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The effect of topical herbal lipogel containing extracts of *Ziziphus jujube* and *Echium amoenum* on pruritus in hemodialysis patients: A double-blind randomized placebo trial

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Abstract

Background: Pruritus is a troublesome symptom in patients with chronic kidney failure (CKF). Topical treatment is the first choice for many skin conditions including pruritus.

Objectives: This study examined the effect of topical lipogel containing *Ziziphus jujube* and *Echium amoenum* extracts on pruritus in hemodialysis (HD) patients.

Methods: A double-blind crossover trial was conducted with 50 HD patients. A demographic and medical information form and the 12-item Pruritus Severity Scale were used to collect data. Participants were randomly assigned into a placebo group and an intervention group. The intervention was carried out for four weeks. The groups were then switched after a 2-week washout period and followed for the next four weeks. The severity of pruritus was measured before and once a week after the intervention for 4 weeks. The independent samples t-test, the Mann-Whitney U test, the chi-square test, and repeat measures analysis of variance (RMANOVA) were used to analyze the data.

Results: The mean baseline pruritus scores were 15.14±2.59 and 14.34±2.6 in the intervention and placebo groups, respectively (P=0.581). The mean pruritus score decreased by three points in the intervention group and one point in the placebo group at the end of the intervention. The results of the RMANOVA also showed that over time, the herbal lipogel significantly reduced the mean pruritus scores in the intervention group (P<0.0001), while it remained relatively unchanged in the placebo group.

Conclusion: The use of a topical lipogel containing extracts of *Ziziphus jujube* and *Echium amoenum* can effectively reduce pruritus in HD patients. Therefore, this lipogel may safely be used to relieve pruritus in patients receiving HD.

Keywords: Pruritus, Renal Dialysis, Patients, *Echium amoenum*, *jujube extract*, Lipogel.

Introduction

Pruritus or itchy skin is one of the most common irritating symptoms in patients with chronic kidney failure (CKF).[1] It affects 55% of adults undergoing hemodialysis worldwide. Pruritus seems to be more common in patients undergoing hemodialysis (HD) than in those receiving peritoneal dialysis.[2] A study of 67 patients undergoing HD reported that over 80% of them suffered from pruritus.[3] Pruritus disrupts sleep-wake rhythm, daily activities, and social relationships, leading to anxiety, depression, and mood disorders.[4]

The actual cause of pruritus in CKF is unknown,

although it has been attributed to factors such as immune system dysfunction, increased proinflammatory cytokines, electrolyte imbalance, and altered endogenous opioid levels.[5] As the pathophysiology of pruritus in patients with CKF is not fully understood, its treatment is still challenging.[6]

Topical treatment is the first choice for many skin conditions including pruritus. As hemodialysis patients take many oral medications, topical treatments would be more recommended. Topical moisturizers can restore the skin barrier and conserve water within the epidermis layer, which is crucial in reducing skin dryness and relieving pruritus.[7]

Ziziphus jujube (*Z. jujube*) and *Echium amoenum (E. amoenum)* have anti-inflammatory effects and strengthen the immune system due to having fatty acids, saponin, and flavonoids. They also contain mucilages and polysaccharides that moisturize the skin.[8-10]

Several studies have examined the effects of herbal medicines such as *Sambuca ebulus extract,*[11] *violet* essential oil,[12] and *Aloe vera* gel[13] on pruritus in HD patients. However, we found no studies on the effects of *Z. jujube* and *E. amoenum* on pruritus in these patients. Considering the anti-inflammatory, antioxidant, and highly moisturizing properties of *Z. jujube* and the abundant essential fatty acids in the *E. amoenum* plant, which can moisturize and soften the skin, the question arises whether a mixture of *Z. jujube* and *E. amoenum* extracts can relieve pruritus in HD patients?

Objectives

This study aimed to examine the effect of a topical lipogel containing herbal extracts of *Z. jujube* and *E. amoenum* on the severity of pruritus in HD patients.

Methods

Study design and participants

This double-blind, randomized, placebo, crossover trial was conducted from September 23, 2022, to January 30, 2023, in 50 patients receiving HD at the Shahrvand Center in Sari, Iran. The sample size was calculated using the findings of a previous study investigating the effect of sweet almond oil on pruritus in HD patients. The baseline pruritus score in the intervention group was 19.63+11.67 which decreased to 7.27+5.74 two weeks after the intervention.[14] Accordingly, using the formula for the comparison of two means and with a type I error of 0.01, power of 0.90, $\mu 1$ of 19.63, $\mu 2$ of 7.27, $S1$ of 11.67, and $S2$ of 5.74, the sample size was estimated to be 17 per group. However, considering the possibility of dropouts, we recruited 25 patients in each group.

Of the eligible patients, 50 were conveniently recruited and randomly assigned into two groups to receive either lipogel containing extracts of *Z. jujube* and *E. amoenum* or placebo. Before the data collection, the researcher arranged a permuted block randomization plan using an online randomization software (i.e., https://www.sealedenvelope.com/simple-randomiser/v1/lists/), and the assumed patients were randomly assigned into 9 blocks, each with 6 members to be appointed to an intervention or a placebo group, with 25 people each.

Inclusion criteria included age of 18 and over, receiving regular HD at least 2-3 times a week for six months,[14] no skin wounds and no known chronic disorders other than CKF, no known allergies to herbal products, complete orientation and ability to communicate, receiving no other topical medications, experiencing moderate to severe pruritus on the 12-item Pruritus Severity Scale (12-PSS), parathyroid hormone (PTH) <300 pg/mLand phosphor < 6 mg/dL (except for those who were treated with Renagel and Cinacalcet for three months). Patients were excluded if they developed skin wounds and obvious edema, showed allergic reactions to the lipogel, became pregnant or intended to get pregnant, started breastfeeding,[15] were absent in more than three HD sessions, and decided to withdraw from the study.

Data collection instruments

A two-part instrument was used in this study. The first part included a demographic and medical information form and the second part was the 12-PSS. The demographic and medical information form that was completed at the entry of the patients included items on the patients' age, gender, education level, place of residence, employment status, number of HD sessions per week, cause of CKF, and additional *anti-pruritus* medications received. Laboratory values for hemoglobin and hematocrit in the last months, and the Kt/V value (a criterion for the efficacy of HD) were extracted from the patients' medical records.

The 12-PSS was used to measure the severity of pruritus. The 12-PSS has five domains, namely pruritus intensity, pruritus extent, frequency and duration of pruritus, impact of pruritus on daily activities and mood, and assessment of scratching. The total score ranges from 3 (no pruritus) to 22 (most severe pruritus). Scores over 6, 6-12, and 13-22 indicate mild, moderate, and severe pruritus, respectively.[16,17] Esmaeili et al. have translated the 12-PSS into Persian. The content validity index (CVI) of the items

in the Persian translation was reported to be between 0.83 and 1, and the Cronbach's alpha of the scale was 0.88.[18] This scale was completed by the researcher through interviews with the participants at the beginning of the study and at the end of each week during the study.

Preparation of herbal lipogel and placebo

Lipogel and placebo were made in the pharmacy laboratory of Mazandaran University of Medical Sciences. *E. amoenum* (Gol-gav-zaban) and *Z. jujube* fruit and leaves were identified and registered with herbarium number of: A-1015 and MAZUMS-1036, respectively, at the Herbarium of the Faculty of Pharmacy of Mazandaran University of Medical Sciences. The active ingredients of *E. amoenum* flowers (mainly flavonoids and anthocyanins) and seeds were extracted by the maceration method using 70% hydroalcoholic solvent and then pressing. The active ingredients of *Z. jujube* leaves (mostly saponins) and fruits were extracted using 70% hydroalcoholic solvents and the Karawya and Patumi methods, respectively. These compounds were added to the lipogel base to form the final formulation of the herbal lipogel. The lipogel base that was also used as the placebo included 94% paraffin, 5% linear light polyethylene, and 1% methylparaben and propylparaben as excipients. The herbal lipogel and placebo were poured into identical 30 g tubes, and the tubes were labeled with confidential codes. Two tubes containing 30 g of lipogel or placebo were given to the participants at the beginning of the study, to be used for 4 weeks[19] according to the instructions presented below.

Intervention

All patients were trained to apply a finger-tip unit (FTU)[20] of the medication twice a day (at 9 AM and 9 PM), depending on the scratched area, so that a thin layer of the lipogel was rubbed and spread on the itchy area. They were also asked to record the amount of the medication used for each body part based on FTUs. One FTU is defined as the amount of medication squeezed out from a tube with a 0.5 cm nozzle, applied from the tip of the index finger to its first joint (0.5 g in male and 0.4 g in female patients). Patients also received the necessary warnings about the authorized use of the medication on the organs[21] (7 FTUs on the chest and abdomen, 7 FTUs on the back and waist, 2.5 FTUs on the face and neck, 6 FTUs on each thigh and leg, 3 FTUs on each arm and forearm, 1 FTU on the palm of the hand and wrist, and 2 FTUs on the sole and ankle). Patients were also instructed to avoid contact between the medication and the eyes, to wash their hands with cold water after applying the medication, to keep the medication at room temperature (20-25°C), and not to replace their own medication with other participants. The medication was quite safe and could be used up to three times a day.[22] Patients were also taught about good nutrition and skin care. The intervention was carried out for four weeks. The groups were then switched after a 2-week washout period and followed for the next four weeks. Patients and the one who gathered the data were blind to the type of the intervention.

Ethical considerations

This study sought ethical approval from the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (approval number: IR.MAZUMS.REC.1399.477) and was registered at the Iranian Registry of Clinical Trials (code: (IRCT201190600749N33). At the beginning of the study, participants were informed about the research methods and the purpose of the study, without being told which group they belonged to, and were asked to sign a written informed consent form. Participants were also informed of their right to either participate in the study or withdraw at any time. They were assured that their personal data would be treated confidentially.

Data analysis

The data were analyzed using SPSS v.16 (SPSS Inc., Chicago, IL, USA). The characteristics of the participants in the two groups were described using descriptive statistics and compared using the chi-square and independent samples *t*-test. Intention-to-treat analysis was conducted. The Shapiro-Wilk test was used to examine the normal distribution of the quantitative data. The independent samples *t*-test was used to compare the mean pruritus scores between the two groups. Repeated measures analysis of variance was employed to compare the mean pruritus scores across the five consecutive measurements. The Mann-Whitney U test was employed if the data were not normally distributed. The significance level was set at $P<0.05$.

Results

Of the 50 patients participated in the first phase of the study no one were excluded or lost to follow-up. However, three patients were excluded from the study in the first week of phase 2, because of taking hydroxyzine tablets. Finally, 47 cases in the placebo group and 50 in the intervention group were entered into the statistical analysis [Figure 1].

The mean duration of dialysis was 38.80±42.3 and 37.18±28.59 months in the intervention and placebo groups, respectively (P= 0.88). Moreover, the mean HD

efficacy (i.e. Kt/V value) was 1.18±0.28 and 1.18±0.28 in the intervention and placebo groups, respectively (P= 0.31). No significant differences were found between the intervention and placebo groups in terms of other demographic and medical characteristics [Table 1].

The frequency of pruritus before the intervention showed that 23.3% of patients experienced pruritus all over their bodies, which decreased to 8.7% after the intervention. The duration of pruritus also declined of 34% to 27% daily after the intervention. The treatment reduced the frequency of skin peeling by decreasing the pruritus severity from 52% to 8%.

The mean baseline pruritus score was 15.14±2.59 and 14.34±2.6 in the intervention and placebo groups, respectively, and did not differ significantly between the two groups (P=0.581). However, this was not the case at the end of the fourth week (P=0.013).

The results were also compared with regard to the order in which the drugs were taken (i.e. whether the patients received liopgel first and then the placebo, compared with whether they received the placebo first and then lipogel). The results of the t-test before and after the different time sequences showed that there were no significant differences between them.

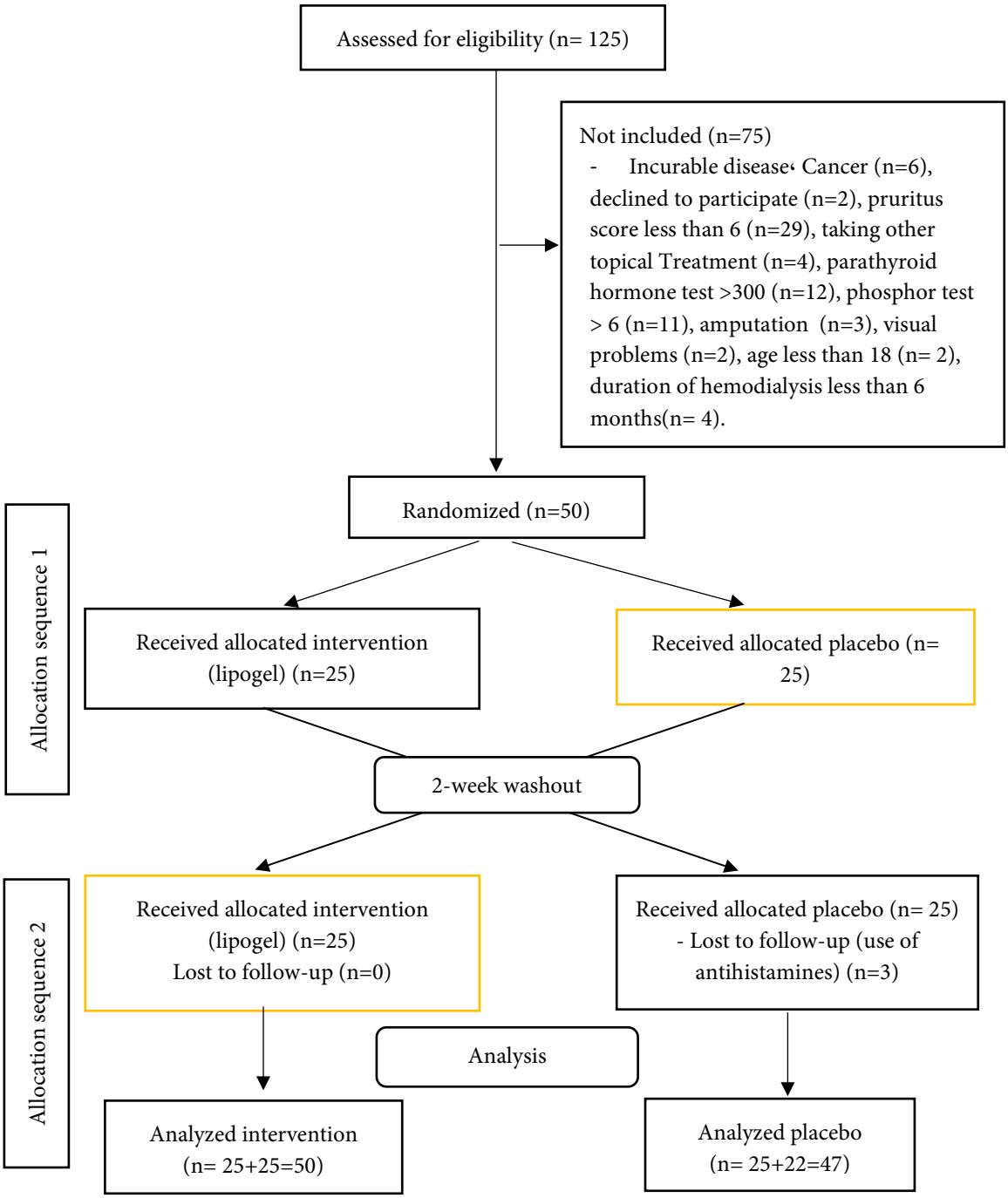

Figure 1. The study flow diagram

The mean pruritus score decreased by three points in the intervention group and one point in the placebo group at the end of the fourth week. The results of the RMANOVA also showed that over time, the herbal lipogel significantly reduced the mean pruritus scores in the intervention group (P<0.0001), while it remained relatively unchanged in the placebo group. However, as a significant interaction was observed between time and the pruritus scores in the two groups (P<0.001), the t-test was used for pairwise comparison between the two groups at different time points. The results showed that the mean pruritus intensity was significantly different between the two groups at the end of the third and fourth weeks [Table 2]. No specific complications were observed in the participants during the study.

Table 1. Comparison of demographic and medical variables in the intervention and placebo groups

Variable		Group [a]		P-Value
		Intervention (N=25)	Placebo (N=22)	
Age		60.64 ± 15.44	54.36± 11.33	0.124[b]
Duration of hemodialysis therapy (Month)		38.80 ± 42.3	37.18 ± 28.59	0.880[b]
Kt/v		1.18 ± 0.28	1.08 ± 0.26	0.311[c]
Gender				
	Male	16 (64)	11 (50)	0.333[d]
	Female	9 (36)	11 (50)	
Number of hemodialysis sessions				
	Twice a week	5 (20)	4 (18.2)	0.381[d]
	Three times a week	20 (80)	18 (81.8)	
Place of residence				
	City	16 (64)	16 (72)	0.522 [d]
	Village	9 (36)	6 (28)	
Education level				
	Illiterate	8 (32)	3 (13.6)	0.234 [d]
	Primary Guidance	12 (48)	11 (50)	
	High school or higher	5 (20)	8 (36.4)	
Occupation				
	Unemployed and Housewife	20 (80)	10 (54.5)	0.062 [d]
	Employed	5 (20)	12 (45.5)	
ESRD etiology				
	Hypertension	4 (32)	7 (13.6)	0.396 [d]
	Diabetes Mellitus	8 (16)	3 (31.8)	
	Diabetes and Hypertension	9 (36)	8 (36.4)	
	Other Causes	4 (16)	4 (18.2)	

[a] Data presented as Mean ± SD or n (%), [b] t-test, [c] Mann -Whitney U test, [d] Chi-square test

Table 2. Comparing the pruritus mean scores between the two groups at the five assessment time points

Time	Group		P value (t test)	Repeated measures analysis of variance		
	Intervention	Placebo		The effect between the two groups	The interaction of time and group	Time effect
Baseline	15.4 ± 2.59	14.64 ± 2.36	0.581	f=2.071 P=0.0153	f=17.95 P<0.0001	f=194.97 P<0.0001
First week	13.0 ± 2.46	13.60 ± 2.46	0.230			
Second week	12.96 ± 2.50	13.55 ± 2.33	0.236			
Third week	12.43 ± 2.18	13.51 ± 2.36	0.023			
Fourth week	12.12 ± 2.22	13.34 ± 2.49	0.013			

Discussion

The current study showed that lipogel having extracts of *Z. jujube* and *E. amoenum* could reduce the severity of pruritus in HD patients more effectively than a paraffin-containing placebo. The mean pruritus score for both groups was severe at baseline and remained in the same range until the end of the study in the placebo group, whereas the mean pruritus score for the intervention group was moderate at the last two measurement time points, confirming the effectiveness of the herbal lipogel in reducing pruritus. We found no previous study examining the effect of *Z. jujube* or *E. amoenum* on pruritus in HD patients. However, some studies investigated the effects of other herbs or materials. A study reported that using *aloe vera* gel for 4 weeks could reduce pruritus scores by 3 points in HD patients.[13] A study used a marine mineral-enriched body lotion to treat pruritus in HD patients and reported that this lotion was not significantly effective in relieving uremic pruritus.[23] A Turkish study also investigated the effect of baby oil on uremic pruritus in dialysis patients and reported that baby oil could significantly reduce the patients' pruritus scores. However, its high concentration made some patients reluctant, especially at night.[24] Lipogel has strong softening and moisturizing effects and may therefore be preferable to baby oil. Another study investigated the effects of 15% glycerin and 10% paraffin on uremic pruritus in HD patients. Patients were followed up for 56 days and it was found that their pruritus score decreased by 3 points at the end. Glycerin has moisturizing and soothing effects on the skin. Paraffin is also an effective emollient that protects the skin from irritants and relieves uremic pruritus.[25] However, the herbal lipogel used in our study could achieve similar results in a shorter time. A study also examined the effect of capsules containing omega-3 fatty acids (which have anti-inflammatory properties) on pruritus in HD patients. Although this treatment significantly reduced pruritus, some patients experienced diarrhea and vomiting (side effects of oral intake of omega-3 fatty acids).[26] The herbal lipogel used in the current study, which is also rich in omega-3 fatty acids, reduced the pruritus without causing any side effects. Therefore, the topical lipogel containing extracts of *Z. jujube* and *E. amoenum* seems to be superior to the capsules used in the above research in relieving pruritus in HD patients. Another study also reported that oral administration of hydroxyzine 25 mg tablets twice daily for 6 weeks significantly relieved pruritus in HD patients. However, patients experienced anticholinergic symptoms such as reduced sweating and dry skin.[27] Besides, patients cannot take antihistamines for a long time. Hence, the lipogel we used may be superior to antihistamines in patients receiving HD. *Z. jujube* leaf and fruit extracts have strong anti-inflammatory, antioxidant, and moisturizing effects. The oil extracted from *E. amoenum* seeds contains large amounts of essential fatty acids, which cause its moisturizing and softening effects.

For the first time, we examined the effect of a topical lipogel containing *Z. jujube* and *E. amoenum* extracts on pruritus in HD patients. However, the sample size was relatively small and the study was conducted in an HD center. Therefore, it is recommended to conduct similar multicenter studies with a larger sample size.

Conclusions

This study showed that the use of a topical herbal lipogel containing extracts of *Z. jujube* and *E. amoenum* can effectively reduce pruritus in HD patients. Moreover, no side effects were observed in patients. Therefore, this lipogel may safely be used to relieve pruritus in patients receiving HD. However, further studies with longer follow-up periods are required before routine use of this lipogel can be recommended.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Hemodialysis: HD; C
hronic kidney failure: CKF;
Parathyroid hormone: PTH;
Finger-tip unit: FTU;
12-Item Pruritus Severity Scale: 12-PSS;
Kt/V:(K – dialyzer clearance of urea t – dialysis time V – volume of distribution of urea, approximately equal to patient's total body water).

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by Vice Chancellor for Research of Mazandaran University of Medical Sciences (Ethics code: IR.MAZUMS.REC.1399.474).

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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