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ORIGINAL ARTICLE

Miscellaneous

Effectiveness of topical gabapentin cream in treating pruritus in dialysis patients: A randomized controlled trial

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Abstract

Introduction: Gabapentin is an antiepileptic drug that alleviates neuropathic pain. Its oral use reduces the intensity of pruritus in patients receiving chronic dialysis therapy. However, it could lead to toxicity because of the patients' renal deficiency. In this study, we assessed the use of gabapentin topical in treating pruritus in dialysis patients.

Methods: This randomized, triple-blinded trial was performed on 80 patients divided into two groups randomly (40 in each group). In intervention group, 92.5% of the patients were on hemodialysis. Patients in intervention and control groups were provided with 5% gabapentin and placebo topical creams every 2 weeks for a month. Both Visual Analog Scale and 12-item Pruritus Severity Score questionnaire were used to evaluate itching intensity and score before treatment, a month, and 2 months after starting treatment in both groups. In addition, the effect of itching on quality of life was investigated with the same questionnaire.

Findings: Eighty patients (40 in each group) participated in our study. No complication was found in our intervention group. Itching score significantly decreased after a month and 2 months of follow-up in intervention group ($p < 0.001$).

Discussion: Our results showed that 5% gabapentin topical cream can be effective in reducing itching in different areas of the body. None of our patients reported complications.

KEYWORDS
12-item severity score, pruritus, dialysis, gabapentin, pruritus

INTRODUCTION

Pruritus is common in patients receiving either peritoneal dialysis or hemodialysis. It affects 67% of hemodialysis patients among which 37% of them reports moderate to extreme pruritus.[1,2] It negatively affects health-related quality of life, causes distress, and is usually associated with sleep disturbance, depression, and increased mortality.[3] The pathogenesis of pruritus in dialysis patients is unknown, and it could be multifactorial. Some risk factors associated with pruritus in hemodialysis patients are old age, gender, calcium–phosphate imbalance, longer duration of dialysis, and comorbidities such as concurrent anemia and neurological, cardiovascular, lung, and liver diseases.[4,5]

Among different available therapies, gabapentin is preferred because of its effectiveness, few reported side

effects, relative safety, and off-label use.[6,7] Gabapentin, an analog of gamma-aminobutyric acid, was primarily FDA-approved for use in treating epilepsy; however, it is also used for other conditions such as pruritus.[8] Gabapentin modulates excitatory neurotransmitters, but its exact mechanism is not understood. It is suggested that gabapentin increases the threshold for neuronal excitation by inhibiting voltage-dependent calcium channels in the dorsal root ganglion and the spinal cord dorsal horn.[4,9]

Oral use of gabapentin is limited due to side effects such as dizziness, somnolence, ataxia, and fatigue.[10–12] Reports show that gabapentin topical creams are as effective as oral gabapentin.[13] Because gabapentin is exclusively eliminated by renal excretion, patients on dialysis are at risk for toxicity. Therefore, it is essential to develop novel treatments for pruritus. Gabapentin topical creams are suitable treatments and have been already used for other conditions such as vulvodynia.

There are limited studies on use of gabapentin topical creams for controlling pruritus.[14] The study was designed to evaluate the efficacy of the cold cream containing 5% gabapentin for the treatment of pruritus in patients receiving chronic dialysis therapy.

SUBJECTS AND METHODS

In this triple-blind clinical study, 80 patients with pruritus undergoing hemodialysis/peritoneal dialysis at the referral center of dialysis affiliated to the Isfahan University of Medical Sciences were included. Inclusion criteria were[1] patients aged between 20 and 80 years old and[2] an interval between 6 months and 10 years since their first time on dialysis. Those patients having itching because of other factors, being allergic to gabapentin, prescribed anti-psychotic medications or other types of treatments for pruritus, or diagnosed with neurological diseases such as multiple sclerosis were excluded from the study. The "Institutional Review Board" of Isfahan University of Medical Sciences approved the study protocol. This study was approved by the medical ethics committee of Isfahan University of Medical Sciences with the IRCT number IRCT20220306054206N1. Informed consent was also obtained from all participants.

After obtaining informed consent form, demographic information was gathered using a checklist including questions about age, gender, age at kidney diagnosis, age starting dialysis, the disease leading to dialysis, type of dialysis, and the time passed since their first time on dialysis. A thorough dermatological examination was also carried out. Patients were divided into two groups, intervention or control, randomly using a random allocation software.[15]

To prepare 100 mL of a 5% gabapentin cream, we dissolved 5 g of pharmaceutical grade gabapentin powder (Actopentin, Actover pharmaceutical company) in 10 mL of warm (40°C) deionized distilled water and then added it to cold cream (75 mL) to have a consistent 100 mL of the cream. The placebo was a water-in-oil topical cold cream packaged identically as gabapentin cream.

Randomly and on a blinded basis, one group of patients received gabapentin and another group placebo topical creams. Patients received one jar of cream every 2 weeks with instructions to apply it to the most itching area once a day. They were advised not to use more than 50 g per week. The intervention lasted for 4 weeks. In addition to Visual Analog Scale (VAS), each patient filled the Persian version of the 12-Item Pruritus Severity Score (12-PSS) questionnaire scoring itching before treatment, a month, and 2 months after starting treatment.[16] Questions in 12-PSS questionnaire are categorized into five groups including recurrence and duration of itching, effect on quality of life and behavior, scratch after itching, itching severity, and itching area. The minimum and maximum scores were 3 and 22, respectively.[16,17]

STATISTICAL ANALYSIS

All statistical analyses were conducted using SPSS software package for Windows, version 25 (SPSS Inc., Chicago, USA). Continuous variables were presented as mean ± standard deviation (mean ± SD), and qualitative variables were expressed as number (percent). Inferential analysis of quantitative variables was performed using independent samples *t*-test, repeated measures ANOVA, and ANCOVA. The chi-square test was utilized for comparing frequencies. For the comparison of percentage changes in itching with baseline between groups at each follow-up, McNemar test was employed. The comparison of the trend of itching between groups was assessed using Generalized Estimating Equation (GEE). *p*-values <0.05 were considered statistically significant.

RESULTS

Eighty patients were randomly assigned to an intervention or control group (40 in each group). The mean ± SD age of all the patients was 54.68 ± 15.66 years old (ranging between 20 and 80 years old), 67.5% of whom were men and 32.65% were women. A summary of the patients' data is available in Table 1. The mean ± SD age at onset was significantly different between two groups ($p = 0.037$). In addition, the number of patients with

TABLE 1 Demographic characteristics of the patients by group.

Characteristics	Group		
	Gabapentin $n = 40$	Control $n = 40$	p-Value
Age (years)	52.08 ± 14.77	57.28 ± 16.27	0.139
Age at onset	40.43 ± 17.89	48.78 ± 7.37	0.037
Gender M/F	26/14	28/12	0.812
Type of dialysis			
HD	37 (92.5)	34 (85.0)	0.481
PD	3 (7.5)	6 (15.0)	
Background disease			
HTN	26 (65.0)	26 (65.0)	>0.999
DM	14 (35.0)	21 (52.5)	0.176
HPT	29 (72.5)	38 (95.0)	0.013
Comorbid conditions			
PCKD	8 (20.0)	6 (15.0)	0.770
RAS	1 (2.5)	1 (2.5)	>0.999
KS	4 (10.0)	0	0.116
SLE	1 (2.5)	1 (2.5)	0.100

Note: Data are presented as mean ± SD and number and number (percent). p-values calculated by independent sample t-test and chi-square.
Abbreviations: DM, diabetes mellitus; F, female; HD, hemodialysis; HT, hyperthyroidism; HTN, hypertension; KS, kidney stone; M, male; PCKD, polycystic kidney disease; PD, peritoneal dialysis; RAS, renal artery stenosis; SLE, systemic lupus erythematosus.

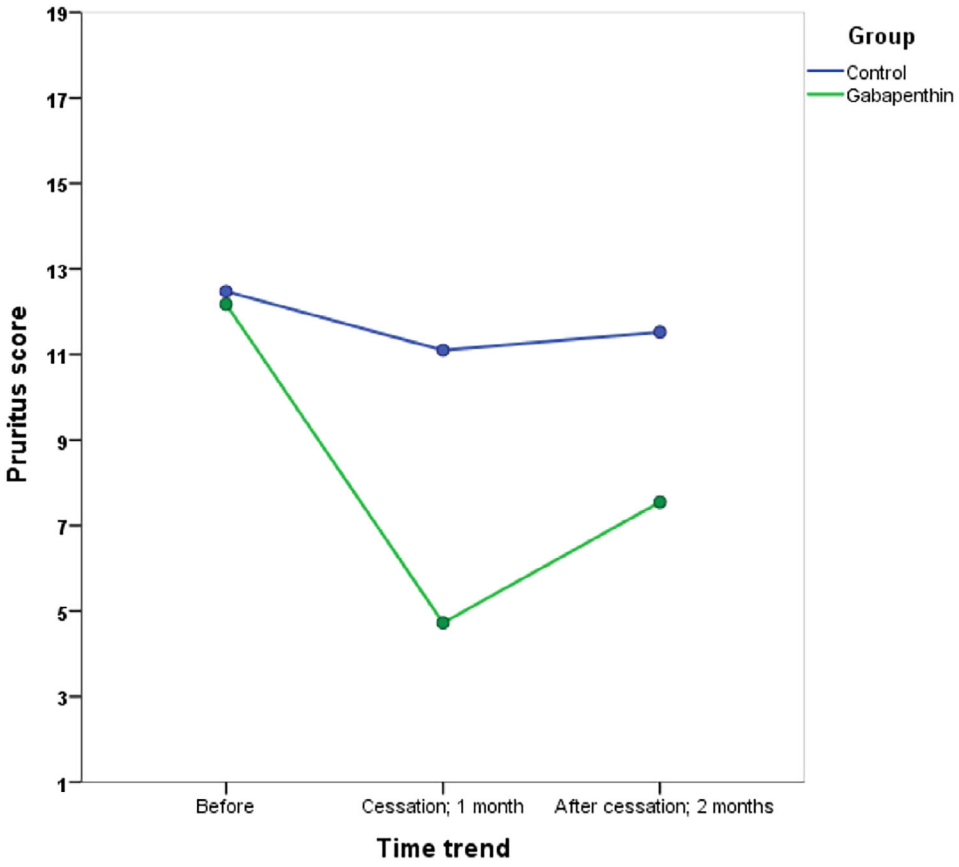

FIGURE 1 Changes in total mean pruritus score using 12-Item Pruritus Severity Score questionnaire at the baseline, a month, and 2 months of follow-ups.

TABLE 2 The mean and trend of pruritus score using 12-Item Pruritus Severity Score questionnaire (12-PSS) and Visual Analog Scale (VAS) by groups.

	Baseline and follow-up measurements							
Measurements	**Baseline**	**Week-4**	p^2	**Week-8**	p^3	p^4	p^5	p^5
12-PSS								
Gabapentin	12.18 ± 3.89	4.73 ± 2.34	<0.001	7.55 ± 3.08	<0.001	<0.001	<0.001	<0.001
Control	12.47 ± 3.75	11.10 ± 3.57	<0.001	11.53 ± 4.08	0.001	<0.001		
p^1	0.727	<0.001		<0.001				
VAS								
Gabapentin	7.98 ± 1.56	2.88 ± 1.81	<0.001	3.98 ± 1.80	<0.001	<0.001	0.012	<0.001
Control	6.58 ± 2.65	5.70 ± 2.39	<0.001	6.05 ± 2.41	<0.001	<0.001		
p^1	0.006	<0.001		<0.001				

Note: Data are presented as Mean ± SD. p^1, assessed variables between groups at each time point and was calculated by independent sample *t*-test. p^2, assessed variables within groups in week-4 compare to baseline and was calculated by paired sample *t*-test. p^3, assessed variables within groups in week-8 compare to baseline and was calculated by paired sample *t*-test. p^4, assessed the trend of variables within groups by repeated measurements of ANOVA. p^5, assessed the trend of variables between groups by repeated measurements of ANOVA. p^6, assessed variables between groups in week-8 by ANCOVA after controlling baseline values as covariate.

TABLE 3 Frequency of itching and comparison of percentage changes in itching among studied patients.

		Baseline and follow-up measurements					
Location	**Group**	**Baseline**	**Week-4**	**Δ%**	**Week-8**	**Δ%**	p^2
Chest	Gabapentin	32	26 (81.25)	−0.188	32 (100)	0.031	0.256
	Control	28	23 (82.14)	−0.179	28 (100)	0	
	p^1			0.929		0.351	
Inferior	Gabapentin	36	11 (30.56)	−0.694	25 (69.4)	−0.306	0.083
	Control	34	24 (70.59)	−0.294	30 (88.23)	−0.118	
	p^1			0.0009		0.057	
Superior	Gabapentin	21	2 (9.52)	−0.905	7 (33.33)	−0.667	0.006
	Control	22	17 (77.27)	−0.227	18 (81.82)	−0.182	
	p^1			< 0.0001		0.0014	
Hand-feet	Gabapentin	15	1 (6.67)	−0.933	4 (26.67)	−0.733	0.011
	Control	16	14 (87.50)	−0.125	13 (81.25)	−0.188	
	p^1			< 0.0001		0.0027	
Underwear	Gabapentin	14	2 (14.28)	−0.857	3 (21.43)	−0.786	0.003
	Control	18	16 (88.89)	−0.111	13 (72.22)	−0.278	
	p^1			<0.0001		0.0050	

Note: Data are presented as Number and Number (percent). p^1, assessed the comparison of percentage changes with baseline between groups at each follow-up and was calculated by McNemar test. p^2, assessed the comparison of the trend of itching between groups and was calculated by Generalized Estimating Equation (GEE).
Abbreviations: NS, non-significant; Δ%, percentage changes with baseline.

hyperthyroidism as the underlying disease leading to dialysis was higher in control group compared to the intervention group ($p = 0.013$). There was no significant difference between comorbidities (polycystic kidney disease, renal artery stenosis, kidney stone, and systemic lupus erythematosus) between the two groups.

Using 12-PSS before starting treatment, the mean ± SD pruritus score in intervention and control groups was 12.18 ± 3.89 and 12.47 ± 3.75, respectively. A month after starting therapy, the mean score in intervention group significantly decreased to 7.55 ± 3.08 ($p < 0.001$) (Figure 1).

In Table 2, the change in mean pruritus score using both 12-PSS and VAS is provided. The reduction in 12-PSS was significant in intervention group; however, no significant change was observed in control group. The change of VAS obtained at the beginning of the study (7.98 ± 1.56) compared to the VAS at the end of 2 months (3.98 ± 1.80) was significant in the intervention group ($p < 0.001$) (Table 2).

There was significant difference in sleep disturbance between two groups at the beginning of the study ($p = 0.004$); however, at the end of the first and second month of the follow-up, there was no significant difference between the two groups ($p = 0.843$ and $p = 0.820$). In addition, the total number of hours a person itch was not significantly different at the beginning of the study between two groups ($p = 0.327$), but at the end of the treatment and second month of the follow-up, the difference between two groups was significant ($p = 0.001$ and $p = 0.025$, respectively). The difference of itching between intervention and control groups was significant in superior, hand-feet, and underwear areas at week 4 and week 8 of study (Table 3).

DISCUSSION

Our study shows that gabapentin topical creams are effective in reducing itching score. Despite the introduction of new interventions for treating pruritus in dialysis patients, it is still a clinical priority in patients undergoing dialysis.[18] Difelikefalin, a novel κ-opioid receptor agonist, is approved in the United States and Europe for use in treatment of moderate-to-severe pruritus in hemodialysis patients.[19] However, this medication is not commercially available in Iran and, even if it were it would have been too expensive for the patients. Among other available treatments for pruritus, gabapentin is a treatment of choice. Previous studies show that oral gabapentin is effective in treating pruritus in patients receiving chronic dialysis therapy.[1] In previous studies investigating oral gabapentin significant difference between intervention and control groups was reported.[6,7,20–22] In a study, Naini et al.[22] reported the efficacy of gabapentin (400 mg) compared to placebo in 34 adults in Iran. Studies in other populations similarly concluded the effectiveness of different doses of oral gabapentin.[6,7,20–22] There are few studies investigating the effectiveness of topical gabapentin. In a well-designed study by Boardman et al., topical gabapentin was used in management of vulvodynia for the first time.[23] In another study by Aquino et al.,[24] the authors reported the 6% gabapentin topical cream is effective in alleviating pruritus in patients on dialysis. Our study also shows that topical gabapentin significantly reduces itching score in patients with pruritus with lasting effect even a month after treatment cessation.

The current trend in treating pruritus using oral gabapentin is the initiation dose of 100 mg after each dialysis session which can be increased to 300 mg daily.[25] Oral gabapentin is considered a fairly safe medication and, generally, higher doses are associated with complications such as dizziness and somnolence in dialysis patients.[26] Previous studies using topical gabapentin creams did not report any adverse side effects.[24,27] Likewise, none of our patients reported complications using our 5% gabapentin topical cream. Urine concentration of gabapentin suggests absorption rate is very low in patients using topical gabapentin.[28] It is possible that systemic toxicity is limited when using topical creams but there could still be systemic effects because of damaged skin barrier.

In our study, we used a sample size of 80 which was comparable to previous studies assessing gabapentin. Nevertheless, use of a larger sample size is recommended for a more precise estimation of the treatment efficacy and generalization of the results. In our study, treatment period was 4 weeks and the last follow-up was a month after treatment cessation. This short period might not have been enough for observing side effects or effectiveness of the treatment. Therefore, longer duration of the treatment and follow-up could be useful in identifying the lasting effect and complications related to the treatment. The limitation of our study was short follow-up period and presence of other factors affecting pruritus. The advantage of our study was a relatively good sample size resulting in a better estimate of the treatment effect.

CONCLUSION

In this study, the use of topical 5% gabapentin cream for 4 weeks significantly decreased the severity of pruritus in patients receiving chronic dialysis therapy. The significant decrease in VAS and itching score was still detectable a month after treatment cessation. The treatment effect lasted for a month after treatment cessation. None of the patients reported adverse side effects.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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