow

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 8, 2015

Faculty Advisors: Annjanette Sommers, PA-C, MS and Mr. George Olson
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

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Keywords: Lysine, herpes labialis, prophylactic, herpes simplex, human
Acknowledgements

[Redacted for privacy]
# Table of Contents

- Biography ............................................................................................................................ 2
- Abstract ............................................................................................................................... 3
- Acknowledgements ............................................................................................................. 4
- Table of Contents ................................................................................................................ 5
- List of Tables ...................................................................................................................... 6
- List of Abbreviations ........................................................................................................... Error! Bookmark not defined.
- BACKGROUND ................................................................................................................ 7
- METHODS ....................................................................................................................... 10
- RESULTS .......................................................................................................................... 10
- DISCUSSION ................................................................................................................... 16
- CONCLUSION ................................................................................................................. 19
- References ......................................................................................................................... 21
- Table I. Characteristics of Reviewed Studies ................................................................... 22
- Summary of Findings Tables ............................................................................................ 22
List of Tables
Table I: Characteristics of Reviewed Studies
Table II: Summary of Finding: Thein and Hurt—Student’s t-test
Table III: Summary of Finding: Milman et al—Recurrence patterns of herpes simplex
Table IV: Summary of Finding: Milman et al—Number of herpes simplex recurrences
Table V: Summary of Finding: Thein and Hurt—Herpetic lesion frequency

List of Abbreviations
HSV1: Herpes Simplex Virus Type 1
NIH: National Institute of Health
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
RCT: Randomized Control Trial
BID: Twice Daily
FDA: Food and Drug Administrations
TTP: Thrombocytopenia Purpura
HUS: Hemolytic Uremic Syndrome
ARF: Acute Renal Failure
L-Lysine Hydrochloride: An Alternative Prophylactic Therapy
Reducing the Recurrence Rate of Herpes Labialis

BACKGROUND

Of the US population, 57.7% of individuals between the ages of 14-49 years are seropositive for antibodies to herpes simplex virus type 1 (HSV1).\(^1\) Herpes simplex virus -1 is part of the herpesviridae family, a large family of DNA viruses that are known to instigate recurring infections. The lingering latent characteristic of HSV1 and its ability to reactivate, inducing recurrent infections such as herpes labialis, invoke distress and visual sores in the effected population. These lesions along the vermillion boarder of the lip contain infectious viral particles from the viral shedding of the herpes virus, can be very painful and potentially disfiguring.\(^2\) The repetitive recurrence of these lesions can induce depression, missed work or life experiences from the fear of rejection, and possibly even isolation from a fear of being found out to have “a cold sore”.\(^3\)

There are no vaccines to prevent the primary herpes simplex infection in patients. Until a vaccine can be found, the therapies available to treat the HSV infections focus on decreasing the number of days in an outbreak, severity of the lesions and on preventing outbreaks from occurring altogether. Taking medication to prevent lesions from recurring (prophylactic therapy) is a top priority to decrease the suffering of individuals. Available antiviral agents approved by the FDA for chronic suppressive therapy of herpes labials include acyclovir and valacyclovir. These two drugs interfere with the synthesis of viral DNA.\(^4\) Antiviral drugs cannot eradicate the virus from its dormant (latent) state within the nerve cells—neural ganglia that supply sensation.
to the skin. The cost consideration and the side effects of these antiviral drugs must be included in decision making when considering the use of them chronically.

Amino acids, such as lysine and arginine, are organic compounds that make up proteins. Studies have demonstrated that arginine, a natural amino acid building block, is required for HSV1 replication. \(^5\) HSV1 is highly dependent on arginine. \(^6\) It has been determined that HSV1 synthesizes proteins higher in arginine content than lysine. \(^7\) Lysine, an essential amino acid, is involved in making proteins and metabolizing carbohydrates and fatty acids. Lysine inhibits the multiplication of HSV1 in cell cultures when there is high concentration of lysine in the culture medium. \(^6\) Lysine is not synthesized in humans; therefore, it must be ingested as L-lysine or contained within ingested proteins. Dietary sources of lysine include meat, cheese, yogurt, brewer's yeast, legumes, and wheat germ. \(^8\) Lysine, a herpes virus inhibitor, antagonizes arginine \(^9\) by way of the following five mechanisms. Lysine functions as an antimetabolite of arginine. Lysine competes with arginine for reabsorption in the renal tubules thereby increasing arginine excretion in urine. Lysine also competes with arginine for transport into cells and at absorption sites in the intestines. If there is excess concentration of lysine in the gut, than absorption of arginine is decreased. Lastly, lysine induces enzyme arginase, which degrades arginine.

An effective, safe, and inexpensive long-term prevention therapy of recurrent HSV1 outbreaks has the potential to impact daily living. Could lysine become a daily oral supplement that reduces the recurrence rate of herpes labialis outbreaks, consequently becoming an effective prophylactic therapy?
METHODS

An exhaustive literature search was conducted using Medline-OVID, CINAHL, Web of Science, Google Scholar. The following search keywords were utilized: lysine, L-lysine, oral herpes simplex, herpetic stomatitis, herpes simplex, HSV-1, herpesvirus 1, herpes labialis, prevention, and prophylactic. The search was narrowed to include only English language articles and research on humans. Articles evaluating L-lysine as a prophylactic agent for herpes labialis were included. The bibliographies of the articles were further searched for relevant sources. Trials that did not separate the data between herpes labialis and genital herpes were excluded. Review articles and editorials were used for background research. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE). A search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to the use of L-lysine for prophylactic treatment of herpes labialis.

RESULTS

Initial results of the search yielded 301 articles for review. After filtering the articles, weeding out non-human trials, a total of 8 articles were reviewed further for relevancy. Two additional articles were located through the references. Of these 10 articles, three randomized control trials (RCT) were excluded due to the inclusion of patients with genital herpes where the data collected did not differentiate between orolabial and genital lesions. Four articles were secondary analysis reviews and one was descriptive research—a case report, which was excluded due to low GRADE criteria and the inclusion of genital lesions. A total of two articles fit inclusion criteria and both are randomized control trials. See Table I.
Thein and Hurt

This randomized control trial examined the host environment to determine the efficacy of long-term prophylactic L-lysine supplementation for treating the clinical symptoms of recurrent herpes simplex labialis in a double-blind, placebo-controlled, crossover study. The 52-week trial had an uninterrupted crossover from lysine treatment to placebo or placebo to lysine at the 6-month mark. An identical-appearing cellulose placebo was used as the control. The trial enrolled study participants, all otherwise healthy volunteers, with at least three circumoral herpes lesions in the preceding 12 months. Frequency of recurrences ranged from 4-16 per year (median number: 12 episodes in the past year). Twenty-six participants included in the statistical analysis were comprised of 23 females and three males, between the ages of 8-50 years (median 29 years). The primary outcome was the frequency of herpes simplex recurrences during a 52-week prophylactic treatment with L-lysine and placebo. Patients were directed to contact the authors at the appearance of a lesion for a positive diagnosis to be made on the basis of standard cytologic criteria. And patients were given journals, at the initial visit and at the 6-month appointment, to record pertinent information regarding outbreaks. A secondary outcome was the individual serum levels of lysine and arginine and the lysine:arginine ratio (L/A). Serum samples were collected at scheduled intervals: initial visit, 6 months, and 12 months. At the conclusion of the 52-week trial, all serum samples were prepared for analysis and examined in an automated amino acid analyzer. Student’s t-tests were used to determine any significance between the two sample means.

Eligibility criteria included at least three circumoral herpes simplex lesions 12 months prior in otherwise healthy individuals. Participants’ medical anomalies were recorded on medical health history questionnaires. The participants were randomly divided into two groups at the
onset of the trial. Group A: 15 members began with lysine tablets. Group B: 11 members started with cellulose placebo. No significant difference was noted between the two treatment groups in the two 6-month periods immediately preceding the study in regards to frequency of lesions, serum lysine and arginine levels, or the lysine:arginine ratio. There was insignificant difference in the health profiles between the two groups. The number and kind of medical problems reported by the participants appeared consistent with that of the general population of similar age.\textsuperscript{11}

The patients were given a journal on initial visit along with tablets containing 500 mg L-lysine monohydrochloride or cellulose placebo and instructed to take two tablets every morning before breakfast, a daily dose of 1000 mg. Nuts, seeds, chocolate, and cereal products are foods high in arginine content\textsuperscript{12}. These food products, high in dietary arginine, were recommended for reduction. Crossover occurred at 6 months with a 6-month supply of tablets distributed to the participants. A closing interview was conducted to obtain information from each participant regarding the experiment.\textsuperscript{11}

Results suggest that prophylactic lysine may be useful in managing selected cases of recurrent herpes simplex labialis if serum levels can be maintained at adequate concentrations.\textsuperscript{11} When a person’s serum lysine concentration exceeded 165 nmol/ml, it yielded a significant decrease in recurrent lesions (p < 0.05). There was also a corresponding increase in frequency rate of herpetic lesions as serum lysine concentration levels fell below 165 nmol/ml. At the end of the first 6-month period, the frequency of lesions in those subjects given lysine did not differ significantly from the frequency in those given placebo. See Table II. In contrast, the subjects who began taking lysine during the second 6-month test period reported a significantly fewer
lesions than those who had reverted to placebo (p< 0.05). Between months 6-12 subjects in Group B who were put on lysine supplementation demonstrated a significant greater blood lysine concentration than those in Group A whom lysine was not supplemented (p< 0.01). Similarly, during the second 6-month test period, when Group A was taken off the lysine supplementation, there was a significant increase in the frequency of lesions (p< 0.01) while Patients in Group B, in which lysine was added at the 6-month mark, reported a significant decrease in lesion recurrence (p <0.01). In addition, there was a significant decrease in blood lysine levels between the first 6-months test period and the second in group A patients (p <0.05).\textsuperscript{11}

The authors found that limitations to this study included the puzzling aspect of the results pertaining to the lack of statistical significance obtained during the first 6-months of the trial. Certain persons in the placebo group may have been supplementing their dietary intake of lysine unknowingly and consequently raising their serum lysine levels in excess of >165 nmol/ml thereby having a therapeutic effect without the L-lysine monohydrochloride treatment. Another limitation is the fact that some participants appeared to have different capacities to absorb lysine than others. The authors postulate on a possible lysine transport defect across intestinal villi or in target cells, other metabolic products competing for same transport receptors or a higher than normal lysine concentration needed to have an inhibitory effect in persons with recurrent herpetic lesions. They also discussed the unquestioned clinical value in determining the specific quantitative figures regarding the blood levels of lysine needed to reduce recurrent lesions in future research.\textsuperscript{11}

\textbf{Milman et al}

This randomized control trial,\textsuperscript{13} evaluating the prophylactic effect of L-lysine
monohydrochloride on recurrent herpes simplex labialis, was a double-blind, placebo-controlled, crossover study. The 24-week trial had an uninterrupted crossover from lysine treatment to placebo or placebo to lysine at the 12-week mark. Every second patient started with lysine and alternate patients with placebo. The trial enrolled 79 initial study participants all otherwise healthy volunteers with at least three perioral and/or prolabial herpes simplex episodes in the preceding 12 months. Of the 79, 14 did not complete the investigation and were excluded. Final material comprised 65 patients: 52 females and 13 males, all of whom are between the ages of 16-73 years (median 36 years). The primary outcome was the number of herpes simplex recurrences during a 12-week prophylactic treatment with L-lysine or placebo.\textsuperscript{13}

A secondary outcome was the duration of the outbreak. The start of an episode was defined as the appearance of burning, itching, tingling (prodrome) and/or erythema. The end of an episode was noted when the surface crust of the lesion had been discharged and all discomfort and swelling resolved, residual erythema could be present. Another secondary outcome was the classification of the lesion when judged to be at its worst according to the following scale: (1) itching, burning, tingling, or tenderness but no visible lesion; (2) erythema with induration (papule) and/or vesicles without exudate; (3) vesicles with exudation and/or crust, lesion 15 mm or less, measured along the largest diameter; (4) vesicles with exudation and/or crust, lesions greater than 15 mm.\textsuperscript{13}

Eligibility criteria of at least three perioral and/or prolabial herpes simplex episodes in preceding 12 months was verified by the observation of lesions and the remaining cases upon a thorough history. The patients were given a questionnaire on initial visit with tablets containing 500 mg L-lysine monohydrochloride or starch powder (placebo) and instructed to take one tablet
by mouth twice daily (BID); daily dose of 1000 mg. The patients were directed to record the
duration and course of the herpes simplex recurrences plus classify the lesions. Every four
weeks the questionnaires were returned along with residual tablets and new questionnaires and
tablets were sent to the study participants.\textsuperscript{13}

A significantly greater number of participants were recurrence-free during lysine than
during placebo treatment. See Table III. Fourteen patients had no recurrences during lysine
treatment but did have recurrence during placebo treatment. Four patients starting with lysine
had no recurrences during either treatment. Four patients had no recurrence during placebo but
recurrence during treatment with lysine. This difference is at the limit of significance (p=0.05).\textsuperscript{13}
Looking at Table IV, none of the differences in effect of placebo or L-lysine were statistically
significant. What is discerned from Table IV is there is a 33.3\% drop in recurrences when
patients switched from placebo (66 total recurrences) to L-lysine treatment (46 total recurrences).
In patients initially treated with placebo there was a reduction in recurrence during subsequent
lysine treatment. Also, patients initially treated with lysine had a lower number of recurrences on
placebo treatment (38 total recurrences) than had patients initially treated with placebo (66 total
recurrences). The authors observed that a possible prophylactic long-term effect of lysine could
be postulated from these numbers. Looking at the secondary outcome of rate of healing and the
appearance of the recorded herpes lesions at their worst, there was no significant difference
between L-lysine and placebo treatment series.\textsuperscript{13}

The authors found that limitations to this study included a large placebo response, short
observation period, and complicated interpretation of results. They also discussed the
investigative problems arising from the inter- and intra-individual variations in the frequency and
course of recurrent herpes labialis when evaluating the prophylactic treatment of lysine. The author recommended large patient population, long observation periods, and emphasized the absolute necessity of double-blind controlled trials.  

**DISCUSSION**

Oral lysine supplementation can reduce the recurrence rate of herpes labialis outbreaks in select cases when taken as a prophylaxis treatment. The Thein and Hurt study\textsuperscript{11} ran Student’s t-test to look at the correlations between patient’s serum lysine levels and the number of lesion recurrences. Results from their study population indicated that when a person’s serum lysine concentration exceeded 165 nmol/ml, there was a corresponding significant decrease in recurrent lesions (\(p < 0.05\)).\textsuperscript{11} Likewise, when the serum concentration dropped below 165 nmol/ml lesion frequency increased significantly.\textsuperscript{11} Whether the lysine serum concentration is from food sources containing the amino acid lysine or supplemental L-lysine tablets 1000 mg/day, it is the increased serum concentration in excess of 165 nmol/ml that decreases the frequency of herpes labialis. Although, the Milman et al\textsuperscript{13} trial showed no significant prophylactic effect of lysine therapy on the recurrence rate and duration of herpes simplex labialis the research does suggest that certain patients may benefit from the treatment. Significantly more patients were recurrence free during lysine than placebo treatment. There were eighteen patients who had no recurrences during lysine treatment, while fourteen of those eighteen patients had recurrences during placebo treatment.\textsuperscript{13} This correlates with past research that lysine is a suppressant not a curative treatment once viral replication has begun within an oral lesion.\textsuperscript{6}

Six studies\textsuperscript{11,13-17} were conducted between 1980-1987 on prophylactic therapy of recurrent herpes simplex virus with L-lysine. Four of the studies\textsuperscript{14-17} are not included in this
review because they included data on genital herpetic lesions. All but one of these studies showed favorable results for the use of L-lysine in the prevention of HSV outbreaks. Even though these studies did not meet inclusion criteria, they should not be ignored. The most recent study conducted in 1987 by Griffith et al\textsuperscript{17} found statistical significance of L-lysine monohydrochloride therapy (1,000 mg L-lysine per dose, three times a day for 6 months) with an average 2.4 (p >0.05) less HSV recurrences, symptoms were significantly (p <0.05) diminished in severity and healing time was significantly reduced (p <0.05).\textsuperscript{17}

While the studies\textsuperscript{11,13} demonstrated that some patients benefit from lysine prophylaxis in recurrent herpes simplex labialis, they both have limitations. The major limitations detected include length of study, study size, and risk of bias specifically attrition bias, detection bias, performance bias, and carryover effect. Milman et al\textsuperscript{13} conducted a 24-week trial with 79 participants. There were 14 participants who did not complete the study and were excluded. The authors do not address the 17.7% withdrawal from the study leading to incomplete outcome data. Only 12-weeks of the 24-week Milman et al\textsuperscript{13} trial had the patients on L-lysine monohydrochloride therapy. The short therapy window makes it difficult to base future treatment protocols off this study. Thein and Hurt\textsuperscript{11} investigated lysine therapy for 52-weeks with the crossover at 6-months. Thein and Hurt\textsuperscript{11} had an impressive length of study in comparison to all previous studies addressing lysine as a prophylactic treatment in humans but failed to capture a large sample population, only 26 participants (three males, twenty-three females). Thein and Hurt\textsuperscript{11} efficiently documented their data into a table showing herpetic lesion frequency per patient. See Table V. This empowered the reader to realize that patients had dramatic decreases in herpetic lesions with treatment. It would have been beneficial to see a correlation between the lysine serum levels and lesions per patient. Milman et al\textsuperscript{13} aggregated the number of herpetic
lesion recurrences only by treatment group, failing to breakdown the data by lesions per individual before and during the study. This makes it impossible to discern which participants had dramatic decreases in HSV1 outbreaks and who were the outliers that did not respond to treatment.

Milman et al\textsuperscript{13} collected data on recurrent herpes lesions with a questionnaire. This can lead to detection bias and is apparent due to a lack of definitive diagnosis of the lesions: subjective accounting of evidence from the participants without standard criteria. Thein and Hurt\textsuperscript{11} based their positive diagnosis of recurrent herpes simplex labialis off standard cytologic criteria.\textsuperscript{18} Thein and Hurt\textsuperscript{11} addressed a risk of performance bias regarding the possible diet supplementation with lysine from sources other than the experimental tablets provided in the placebo group. Patients inadvertently raising their serum lysine levels with the ingestion of foods high in the amino acid, lysine. Regardless, Thein and Hurt\textsuperscript{11} conclude that if lysine levels exceed 165 nmol/ml lesion recurrence significantly declines. The participants in this study\textsuperscript{11} were also asked to limit the intake of arginine containing foods. It was discovered that most participants did not adhere to this recommendation. Until this variable can be controlled, researchers will not be able to determine if it is an inadequacy of lysine or an excess in arginine consumption that leads to the preferential environment for viral replication.\textsuperscript{11}

The final risk of bias to be addressed is the carryover effect in crossover studies. Both studies\textsuperscript{11,13} had the two groups of patients switch from lysine therapy to placebo or from placebo to lysine therapy. In the Milman et al\textsuperscript{13} study, patients initially treated with lysine had a lower number of recurrences on placebo treatment than has patients initially treated with placebo. This could be attributed to a prophylactic long-term effect of lysine but the authors demonstrate that
the data does not support this interpretation. In patients with serum levels in excess of 165 nmol/ml there is a significant decline in lesion recurrences. \textsuperscript{11} Although it is possible that there was a carryover effect in the Thein and Hurt\textsuperscript{11} study, the potential bias does not skew these favorable end results.

Moving forward, further studies need to be done on this topic in order to truly evaluate the quantitative figures regarding the blood levels of lysine needed to reduce the recurrence of herpes labialis and to determine the effect of arginine ingestion that could be sabotaging the increased L-lysine supplementation. The results from the Thein and Hurt study\textsuperscript{11} hold a moderate GRADE\textsuperscript{10} with significant findings that connect serum lysine levels with herpetic lesion. Because of the overall low quality of evidence of the Milman et al study,\textsuperscript{13} the results are not reliable to change or alter practice decisions. A larger, randomized control trial, focusing on finding a relative range of lysine serum values in correlation with arginine dietary restrictions could lead to better results that support the prophylactic use of L-lysine.

L-lysine hydrochloride, an amino acid building block for protein, is available as an over-the-counter dietary supplement at low cost to consumers: 1000mg/ day works out to $0.07/day, $26.22/year.\textsuperscript{19} The price tag for yearly prophylaxis with generic acyclovir is approximately $274.00 and valacyclovir approximately $1,080.00.\textsuperscript{19} Contraindications for lysine supplementation are patients with renal disease or hepatic impairment due to catabolism taking place in the liver and potential inability to eliminate large amounts of nitrogen produced upon the breakdown of supplemented amino acids.\textsuperscript{20} Interactions with lysine supplementation include calcium with the possible side effects of increased gallstones and aminoglycoside antibiotics, which could increase the risk of nephrotoxicity.\textsuperscript{21}
Side effects of the antiviral drugs acyclovir and valacyclovir are extensive and include headache, neutropenia, elevated liver enzymes, nausea, abdominal pain, and malaise. Warnings include hypersensitivity, thrombotic thrombocytopenia purpura (TTP), hemolytic uremic syndrome (HUS), acute renal failure (ARF), and central nervous system involvement. Acyclovir has a safer profile and is more cost efficient than valacyclovir but both cost exceedingly more than L-lysine hydrochloride and L-lysine has a safer profile.

CONCLUSION

The effects of L-lysine prophylactic therapy in suppression of herpes labialis is clear but not for all individuals. There are many variables such as individual diets containing lysine and arginine, the personal ability to absorb or utilize L-lysine, and manipulating the correlation between L-lysine supplementation and the serum lysine concentration. A prophylactic treatment of 1000 mg L-lysine per day dramatically reduced the recurrence rate when a person’s serum lysine concentration exceeded 165 nmol/ml but as Thein and Hurt stated, this is the threshold value for their particular sample population which may not be the level needed to provide protection from herpetic outbreaks in all persons. The question remaining is, what is the optimal lysine serum level to provide protection for the majority of persons from herpetic outbreaks and is it consistently attainable with life variables?

Supplemental L-lysine taken at recommended dosages provides a prophylactic therapy benefit to patients whose bodies responds to the supplementation with an increase in serum lysine levels. It is a safe therapy to consider for patients without renal disease who are looking for a cost efficient treatment option for recurrent herpes labialis. A large, randomized control trial, focusing on finding a relative range of lysine serum values in correlation with lysine...
supplementation and arginine dietary restrictions could lead to more consistent results. This study needs to have statistical data, broken down per patient that can help to determine the population that will respond to L-lysine treatment. A safe cost effective treatment option for patients with herpes labialis will make a difference in daily living and decrease the suffering of patients with frequent herpes labialis outbreaks.
References


Table I. Characteristics of Reviewed Studies

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<td>No serious indirectness</td>
<td>Serious imprecision(\alpha, \beta)</td>
<td>No serious inconsistencies(\alpha, \beta)</td>
<td>No bias likely</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
<td>Classification of Lesion at its Worst</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Milman et al13</td>
<td>1 RCT</td>
<td>Serious limitations(\alpha, \beta)</td>
<td>No serious indirectness</td>
<td>Serious imprecision(\alpha, \beta)</td>
<td>No serious inconsistencies(\alpha, \beta)</td>
<td>No bias likely</td>
<td>Low</td>
<td>Important</td>
</tr>
<tr>
<td>Serum Levels of Lysine and Arginine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thein and Hurt11</td>
<td>1 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision(\alpha, \beta)</td>
<td>No serious inconsistencies(\alpha, \beta)</td>
<td>No bias likely</td>
<td>Moderate</td>
<td>Less</td>
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<tr>
<td>Serum Lysine:Arginine Ratio</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thein and Hurt11</td>
<td>1 RCT</td>
<td>No serious limitations</td>
<td>No serious indirectness</td>
<td>Serious imprecision(\alpha, \beta)</td>
<td>No serious inconsistencies(\alpha, \beta)</td>
<td>No bias likely</td>
<td>Moderate</td>
<td>Less</td>
</tr>
</tbody>
</table>

\(\alpha\) Risk of Recall bias and risk of attrition bias in the Milman et al study
\(\beta\) Risk of carryover effect in the Thein and Hurt study
\(\alpha, \beta\) Outcomes of interest are underpowered in the Milman et al study
\(\alpha, \beta\) Small sample size and length of study in the Milman et al study and
\(\alpha, \beta\) Small sample size in the Thein and Hurt study
\(\alpha, \beta\) No reporting of prognostic balance in the Milman et al study

Table II. Thein and Hurt11

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Test Period 1 (0-6 months)</th>
<th>Test Period 2 (6-12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Frequency (X)</td>
<td>4.9</td>
<td>4.05</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td>± 1.49</td>
<td>± 2.25</td>
<td>± 2.58</td>
</tr>
<tr>
<td>Serum lysine concentration (nmol/ml) (X)</td>
<td>173.78 ± 53.40</td>
<td>175.17 ± 42.45</td>
<td>197.05 ± 30.26</td>
</tr>
</tbody>
</table>

* Indicates a statistically significant difference between the two groups (p ≤ 0.05)
± Values indicate standard deviation
Table III. Milman et al<sup>13</sup>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients starting with L (n=31)</th>
<th>Patients starting with P (n=34)</th>
<th>Total (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients having no recurrence during L treatment (but recurrences during P treatment)</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Patients having no recurrence during P treatment (but recurrences during L treatment)</td>
<td>2</td>
<td>2</td>
<td>4 P=0.05</td>
</tr>
<tr>
<td>Patients having recurrence during Both L and P treatment</td>
<td>20</td>
<td>23</td>
<td>43</td>
</tr>
<tr>
<td>Patients having recurrence no during Both L and P treatment</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Table IV. Milman et al<sup>13</sup>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients starting with L (n=31)</th>
<th>Patients starting with P (n=34)</th>
<th>Total (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of recurrences during L treatment</td>
<td>45</td>
<td>46</td>
<td>91</td>
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<tr>
<td>Median and range</td>
<td>1 (0-4)</td>
<td>1 (0-6)</td>
<td>1 (0-6)</td>
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<tr>
<td>Total no. of recurrences during P treatment</td>
<td>38</td>
<td>66</td>
<td>104</td>
</tr>
<tr>
<td>Median and range</td>
<td>1 (0-4)</td>
<td>2 (0-6)</td>
<td>1 (0-6)</td>
</tr>
</tbody>
</table>

Table V. Thein and Hurt<sup>11</sup>

<table>
<thead>
<tr>
<th>Herpetic lesion frequency (number of episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Group A (Began with lysine tablets 0-6 months then switched to placebo at 6 months)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<td>12</td>
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<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>Group B (Began with placebo 0-6 months then switched to placebo at 6 months)</td>
</tr>
<tr>
<td>16</td>
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