

Comparison of Salicylic Acid and Urea *versus* Ammonium Lactate for the Treatment of Foot Xerosis

A Randomized, Double-Blind, Clinical Study

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Xerosis is defined as dehydration of skin characterized by redness, dry scaling, and fine crackling that may resemble the crackling of porcelain. The present double-blind trial was a randomized paired comparison study evaluating the keratolytic effect of 5% salicylic acid and 10% urea ointment (Kerasal®) on one foot and 12% ammonium lactate lotion (Lac-Hydrin®) on the other foot in mild-to-moderate xerosis. Seventy patients were initially enrolled in the trial. Fifty-four patients were evaluated after 2 weeks of treatment; of those 54 patients, 39 were evaluated after 4 weeks of treatment. Although there was significant improvement in severity of xerosis after 2 and 4 weeks of treatment, there was no statistically significant difference between treatment groups. Irrespective of the mechanism of action, this study shows that both Kerasal and Lac-Hydrin 12% lotion result in reduction in the severity of xerosis after 4 weeks of therapy. (J Am Podiatr Med Assoc 88(7): 332-336, 1998)

In normal skin, the stratum corneum serves as a protective barrier against excessive evaporative water loss and environmental insults. The extensibility of the stratum corneum depends on its water content and environmental temperature.¹ The stratum corneum must contain more than 10% water to remain soft and pliable; when the water content drops below 10%, it becomes rough, with possible scaling and cracking.

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changes are seen most frequently on the extremities, especially the legs and feet.²

The treatment of xerosis has three aspects: replacing water content and maintaining hydration, alleviating the symptomatology, and controlling keratinization to reduce scaling.³ Relief and prevention of dryness of the skin are centered around maintaining the proper hydration of the epidermis, particularly the stratum corneum. Therapy has been limited to topical applications of hydrating emollients designed to soften the stratum corneum and alleviate the scalliness.⁴ One of the primary objectives of using an emollient is to maintain enough water in the stratum corneum to reduce the possibility of cracking and flaking.¹ Emollients such as lanolin and glycerin are hydrophilic, act primarily on the skin's surface, and form an occlusive barrier that decreases evaporation.^{1, 2} Another approach to treating xerosis is the use of skin protectants containing hygroscopic sub-

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stances, also known as humectants.³ These agents increase skin moisture and reduce water loss.

Salicylic acid and urea have been widely used as a topical treatment for xerosis for nearly 3 decades.^{1,5,6} Urea increases water uptake in the stratum corneum and enhances its water-binding capacity.^{1,5} Urea is also thought to exert its keratolytic effect through the process of unfolding proteins, thus denaturing them.⁷ Salicylic acid is a keratolytic agent that dissolves the intracellular matrix and softens the stratum corneum, thereby enhancing the shedding of scales.^{8,9} Skin desquamation is the result of loss of cohesion between corneocytes.⁷

Kerasal^{®1} is a homogeneous blend of salicylic acid and urea in special optimal-release bases. Kerasal is the first product in the United States to contain these two proven agents. It is the only salicylic acid-containing product that is highly occlusive as well as water-soluble.

Many studies have demonstrated the clinical effectiveness of sodium lactate and lactic acid in the treatment of xerosis.¹⁰⁻¹⁴ Lac-Hydrin^{®2} 12% lotion (12% ammonium lactate lotion) is designed to produce humectant effects, thereby reducing the xerotic disease state.¹⁵

This clinical trial was conducted to compare the safety and efficacy of 5% salicylic acid and 10% urea ointment (Kerasal) *versus* 12% ammonium lactate lotion (Lac-Hydrin) in the treatment of mild-to-moderate foot xerosis.

Materials and Methods

The present double-blind trial was a randomized paired comparison study evaluating the keratolytic effect of Kerasal on one foot and Lac-Hydrin 12% lotion on the other foot in mild-to-moderate xerosis. Patients with peripheral vascular disease, pre-existing immunosuppressive disease, known hypersensitivity to Lac-Hydrin 12% lotion, Kerasal, or salicylic acid, and pregnant women were excluded. Patients with known dermatologic diseases such as psoriasis, eczema, Darier's disease (keratosis follicularis), lichen planus, and pityriasis rubra pilaris were also excluded.

Treatment order was randomly predetermined. This was done by using an equation in the Microsoft Excel^{®3} software program that generates random numbers. The randomization provided an even number of right and left feet, which were treated with each test medication. Each patient served as his or her own control, as all had bilateral xerosis and ap-

plied one test medication to one foot and the other test medication to the other foot. This greatly reduced inpatient variation and increased the trial's ability to detect a difference between the two treatments.

Patients were enrolled after the inclusion and exclusion criteria were met and informed consent was obtained. If possible, a dermatophyte test medium culture was taken to rule out fungal infection. In the event of a positive culture, the patient was discontinued from the study. After appropriate patients were selected and initial evaluation of the xerosis site or sites was completed, treatment was begun. The chosen site or sites were reevaluated 2 and 4 weeks after the start of treatment. All patients were at least 18 years of age and had a score of 1, 2, 3, or 4 on the xerosis severity scale as presented by Rogers et al¹³ (Table 1).

The medication was administered in the following manner: To avoid cross-treatment contamination, the patient applied the medication for the left foot with the right hand and applied the medication for the right foot with the left hand. Kerasal and Lac-Hydrin 12% lotion were supplied in identical tubes weighing approximately 35 g each. A label was affixed to each tube indicating the patient number and dosage regimen. The upper part of the label clearly indicated whether the medication was for the right foot (bright pink label) or the left foot (bright green label). The medications were applied twice daily: in the morning and at bedtime. The patients were advised to massage the affected site until the medication had been properly absorbed.

Immediately before the beginning of treatment with the two medications, investigators evaluated the severity of xerosis for each patient according to the scale shown in Table 1. Tenderness was assessed at

Table 1. Xerosis Severity Scale

Mild	0	Normal skin
	1	Dusty appearance, occasional minute skin flakes
	2	Generalized dusty appearance, many minute skin flakes
Moderate	3	Defined scaling with flat borders
	4	Well-defined heavy scaling with raised borders, shallow fissures
Severe	5	Large scale plates, fissures
	6	Large scale plates, deep erythematous fissures

Source: Rogers et al.¹³

^{®1} Spirig, Egerkingen, Switzerland.

^{®2} Westwood Squibb Pharmaceuticals, Inc, Buffalo, NY.

^{®3} Microsoft Corp, Redmond, WA.

each visit by the patient and the investigator. The following 4-point scale based on the level of discomfort experienced by the patient with palpation of the feet was used: 0 = none, 1 = mild (discomfort upon deep palpation), 2 = moderate (discomfort upon moderate palpation), and 3 = severe (discomfort upon slight palpation). The patient was questioned at each visit regarding pruritus and was asked to assess this on the following 4-point scale: 0 = none, 1 = mild (slight), 2 = moderate (somewhat), and 3 = severe (very).

After the fourth week of treatment, the patient and clinician independently rated the overall result on the following 6-point scale: 5 = worse, 4 = no improvement, 3 = slight improvement, 2 = moderate improvement, 1 = good improvement, and 0 = clear.

To ensure patient compliance, both tubes of medication were weighed at all three visits (at the initial screening, after 2 weeks of therapy, and after 4 weeks of therapy). Adverse events occurring during the trial were documented at each evaluation visit.

Statistical Analysis

Demographic data including age, ethnicity, and gender were tabulated, and statistical analyses were carried out for all tabulated efficacy variables. The ordinate scale was assigned the following values: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Each demographic variable was analyzed using the paired *t*-test. The result of the determination of xerosis severity was analyzed using analysis of covariance and baseline measurements were used as covariants. The overall evaluation by the investigator and the patient was analyzed using the nonparametric Mann-Whitney test. Safety and tolerance were evaluated on the basis of the reported adverse events.

Results

The analysis of results was based on evaluation of severity of skin dryness during treatment. Patient demographic data are shown in Table 2. There were roughly equal numbers of males and females. The age range of the 70 patients enrolled was 22 to 86, with the average age being 48. After the initial screening, 14 patients were excluded from the analysis because they were lost to follow-up, and 2 patients were excluded owing to positive fungal culture results. After 2 weeks of therapy, data from 15 patients were excluded owing to noncompliance.

At baseline, there was no statistically significant difference between mean xerosis severity scores prior to treatment with Kerasal and treatment with Lac-Hydrin 12% lotion ($P = 0.7416$, $n = 70$) (Fig. 1).

Table 2. Patient Demographic Data

Race/Ethnicity	No. (%)	Sex	
		Female	Male
Black	53 (76)	26	28
Hispanic	9 (13)	6	3
Puerto Rican	4 (6)	2	2
White	1 (1)	1	0
Indian	1 (1)	1	0
Dominican	1 (1)	0	1
Unknown	1 (1)	0	0
Total	70	36	34

After 2 weeks of treatment, the mean xerosis scores decreased ($P = 0.6589$, $n = 54$). There was a further decrease in mean xerosis scores after 4 weeks of treatment ($P = 0.1466$, $n = 39$). Although there was significant improvement in xerosis scores after 2 and 4 weeks of treatment, no statistically significant difference was observed between treatment groups.

At baseline and prior to receiving study medication, 14 patients in the Kerasal group and 16 patients in the Lac-Hydrin 12% lotion group reported mild pruritus. Six patients in the Kerasal group and two in the Lac-Hydrin 12% lotion group reported severe pruritus. After 4 weeks of treatment, only one case of mild pruritus was reported in association with treat-

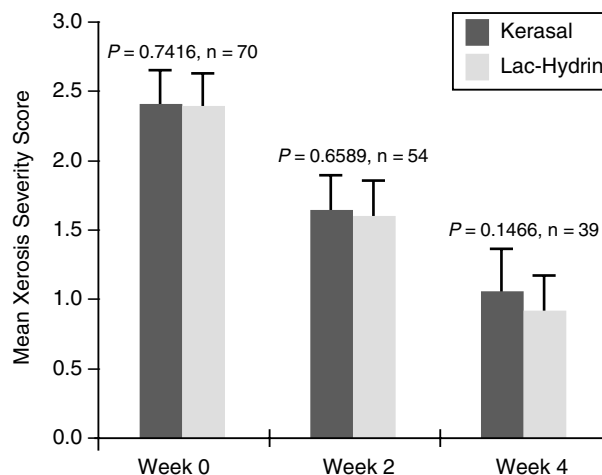


Figure 1. Mean xerosis severity scores at baseline and after 2 and 4 weeks of treatment with Kerasal versus Lac-Hydrin 12% lotion.

ment with Kerasal, while only one case of moderate pruritus was reported with Lac-Hydrin 12% lotion.

At baseline, four patients reported mild tenderness and two reported moderate tenderness in the Kerasal group, while the Lac-Hydrin 12% lotion group had three patients with mild tenderness and two with moderate tenderness. After 2 and 4 weeks of treatment, no tenderness was reported in either group.

Figure 2 shows the mean overall treatment evaluation scores given by the patient and clinician after 4 weeks of therapy. Significant improvement in xerosis was noted for both medications, with no statistically significant difference between treatment groups (patient, $P = 0.0864$; clinician, $P = 0.0767$). Table 3 shows the number of adverse events reported, which were relatively few and did not require discontinuation of the medication. In general, both medications were well tolerated by all patients in the study.

Discussion

Xerosis, a condition involving dehydration of the skin, is an entity commonly assessed and treated by podiatric physicians. In this study, the analysis of variance for effects over time indicated a significant improvement in severity of dryness with both Kerasal and Lac-Hydrin 12% lotion. Kerasal and Lac-Hydrin 12% lotion are both effective in treating xerosis when

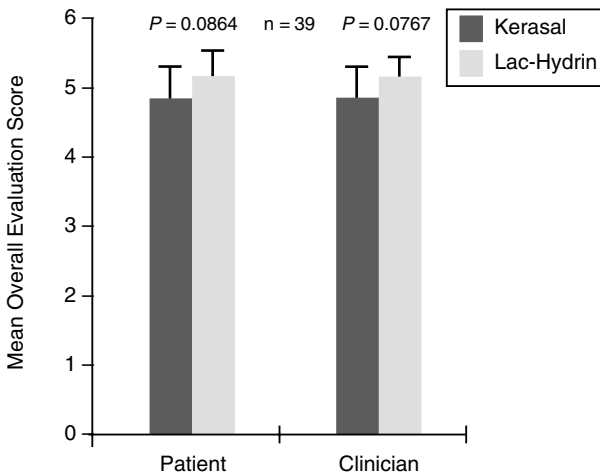


Figure 2. Mean overall treatment evaluation scores given by patient and clinician after 4 weeks of treatment with Kerasal *versus* Lac-Hydrin 12% lotion. 5 = worse, 4 = no improvement, 3 = slight improvement, 2 = moderate improvement, 1 = good improvement, 0 = clear.

Table 3. Number of Adverse Events

Adverse Event	Kerasal	Lac-Hydrin 12% Lotion
Erythema	1	1
Heat sensation	2	1
Pruritus	3	4
Edema	1	1

used twice daily for 4 weeks. No clear patient preference was noted for Kerasal or Lac-Hydrin 12% lotion. Of the 20% of patients who did express a preference for one or the other medication, there was no overall difference in patient assessment of efficacy.

Keratolytic topical formulations have the potential to cause adverse reactions such as stinging, burning, and erythema. This study, however, demonstrated a very low incidence of those events. The most commonly reported adverse event in this study was pruritus, which either resolved or improved in all cases and may have been due to the xerosis and not to the study medication.

Many people with diabetes have autonomic neuropathy, which predisposes them to excessive dryness of the skin, with scaling, fissures, and potential ulcerations. Use of efficacious moisturizers such as Lac-Hydrin 12% lotion and cream and now Kerasal is especially important in this population. With diabetic patients, however, it is prudent to promote the use of any keratolytic product only under the supervision of a health-care professional.

Kerasal is currently marketed to podiatrists for sale in private offices. In the future, it will be available in major drugstore chains without a prescription. Lac-Hydrin 12% lotion and cream are available by prescription only.

Conclusion

The results of this study indicate that both Kerasal and Lac-Hydrin 12% lotion are effective agents for the treatment of xerosis. Both agents resulted in a significant reduction in the severity of skin dryness after 4 weeks of therapy, with no statistically significant difference observed between treatment groups.

Acknowledgment. This study was funded in part by Draxis Health, Inc, Mississauga, Ontario, Canada.

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