

RESEARCH ARTICLE

A randomized, open-label, comparative study of lysine cream 15% with standard therapy in the management of non-diabetic foot ulcer assessing by Bates-Jensen wound assessment tool

Vani J¹, Shashi Kumara², Prathima C³

¹Department of Pharmacology, Akash Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India, ²Department of Pharmacology, Chamarajanagar Institute of Medical College, Chamarajanagar, Karnataka, India, ³Department of Pharmacology, JSS Medical College, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India

Correspondence to: Shashi Kumara, E-mail: samsruthia2@gmail.com

Received: June 07, 2019; Accepted: July 02, 2019

ABSTRACT

Background: Lysine is an essential amino acid that is not synthesized within the body. It is synthesized in higher plants through a biochemical pathway. Many clinical trials have reported that amino acids play an important role in hastening the process of healing by improving the local blood supply as growth factors. **Aims and Objectives:** This study aimed to establish wound healing, efficacy, and tolerability of lysine cream (15%) in non-diabetic foot ulcer by Bates-Jensen wound assessment tool (BWAT). **Materials and Methods:** A randomized, open-label, interventional, comparative, prospective parallel group study was conducted on 20 subjects (participants) with non-diabetic ulcer. Participants were divided into two groups, namely, control and test. The control group was treated with standard treatment and the test group was treated with standard therapy along with lysine cream (15%) twice daily. Participants were screened by BWAT. **Results:** The 20 participants were allocated into two groups. The control group was treated with standard treatment ($n = 10$). The test group received standard treatment followed by lysine 15% cream. The mean \pm standard deviation values indicate size and depth of the foot ulcer from the 1st week to 7th week. Both the groups showed significant decrease in the size and depth of the ulcer over the period of 7 weeks. Assessment of the 1st week showed that there is no significant decrease in the size of the ulcer. Overall mean difference of the control versus test groups indicated that the lysine-treated group significantly decreased both the parameters than the standard therapy (control). **Conclusion:** Treatment with lysine cream significantly improved wound healing in non-diabetic foot ulcer patients when compared to the standard therapy.


KEY WORDS: Non-diabetic; Foot Ulcer; Lysine; Bates-Jensen Wound Assessment

INTRODUCTION

“Foot ulceration” the term may be defined as erosion of the local tissue or a breach of epidermis at the site distal to the ankle.^[1] Many practitioner, podiatrists, and researcher have

reported its diverse range of etiology and careful assessment and recognition of the cause are required to facilitate appropriate management. There are numerous factors that influence person who are at the risk of developing ulceration.^[2]

The common risk factor for developing foot ulceration includes structural deformity of tissues, peripheral vascular disease, trauma, previous history of foot ulceration and or/amputation, peripheral neuropathy^[3] arterial disease, venous disease, metabolic disorders, vasculitis, autoimmune diseases, infections, malignancy, artifact, and hematological diseases.^[3]

Access this article online	
Website: www.njppp.com	Quick Response code 
DOI: 10.5455/njppp.2019.9.0622802072019	

National Journal of Physiology, Pharmacy and Pharmacology Online 2019. © 2019 Shashi Kumara, et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material for any purpose, even commercially, provided the original work is properly cited and states its license.

Incidence of foot ulceration is increasing in diabetic patients and management is difficult in later stages. With diabetes, the prevalence of foot ulcer is difficult to elucidate due to the above-mentioned risk factors. No specific data have been reported under the umbrella of "foot ulcer," but there are very few Indian studies on the epidemiology of chronic wounds in community and are reported as 4.5/1000 population. The prevalence of acute wound was nearly double at 10.5 per population. While the causes for chronic wounds are many, including diabetes, atherosclerosis, tuberculosis, and leprosy, the foremost causes include venous ulcers and pressure sores encountered in India.^[4]

Wound healing is a dynamic process that optimally leads to restoration of tissue integrity and function.^[5] It represents the response of an organism to injury which results in repair or reconstitution of a defect in an organ.^[6] In case of some special situation like patients having ulceration associated with other comorbidities such as peripheral vascular disease and others which do not promote the healing processes due to the absence of pedal pulsations. Amino acids play a supportive role to hasten healing processes in ulcer associated with others comorbidities.^[7] Glycyl-L-Histidyl-L-Lysine (GHK) copper complex is a human tripeptide present in the plasma. Studies conducted in different research laboratories across the world have established that human tripeptide GHK-Cu possesses plethora of biological actions which include activation of wound healing, attraction of immune cells, antioxidant and anti-inflammatory effects, stimulation of collagen and glycosaminoglycan synthesis in dermal fibroblasts, and promotion of blood vessel growth by augmenting the functional concentration of growth factors. A 2% GHK gel showed promising results in the treatment of diabetic patients, increasing the percentage of ulcer closure.^[7]

Lysine is essential amino acids and has supportive role in remarkable improvement of both the rate and the quality of wound healing. On histopathological examination, lysine treated wounds of a rodent showed a thickening of dermoepidermal layer, with increased but controlled cell proliferation. The molecule gives qualitatively better and much quicker healing with less scar and deformation in a clean cut wound model. It is postulated that, lysine, by acting as a cell surface bridge favors angiogenesis by binding the growth factors to their receptors.^[3,8]

MATERIALS AND METHODS

A randomized, open-label, interventional, comparative, prospective parallel group study was conducted on the patients with non-diabetic foot ulcer attending the Outpatient Department of Medicine in Madras Medical College and Government General Hospital, Chennai, Tamil Nadu. The study duration for each patient was 8 weeks with eight visits. The study was conducted after obtaining approval from the institutional ethical committee.

Exclusion criteria included inability to give consent due to a concomitant medical condition (e.g., dementia or psychiatric condition) and individuals with DM.

Ethical Consideration

The study was commenced after obtaining approval from the institutional ethical committee. It was in accordance with the Declaration of Helsinki and good clinical practice guidelines. Patients with non-diabetic ulcer attending the Medicine Department, Madras Medical College and Government General Hospital, Chennai, who were already on standard treatment for the ulcer, were explained about the purpose of the study, study procedure, and possible side effects in vernacular language. Written informed consent was obtained from those who were willing to participate in the study in the prescribed format in regional language. The left thumb impression was obtained from those patients who were illiterates. This was done in the presence of impartial witness.

Treatment Schedule

Twenty participants were screened and divided into two groups, namely, control and test. Each group with allotted 10 participants was followed by drug treatment and management over a period of 8 weeks.

Control: Routine ulcer care ($n = 10$) standard therapy (mupirocin 2%).

Dressing with non-adherent absorbent gauze.

Test: Routine ulcer care ($n = 10$) standard therapy with lysine 15% cream.

Dressing with non-adherent absorbent gauze.

Evaluation and Assessment Tool

The improvement in the patient's wound condition was assessed by:

Bates-Jensen wound assessment tool (BWAT)

BWAT is a reliable, standardized, visual wound assessment tool validated for all chronic wounds. The tool contains 13 items that assess wound size, depth, edges, undermining, necrotic tissue type, amount of necrotic, granulation and epithelialization tissue, exudate type and amount, surrounding skin color, edema, and induration. These are rated using a modified Likert scale; a score of 1 indicates the healthiest and 5 indicates the unhealthiest attribute for each characteristic. A score of 13 of 65 points indicates regeneration.

Size of the ulcer assessed as per BWAT tool

1. Length \times width < 4 sq. cm
2. Length \times width $4 - < 16$ sq. cm

3. Length × width 16.1–<36 sq. cm
4. Length × width 36.1–<80 sq. cm
5. Length × width >80 sq. cm

Depth of the ulcer assessed as per BWAT tool

1. Non-blanchable erythema of intact skin
2. Partial thickness skin loss involving epidermis and/or dermis
3. Full-thickness skin loss involving damage or necrosis of subcutaneous tissue, may extend down to but not through underlying fascia, and/or mixed partial and full thickness and/or tissue layer obscured by granulation tissue
4. Full-thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, and bone or supporting structures obscured by necrosis.

Statistical Analysis

Descriptive statistical analysis was conducted by the SPSS version 16. Individual visit data were computed in Excel sheet. After completion of the study, the data were computed for statistical analysis into SPSS software. Mean ± standard deviation (SD) difference were considered to be a statistically significant ($P < 0.5$) and the results were denoted by tabulation and graphical representation as below.

RESULTS

The 20 participants were allocated into two groups. Control treated with standard treatment ($n = 10$). The test group received standard treatment followed by lysine 15% cream. The mean ± SD values indicate size and depth of the foot ulcer from the 1st week to 7th week. After initial treatment of lysine with standard treatment, there was no significant reduction of size of the ulcer in the test group at the 1st week of assessment ($P < 0.2333$), but later significant decrease, the ulcer depth was noted in all the participants. The result represented in Tables 1 and 2 showed that topical application of lysine in the test group over the period of 8 weeks twice daily reduced the size of the ulcer and ulcer depth as assessed by BWAT tool.

The results depicted in Figure 1 indicate mean values of ulcer depths and size during each visit from the 1st to 8th week in control versus test groups. There was a significant reduction of size of the ulcer and ulcer depth in the test groups when compared to the control group with standard treatment alone.

Data represent mean of depth and size of the foot ulcer treated with topical treatment for 8 weeks twice daily assessed by BWAT scale. The mean differences of peaks of each visit control versus test suggested the reduction in the ulcer size and depth where significant reduction noted in the test group when compared to the control group.

Table 1: Measurement of depth of the foot ulcer assessed by Bates-Jensen wound assessment tool (BWAT)

Visit (weeks)	Mean±SD		Student <i>t</i> -test (two tailed)
	Control	Test	
1	2.8±0.42	2.7±0.037	$P < 0.0001$
2	2.7±0.67	2.8±0.002	$P < 0.0028$
3	2.7±0.032	2.6±0.0	$P < 0.0001$
4	2.5±0.016	2.3±0.022	$P < 0.0001$
5	2.1±0.012	1.9±0.013	$P < 0.0001$
6	1.9±0.0	1.5±0.005	$P < 0.0001$
7	1.9±0.0	1.3±0.1	$P < 0.0001$

Each row and column represents Mean±SD of ulcer depth, measured at every visit by BWAT scale. The differences in Mean±SD show significant decrease in depth of the ulcer with lysine-treated group than control group. $P < 0.05$ was considered to be statistically significant as derived from descriptive method followed by two-tailed Student's *t*-test. BWAT: Bates-Jensen wound assessment tool, SD: Standard deviation

Table 2: Measurement of size of the foot ulcer assessed by BWAT

Visits (Week)	Mean±SD		Student <i>t</i> -test (two tailed)
	Group A (Control)	Group B (Test)	
1	3.6±0.019	4.1±1.3	$P < 0.2333$ (ns)
2	3.3±0.089	3.7±0.02	$P < 0.0013$
3	3.5±0.17	3.3±0.0095	$P < 0.003$
4	3.2±0.03	2.9±0.013	$P < 0.0001$
5	3±0.01	2.9±0.0	$P < 0.0001$
6	2.7±0.001	2±0.01	$P < 0.001$
7	2.4±0.03	2.2±0.19	$P < 0.0035$

Each row and column represents Mean±SD of ulcer size, measured at every visit by BWAT tool. The differences in Mean±SD show significant decrease in size of the ulcer with lysine-treated group than control group. $P < 0.05$ was considered to be statistically significant as derived from descriptive method followed by two-tailed Student's *t*-test. BWAT: Bates-Jensen wound assessment tool, SD: Standard deviation

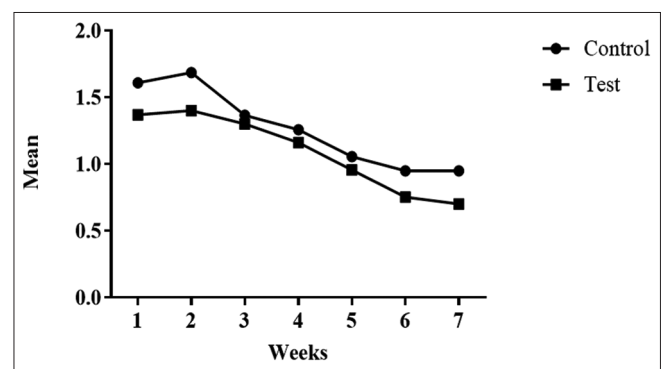


Figure 1: Measurement of depth and size of the foot ulcer assessed using Bates-Jensen wound assessment tool (BWAT)

DISCUSSION

The aim of this study is to evaluate the wound healing efficacy and tolerability of lysine cream (15%) in non-diabetic participants. The control group ($n = 10$) has

shown decrease in size and depth of the ulcer at each visit, assessed by BWAT tool which was statistically significant. The test group ($n = 10$) also showed statistically significant, decrease in both the parameters when compared to the control group which infers that the lysine has wound healing property.

As the data demonstrated, a steep curve is decreased after topical administration of mupirocin 2% twice daily shown significant reduction of ulcer at the 2nd week of assessment ($P < 0.0013$). Followed by the 2nd–7th week, steep curve represents the gradually decrease in size and depth of the ulcer in the control group by reducing the length and width of the ulcer. Hence, standard therapy with management shown significant wound healing activity. In the test group, Y-axis of the graph represents the mean difference of the ulcer, at the 1st week of wound assessment proposed significantly decrease the ulcer size and depth approximately 0.1–0.3% than the control group ($P < 0.0001$). From the 2nd to 7th week assessment shown highly significant when compare to control. Result suggests combination of standard mupirocin 2% and lysine shown better wound healing property.

Comparative steep curves of each visit were shown significantly reduce the size and depth of the foot ulcer from the 1st week to 7th week than the control group. Mean of the 3rd–4th week steep curves meets each other in between 1.0 and 1.5 of data distributed at Y-axis. Hence, meeting points of the curves explain that lysine 15% is tolerable when compare to mupirocin 2%. At 5th, 6th, and 7th weeks of assessment shown that lysine-treated group is highly effective than the control group. The comparative results concluded lysine having wound healing property ($P < 0.0001$).

The role of immunonutrition including lysine in wound healing has been an area of both interest and controversy for many years. The deficient or malnourished patients have increased duration of wound healing or impaired healing. Immune-modulating biological nutrients have been consistently harvested for wound repair. Review literature of these immune modulating nutrients elucidated their roles in wound healing by preventing the infections and thereby enhancing the immune system. However, our study topically treated with lysine shown better wound healing property through upregulate the wound repair mechanism by modulating the wound biological environment. Topically, lysine is a wound healing peptide which was replaced by its D enantiomers, yielding an analog is prevent the bacterial growth and significantly hasten the wound healing activity.

Hypothesis says that in immunocompromised and malnourished patients, there is a scope to speed up the wound healing activity; therefore, a large number of molecules are being tested for the promotion of therapeutic angiogenesis

including vascular endothelial growth factor L-lysine monohydrochloride (L-lysine) which has been shown to promote copper complex of a GHK peptide and acetylserine process. On the other hand, lysine has the potential for closure of the wound by significantly enhanced lysine acetylation in activated keratinocytes.^[9-16]

No adverse events were reported during the study period which suggests that topical lysine was well tolerated. The biochemical parameters such as blood sugar, urea, serum creatinine, and electrolytes which were performed to suggest that topical lysine was well tolerated.

CONCLUSION

From this study, it can be concluded that lysine cream is effective in promoting the healing of non-diabetic ulcer and also well tolerated. Among all participants who had taken treatment for non-diabetic foot ulcer with lysine cream for 8 weeks along with standard treatment showed reduction in the size and depth of the ulcer and there was hastening of the wound healing activity.

REFERENCES

1. Australian Wound Management Association. Standards for wound management. Australian Wound Management Association; 2002. Available from: http://www.awma.com.au/publications/2007/awma_standards.pdf.
2. Sumpio BE. Foot ulcers. *N Engl J Med* 2000;343:787-93.
3. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: A critical review. *Arch Intern Med* 1998;158:1357-64.
4. Biland L, Wiender, LK. Varicose veins and chronic venous insufficiency. *Acta Chir Scand* 1988;544: 9-11.
5. Hansson C, Anderson E, Swanbeck G. Leg ulcer epidemiology in Gothenberg. *Acta Chir Scand* 1988;544 suppl:12-6.
6. Hallbook T. Leg ulcers epidemiology. *Acta Chir Scand* 1988; 544:17-20.
7. Henry G, Garner WL. Inflammatory mediators in wound healing. *Surg Clin North Am* 2003;83:483-507.
8. Galiano RD, Mustoe TA. *Grabb and Smith's Plastic Surgery. Wound Healing*. 6th ed., Ch. 2. Philadelphia (PA): Lippincott Williams and Wilkins; 2007 p. 322-44.
9. Bennet NT, Schulz GS. Growth factors and wound healing biomechanical properties of growth factors and their receptors. *Am J Surg* 1993;165:728-37.
10. Datta D, Bhinge A, Chandran V. Lysine is it worth more? *Cytotechnology* 2001;36:3-32.
11. Datta D. Essential Amino Acid lysine and Its Analogues Support Faster and Qualitatively Better Healing wounds. Available from: http://www.ispub.com/journal/the_internet_journal_of_neurology/volume4_number_1_30/article_printable/reversal_of_acute_human_brain_ischemic_injury_by_lysineinduced_therapeutic_angiogenesis_preliminary_results_of_pilot_study.html.
12. Zeybel M, Hardy T, Wong YK, Mathers JC, Fox CR,

- Gackowska A, *et al.* Multigenerational epigenetic adaptation of the hepatic wound-healing response. *Nat Med* 2012;18:1369-77.
13. Rafehi H, El-Osta A, Karagiannis TC. Epigenetic mechanisms in the pathogenesis of diabetic foot ulcers. *J Diabetes Complications* 2012;26:554-61.
 14. Witte MB, Barbul A. General principles of wound healing. *Surg Clin North Am* 1997;77:509-28.
 15. Novak TE, Babcock TA, Jho DH, Helton WS, Espat NJ. NF-kappa B inhibition by omega-3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. *Am J Physiol Lung Cell Mol Physiol* 2003;284:L84-9.
 16. Chow O, Barbul A. Immunonutrition: Role in wound healing and tissue regeneration. *Critical reviews. Wound healing society. Adv wound care* 2012;3:49-53.

How to cite this article: Vani J, Kumara S, Prathima C. A randomized, open-label, comparative study of lysine cream 15% with standard therapy in the management of non-diabetic foot ulcer assessing by Bates-Jensen wound assessment tool. *Natl J Physiol Pharm Pharmacol* 2019;9(9):907-911.

Source of Support: Nil, **Conflict of Interest:** None declared.