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THERAPY

A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients

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Abstract

Objective: The objective of this study was to evaluate the efficacy of a commercially available anti-itch lotion containing 1% pramoxine hydrochloride versus control lotion in the treatment of uremic pruritus in adult hemodialysis patients. *Methods*: This was a randomized, double-blind, controlled comparative trial set in a community hemodialysis center. The study population comprised 28 individuals (mean age 53.5) with moderate to severe uremic pruritus who had been receiving hemodialysis for at least 3 months. All participants were recruited from one community hemodialysis center. Topical anti-itch lotion containing 1% pramoxine was applied twice daily to all affected areas of pruritus for 4 weeks. The main outcome measure was a reduction in itch intensity. Secondary outcomes included increases in the investigator's global assessment and improvement in skin hydration. *Results*: There was a 61% decrease in itch intensity in the treatment group, whereas a 12% reduction in itch intensity was observed in the control group. The rate of decline in itching was also greater in the treatment arm versus the control arm. No significant differences were displayed in other studied disease-related variables. *Conclusion*: Our study shows that individuals using pramoxine 1% lotion experienced a reduction in pruritus to a greater degree than those using the control lotion. This safe, convenient and effective topical lotion may potentially benefit the large number of patients affected by pruritus associated with end-stage renal disease.

Key words: *Kidney, therapy, trial*

Introduction

The prevalence of end-stage renal disease (ESRD) continues to rise both in the United States and worldwide, making it a major public health issue (1,2). Pruritus is one of the most distressing cutaneous symptoms of ESRD, even in patients who are adequately dialyzed (3). Epidemiologic studies have demonstrated that the prevalence of pruritus amongst ESRD patients is high, ranging between 42% and 75% (4–7). Not only does this debilitating symptom profoundly impact the quality of life and sleep, recent evidence demonstrates that pruritus is also associated with poor patient outcome (8–10).

The pathophysiology of ESRD-associated pruritus is poorly defined and, as a result, the development of specific therapies has proven to be a challenge. Numerous therapies have been attempted; however, none has proven to be definitive. For instance, although based upon an uncontrolled observation, topical tacrolimus was found to be effective (11); a vehicle-controlled study of the same product demonstrated no efficacy (12). Current topical agents recommended without evidence-based support

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for ESRD-associated pruritus include capsaicin, corticosteroids and emollients (13).

Pramoxine is a topical local anesthetic that has been shown to have antipruritic properties when used both alone and in combination with lactic acid (14,15). The primary objective of the present study was to evaluate the efficacy of a commercially available anti-itch lotion containing 1% pramoxine hydrochloride versus control lotion in the treatment of pruritus associated with ESRD in a double-blind, controlled comparative trial. Secondary objectives were to compare the effects of the anti-itch lotion versus control on disease severity, skin hydration and quality of life measures in the same group of patients.

Methods

The study protocol was approved by the Wake Forest University Health Sciences Institutional Review Board, and written informed consent was obtained from all participants prior to enrollment. Eligible individuals were between 18 and 70 years old with moderate to severe uremic pruritus. All participants had a diagnosis of ESRD. Participants were also required to have received hemodialysis for at least 3 months. A total of 28 individuals (aged 21–70 years) with moderate to severe uremic pruritus were recruited from Salem Kidney Center in Winston-Salem, North Carolina. The male to female ratio was 1:1.

Pruritus was defined as: (1) having at least two episodes of itch over a period of 2 weeks, each lasting for 2 minutes or more; and (2) symptoms of itch in a regular pattern over 6 months. There could be no other active disease that could explain the itch. A 10-cm visual analog scale (VAS) was used to evaluate the intensity of itch in three situations: the individual's itch at its worst intensity; at its best intensity; and itch intensity after a mosquito bite. This method has been previously described and validated (14).

This was a 4-week, randomized, double-blind, controlled study. Fourteen individuals received the treatment lotion (1% pramoxine HCl) and the remaining 14 received a bland emollient (Cetaphil lotion). A target lesion limited to one anatomic site, excluding face and genitals, was selected at baseline. Each participant was instructed to apply lotion twice daily to all affected areas of pruritus for 4 weeks. The use of any other topical or systemic medication to treat uremic pruritus was not permitted while participating in the study. Participants were clinically evaluated for erythema, xerosis, lichenification and overall severity at baseline, week 1, and week 4 (end of the study). Erythema, xerosis and lichenification were assessed using a 3-point Likert scale, with '0' indicating no symptoms and with '3' representing severe. In addition, the following measures were also used for assessment of efficacy and safety: (1) individual pruritus history and assessment questionnaire; (2) Investigator Global Assessment (IGA) of response to treatment; (3) skin hydration measurements using the MoistureMeter piko™ (Delfin Technologies Ltd, Kuopio, Finland), at baseline and the end of the study; (4) daily itching severity individual assessment VAS; and (5) adverse events as reported by the patients and investigator.

Statistical analysis

Itch reduction was defined as [(1 – (mean visual analog scores at end of study) / (mean visual analog scores at baseline)*100]. Simple statistics and comparisons were performed with SAS 9.1 software (SAS Institute, Cary, NC, USA). Wilcoxon tests, rank sum sign tests, and F-tests were performed as appropriate.

Results

Figure 1 portrays the disposition of the participants in this trial, including those who were screened and eligible for randomization. Table 1 displays the results of the study. Although there were numeric declines in certain study variables that favored the treatment over the control, none of these achieved statistical significance except itching.

Figure 2 shows trends in VAS daily intensity for medication and control. A sharper decline is observed in VAS for pramoxine lotion use, slope = –0.10, when compared to the decline observed with control lotion use, slope = –0.03 (p-value = 0.0072), suggesting that pramoxine lotion use experiences a larger decrease in VAS.

Figure 3 demonstrates the greater itch reduction with the pramoxine-treated patients versus the control patients. There was a 61% decrease in the average reported VAS for pramoxine lotion from baseline to the end of the study. Only a 12% decrease was observed in the control group for average reported VAS.

No adverse effects, such as burning sensation or itch, were noted in either arm of the study.

Discussion

The present study shows that anti-itch lotion containing pramoxine reduces ESRD-associated pruritus to a greater degree than the control lotion following 4 weeks of topical application. In addition, both the

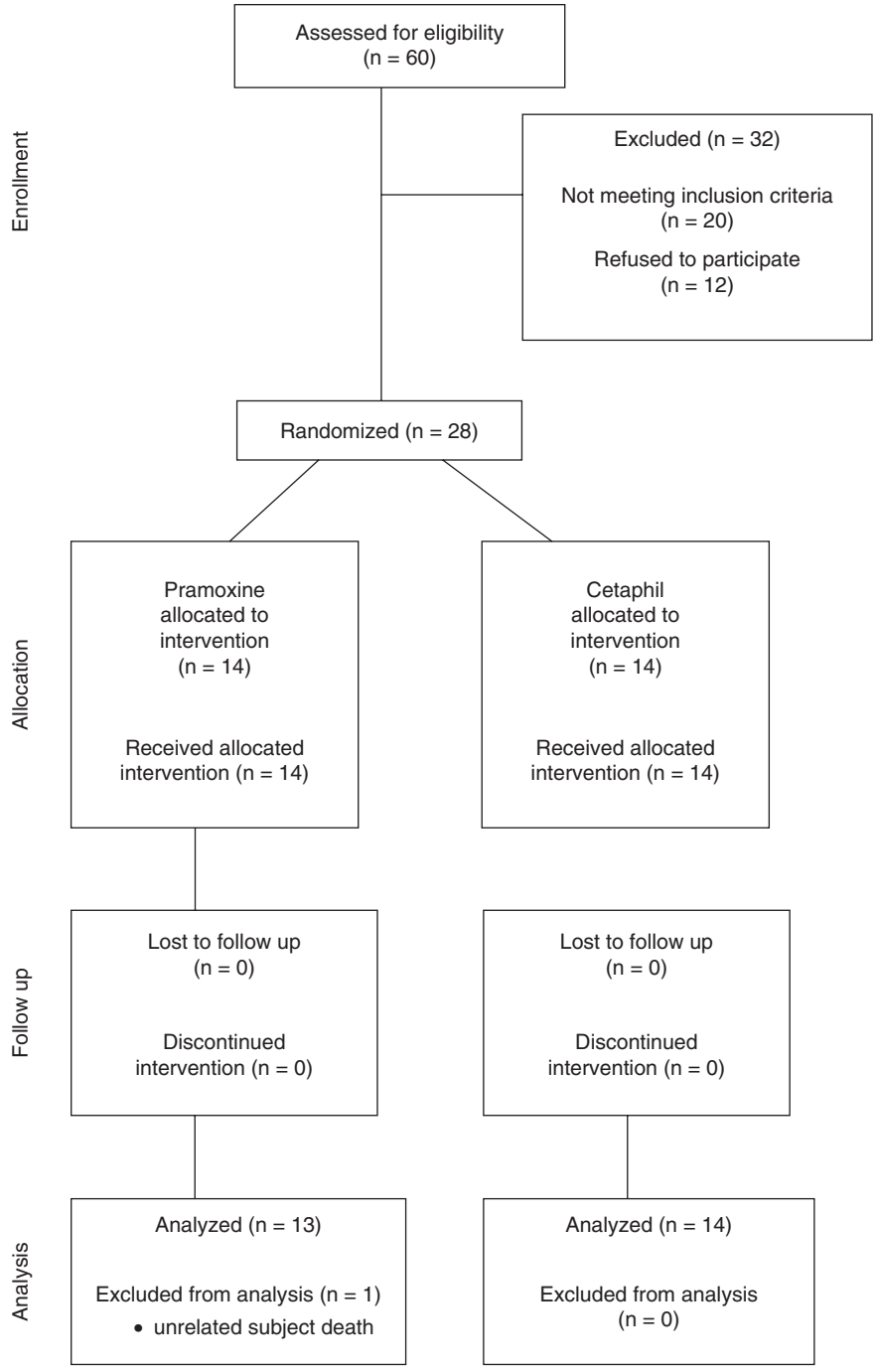

Figure 1. Disposition of study participants.

pramoxine lotion and the control lotion resulted in overall improvements in disease severity, skin hydration and quality of life (in terms of sleep disturbances and mood) at the end of the 4-week study period.

No adverse effects were reported and only one patient failed to complete the study (owing to death from an unrelated event). Treatment with anti-itch lotion containing pramoxine was therefore well tolerated. Previous reports on the safety of pramoxine hydrochloride have described this compound to be well tolerated by tissues in addition to displaying low systemic toxicity and sensitizing potential (16).

Pramoxine lotion and control lotion both resulted in improvements in individual reported itch intensity. Although disease severity obtained by IGA (in terms of erythema, xerosis and lichenification) and skin hydration improved following 4 weeks of topical application, because of the small size of this pilot

Table 1. Results for the Investigator Global Assessment (IGA).

	Baseline	Adjusted means at 4 weeks		
	All (n = 28)	Medication (n = 14)	Control lotion (n = 14)	Medication vs Control p-value
Severity (0 = none, 3 = severe)				
Erythema[a]	0.82 (0.61)	0.30 (0.13) [0.04,0.55]	0.22 (0.12) [–0.024,0.47]	0.7
Xerosis[b]	1.54 (0.58)	0.57 (0.14) [0.29,0.85]	0.33 (0.13) [0.06,0.60]	0.2
Lichenification[c]	1.25 (0.70)	0.45 (0.16) [0.12,0.78]	0.30 (0.15) [–0.025,0.62]	0.5
IGA[d] (0 = clear, 6 = worse)	4.11 (1.13)	2.63 (0.37) [1.86,3.40]	2.34 (0.36) [1.60,3.08]	0.6
Burning/stinging[e] (0 = none, 3 = marked)	0.14 (0.45)	0.08 (0.05) [–0.04,0.19]	0.00 (0.05) [–0.11,0.11]	0.3
Skin hydration measurement[f] (higher score = higher moisture)	23.29 (23.76)	37.81 (9.37) [18.43,57.19]	37.96 (9.37) [18.58,57.34]	1.0

Means adjusted for baseline values.[a]p-value of difference between overall 4 week Score and baseline: t-test = 0.0003; sign test = 0.0010. [b]p-value of difference: t-test < 0.0001; sign test < 0.0001.[c]p-value of difference: t-test < 0.0001; sign test < 0.0001.[d]Week 1 scores used in place of baseline. p-value of difference: t-test < 0.0001; sign test < 0.0001.[e]p-value of difference: t-test = 0.0496; sign test = 0.1.[f]p-value of difference: t-test = 0.2646; sign test = 0.6.

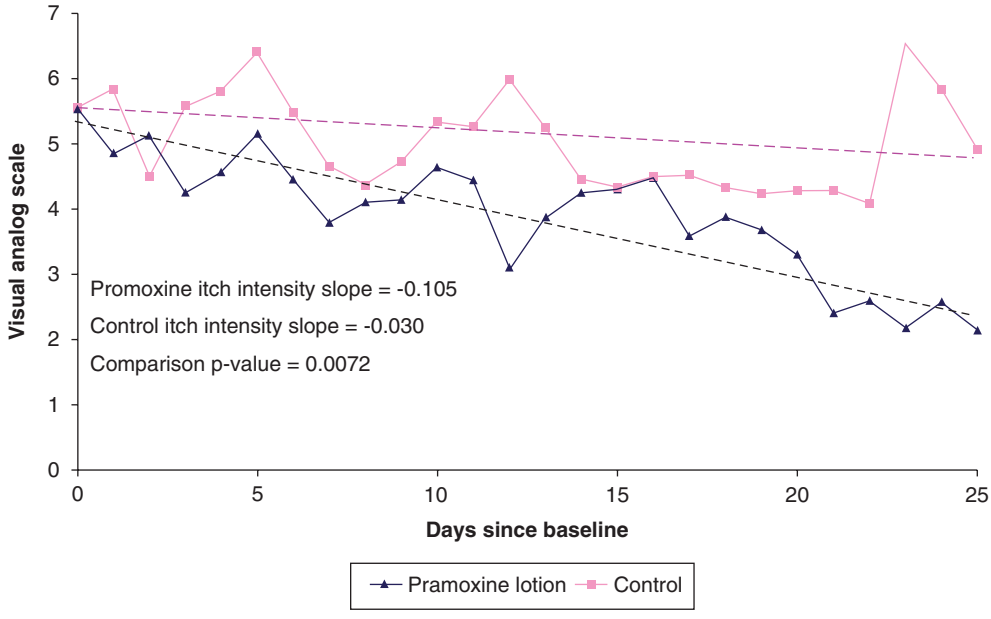

Figure 2. Itch intensity trends for pramoxine lotion and control lotion.

study, the results were not significant. Xerosis is the most frequent cutaneous manifestation of ESRD and has been suggested as a cause of pruritus in such patients (17–21). Although a positive correlation between the severity of clinical xerosis and pruritus has been shown (19,22), others have failed to find a relationship between either trans-epidermal water loss (TEWL) or skin hydration and pruritus (23–24). The reduction in pruritus seen with the control lotion may thus be partially explained by its moisturizing effects on the skin. However, the pramoxine lotion reduces ESRD-associated pruritus to a greater degree than the control lotion, implying the active ingredients in this preparation independently augment the reduction of this symptom. Pramoxine, a local anesthetic, has been suggested to affect itch sensation by interfering with the transmission of impulses along the sensory nerve fibers (23).

In the international Dialysis Outcomes and Practice Patterns Study (DOPPS), evaluating more than 18,000 patients on hemodialysis, pruritus was associated with a 17% higher mortality risk, an effect that was no longer significant after adjustment for measures of sleep quality (6). This observation suggests that

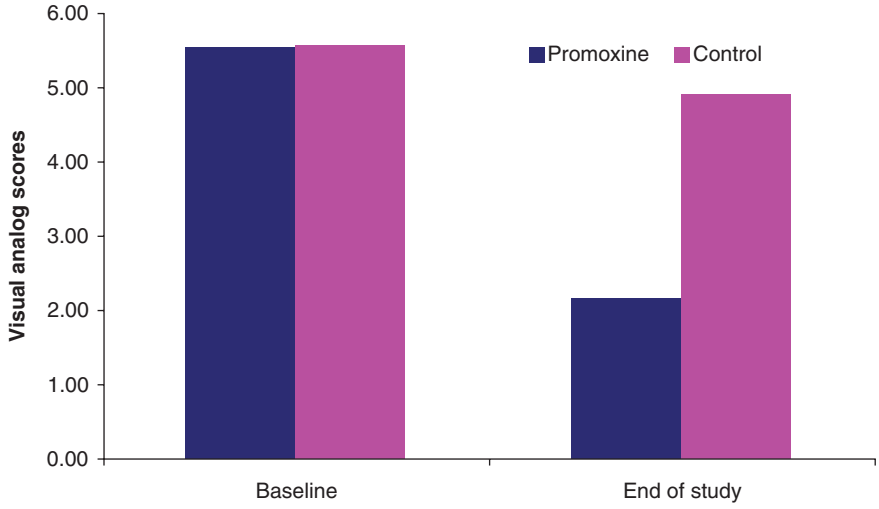

Figure 3. Itch intensity for pramoxine lotion and control at baseline and end of study.

sleep disturbances may play an important role in the higher mortality risk associated with ESRD-associated pruritus.

Some of our study limitations were its small sample size and short duration. Patient selection proved to be another limitation with 93% of the study population being African American. Although ESRD is more prevalent in African American patients, our sample is not reflective of the ethnic make up of this disease. However, it must be noted that most published reports demonstrate ESRD-associated pruritus to be independent of ethnicity as well as sex, age, and underlying renal disease (25–28).

In conclusion, our study shows that the anti-itch lotion containing pramoxine reduces ESRD-associated pruritus to a greater degree than the control lotion. This safe, convenient and effective topical product may potentially benefit the large number of patients affected by ESRD-associated pruritus.

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