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The Effects of Cool Dialysate on Pruritus Status During Hemodialysis of Patients With Chronic Renal Failure: A Controlled Randomized Clinical Trial

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Abstract

Background: Pruritus during dialysis is a common complaint among patients undergoing hemodialysis. Despite progress in medical science and technology in the field of hemodialysis, there is still no cure for pruritus.
Objectives: The aim of this study was to determine the effect of cool dialysate on the severity of pruritus during hemodialysis of patients with chronic renal failure.
Patients and Methods: This study was a two-group, triple-blinded randomized clinical trial, with a parallel design. It consisted of 60 patients with chronic renal failure who were receiving hemodialysis at hemodialysis centers in Mashhad. The patients were divided into two equal groups: 30 patients in an intervention group and 30 patients in a control group. Initially, the patients in both groups underwent dialysis for one week (three sessions) with a standard dialysis solution (temperature of 37 °C). In the next phase, the control group received the standard dialysis solution, whereas the intervention group received a cool dialysis solution (35.5°C) for one week (three sessions). The severity of pruritus was recorded using a visual analogue scale (VAS), with itching scored from 0 - 10 on an hourly basis during the dialysis sessions.
Results: Before the intervention, there was no significant between-group difference in the severity of pruritus ($P < 0.05$). After the intervention, the severity of pruritus was significantly reduced (reduction of 3 points, itching score range of 0 - 10) ($P < 0.0001$).
Conclusions: Dialysis with cool dialysate is a simple and cheap nondrug method, which was readily accepted by the patients. This method could significantly reduce the severity of pruritus in patients during dialysis.

Keywords: Pruritus, Dialysis Solutions, Renal Dialysis, Kidney Failure, Chronic

1. Background

In developing countries, the number of patients undergoing hemodialysis has grown significantly within the past two decades (1). Although hemodialysis is an effective treatment for patients with chronic renal failure, it has undesirable side effects, with one of the most common being pruritus (2, 3). Pruritus is a subjective complaint, which causes the patient to scratch incessantly. The constant scratching damages the protective layer of the skin (3, 4). Although there is a direct relationship between the level of blood urea nitrogen and uremic pruritus, some patients do not experience pruritus until starting hemodialysis (5). The prevalence of pruritus in chronic renal failure is 42%. In patients undergoing hemodialysis, 15% - 90% (6) and 35.6% of patients have pruritus, mainly during dialysis (7). Thus, access to hemodialysis has enhanced the survival of patients with chronic renal failure and improved their general health but increased the numbers of patients with itching (1). Dialysis may be stopped because of pruritus, which renders hemodialysis insufficient to treat renal failure.

Physical, mental, and mood disorders, as well as impaired quality of life and sleep, are side effects of pruritus (8). The physiopathology of pruritus is unknown (1), but various treatments, such as intravenous injections of lidocaine, oral cholestyramine, antihistamines, complementary and alternative therapies, and systemic treatments, have been used to relieve pruritus (3, 4). However, some of these are time consuming and have side effects (4).

Previous research showed that heat aggravated pruritus, so individuals who are prone to pruritus are recommended to avoid heat (9). The process of hemodialysis (a dialysis solution with a standard temperature of 37°C) causes vasodilation of the blood vessels in the skin, which increases the body temperature (10). Cool dialysate can exchange heat between the blood and the dialysis solution, thereby preventing the body temperature from increasing.

Cool dialysate also increases the contractile strength of the heart, thereby improving the oxygen supply to tissues and reducing the stimulation of the sympathetic nervous system. Moreover, it decreases complement activation and reduces the reactivity of monocytes (11). Additional benefits of cool dialysate are the prevention of hypotension, nausea, and dizziness during dialysis, reduction of fatigue, and improvement of sleep quality (12, 13). Currently, most patients use nonpharmacological therapeutic approaches to alleviate or relieve their pruritus (14). According to our comprehensive search of scientific databases, there are no published studies on the impact of cool dialysate on the severity of pruritus during hemodialysis.

2. Objectives

Within the past two decades, access to hemodialysis has improved the survival of patients with chronic renal failure and their general health. However, epidemiology of itch was reported in patients undergoing hemodialysis, so it has increased the number of patients with itching. Therefore, it seems necessary to study methods to reduce pruritus during hemodialysis in patients with chronic renal failure. The aim of this study was to determine the effect of cool dialysate on the severity of pruritus during hemodialysis of patients with chronic renal failure.

3. Patients and Methods

3.1. Design

This study was a two-group triple-blinded randomized clinical trial, with a parallel design. The study consisted of 60 patients with chronic renal failure who underwent hemodialysis from December 2014 to March 2015 in the dialysis center of Imam Reza Hospital and dialysis centers affiliated to Imam Reza hospital (Bentolhoda and AL-Muhammad) of Mashhad city. Imam Reza Hospital is affiliated with Mashhad University of Medical Sciences in Mashhad, Iran. This is a governmental hospital, with specialized medical wards, a CCU, medical intensive care unit (ICU), and hemodialysis unit.

3.2. Participants

The 60 patients were selected according to the following inclusion criteria: completed a consent form, aged between 18 and 65 years, and not blind or deaf. All the patients had chronic renal failure after completing 3 months of hemodialysis, KT/V of $\geq$ 1, and arteriovenous fistulas. They had all undergone hemodialysis three times a week, with each session lasting 4 hours, and had a history of pruritus during hemodialysis for the last 2 months. None of the included patients had taken drugs for pruritus during dialysis (oral medications, complementary medicine, acupuncture, topical lubricants, or radiation), and their hemoglobin values ranged from 10 to 11 mg/dL.

The exclusion criteria were psychological or severe mood and emotional disorders, endocrine disorders (e.g., hypothyroidism or hyperparathyroidism), pregnancy, skin disorders, and pneumonia. Additional exclusion criteria were acute complications during hemodialysis (ataxia syndrome, embolism, dysrhythmia, cardiopulmonary arrest, or coma), high blood pressure during dialysis, pruritic skin disorders (scabies or psoriasis), changes during the dialysis sessions, introduction to transplant during the study, and intolerance to cold dialysis. No patient was excluded during the study (Figure 1).

3.3. Data Collection and Intervention

To determine the severity of pruritus during dialysis, a visual analogue scale (VAS) commonly used in scientific studies was used. The VAS is a subjective assessment of itching. The participants marked the severity of the itching on the 10-cm-long line of the scale, with the start point denoting "no itching" (0 points) and the finish denoting the "worst imaginable itching" (10 points). Based on available data, the VAS can be considered a valid, reliable, and repetitive method of itch measurement.

All the participants also completed a two-part questionnaire containing 20 questions regarding demographic information and disease history. Ten experts (professors of nursing in the nursing and midwifery faculty of Sabzevar and nephrologists) confirmed the validity of the content of the questionnaire. The content validity index was calculated using three criteria (simplicity and fluidity, clarity or transparency, and relevance) and a 4-part Likert scale. The calculation of this index showed that all items were acceptable, with a content validity index value of 0.85. The content validity ratio, each one of the items by using of the three ranges is calculated, that are "essential item," "helpful but not essential," and "unnecessary." We calculated for each item and compared to the numbers provided by Lawshe's table. The results showed that the content validity ratio for all the items in the questionnaire were higher in Lawshe's table ($<$ 0.62), so all of them were preserved to perform. The internal reliability of the questionnaire was assessed using Cronbach's alpha, and the reliability was as high as 82%.

At the beginning of the study, the aims, tools, exclusion criteria, random assignment, and potential benefits of the study were explained to all the patients. The patients were asked to report any possible complications, especially unbearable shivering, during the study. Participation in this

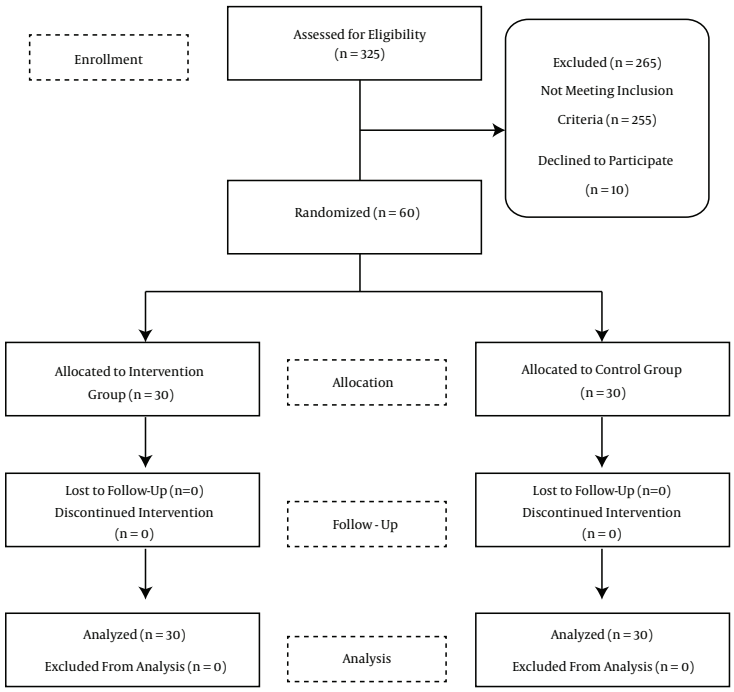

Figure 1. Flowchart of the Design, Groups, and Participants in the Study

study was completely voluntarily and free from any obligation to the physician, nursing staff, or researchers. All the patients completed informed consent forms.

The random permuted block method was used. The patients were divided into two groups as follows: a control group (hemodialysis with a dialysis solution at 37°C) and an intervention group (hemodialysis with a dialysis solution at 35.5°C). Six permuted blocks consisted of the English letters C, B, A, F, E, and D. The letters C, B, and A denoted the intervention group, and F, E, and D denoted the control group. The blocks were selected randomly and blindfolded. Each block was then deleted, and the next random block was selected. With each block, the entrance order to the intervention group or the control group was determined. Assumingly, block D, A, C, E, F, and B meant that the first, fourth and fifth subjects were entered in the intervention group and the second, third, and sixth subjects were entered in the control group. The patients were divided into two equal groups, with 30 patients in the intervention group and 30 patients in the control group.

In the research, in line with the study method (blinding) an interested nursing expert participated in the project as research assistant. So that, she was unaware of the type of intervention or the random allocation. The patients were blinded in this research (i.e., they did not know whether they were assigned to the intervention or control group). Since hemodialysis patients had chronic course and have full control over their intervention treatment, so that they are aware of all the parameters set on the hemodialysis machine. In this research, to prevent bias on the monitor screen parameters hemodialysis devices during the study on both intervention and control groups, with the permission of the doctor, head nurses, and patient under study was hidden from the study. The individual who analyzed the data was also blinded and remained unaware of the allocation of the patients to the two groups. The researcher was in charge of dealing with the treatment team, the participants engaged in the research, and the careful monitoring of the implementation of the research process. In addition, all the subjects were monitored for possible side effects.

Throughout the study, Fresenius model 4008 B dialysis machines, fixed filters, and bicarbonate solution were used for all patients. In all cases, the dialysis fluid flow rate was 500 mL/min. The blood flow rate was 350 mL/min.

Before the intervention, both groups were undergoing three 4-h standard hemodialysis sessions per week (dialysis solution with a temperature of 37°C). During these hemodialysis sessions, the research assistant used the VAS to check the severity of pruritus on an hourly basis. The subjects were asked to respond to all the questions accurately and honestly.

During the intervention phase, the patients in the intervention group underwent dialysis with cool dialysate (solution temperature of 35.5°C) three times per week/4 hour per session. At the same time, the patients in the control group underwent dialysis with a solution temperature of 37°C. During each hemodialysis session, the research assistant used the VAS to check the severity of pruritus on an hourly basis.

3.4. Sample Size and Data Analysis

Due to a lack of research on this subject, a pilot study was first performed with 10 patients from the research groups. Using the obtained data, a sample size with a statistical power of 80% and a confidence level of 95% was determined. Thirty participants for each group were considered.

According to the Kolmogorov-Smirnov test, the distribution of the data was normal. Due to the lack of normality, nonparametric tests were used to analyze the data. The data analysis was performed using statistical tests, such as Fisher's exact test, the Mann–Whitney test, and chi-square tests, and generalized estimating equations (GEEs) at the 5% significance level with R statistical software (version 3.2.0), and the final results of the two groups were compared.

3.5. Ethical Considerations

All codes of ethics that must be observed in a clinical trial were implemented in this study. This study was approved by the research ethics committee of Sabzevar University of Medical Sciences (No. Medsab.Rec.93.66). The clinical trial registration number is IRCT: 2014120920260N1. The aims of the study were explained in detail to the participants. Participation in this study was completely voluntarily and free from any obligation to the physician, nursing staff, or researchers. All the patients completed informed consent forms patients.

4. Results

4.1. Demographic Data

Most of the participants were males (53.3%). The mean age of the patients in the control group was 55.83 ± 8.45 years, with a range of 27 - 65 years. The mean age of the patients in the intervention group was 53.1 ± 10.02 years, with a range of 30 - 65 years. In terms of educational level, 78.4% of the participants had less than a diploma, 13.3% had a diploma, and 8.3% had higher than a diploma. The mean duration of chronic renal failure of the participants in the control group was 5.00 ± 4.07 years, and it was 6.12 5.41 years in the intervention group. The mean hemodialysis treatment duration of the patients in the control group was 4.19 ± 3.88 years and 3.81 ± 2.97 years in the intervention group. The mean KT/V of the participants in the control group and intervention group was 1.46 ± 0.05 mg/dL and 1.35 ± 0.04 mg/dL, respectively.

As shown in Table 1, there was no significant difference between the intervention and control groups with regard to various characteristics, such as age, sex, education level, KT/V, duration of chronic renal failure, and hemodialysis treatment duration (P > 0.05).

Table 1. Demographic Characteristics of the Subjects[a]

Participants' Characteristics	Intervention Group	Control Group	P Value
Age	53.10 ± 10.02	55.83 ± 8.45	0.26[b]
Sex			0.27[c]
Male	17 (56.7)	15 (50)	
Female	13 (43.3)	15 (50)	
Duration of chronic renal failure in years	6.12 ± 5.41	5.00 ± 4.07	0.62[b]
Hemodialysis treatment duration in years	3.81 ± 2.97	4.19 ± 3.88	0.74[b]
KT/V, , mean ± Std. error	1.35 ± 0.04	1.46 ± 0.05	0.20[b]
Education level			
Less than a diploma	24 (80)	23 (76.6)	0.69[d]
Diploma	4 (13.3)	4 (13.3)	
Higher than a diploma	2 (6.7)	3 (10)	

[a] Values are epressed as mean ± SD.
[b] Mann-Whitney test.
[c] Chi-square test.
[d] Fisher's exact test.

4.2. Pruritus History

The mean of the most severe pruritus scores of the participants during dialysis within the last 2 months was 6.62 ± 0.49 in the intervention group and 6.02 ± 0.41 in the control group. As shown in Table 2, the results of the Mann–Whitney test confirmed that there was no significant difference between the groups (P = 0.34).

4.3. Comparing Outcomes

Finally, to evaluate the effect of cool dialysate on the severity of pruritus during hemodialysis within 2 weeks of the study, a correlated data regression model that was fitted with a GEE was used. According to the logarithmic link function, the results demonstrated that in the presence of

Table 2. Comparison of the Mean of the Most Severe Itching Scores During Dialysis Within the Last 2 Months

Pruritus History	Intervention Group	Control Group	P Value[a]
Mean ± Std. error	6.02 ± 0.41	6.62 ± 0.49	0.34

[a] Mann-Whitney test.

the variable "hemodialysis treatment duration" ($P < 0.05$), the intensity of pruritus was 3 points higher in the control group than in the intervention group. Other variables (age, sex, and duration of chronic renal failure) had no effect on the severity of itching ($P > 0.05$). Thus, the intervention reduced the severity of pruritus by more than 3 points, which was significant considering that the pruritus range was 0 - 10 ($P < 0.0001$) (Table 3, Figures 2 and 3).

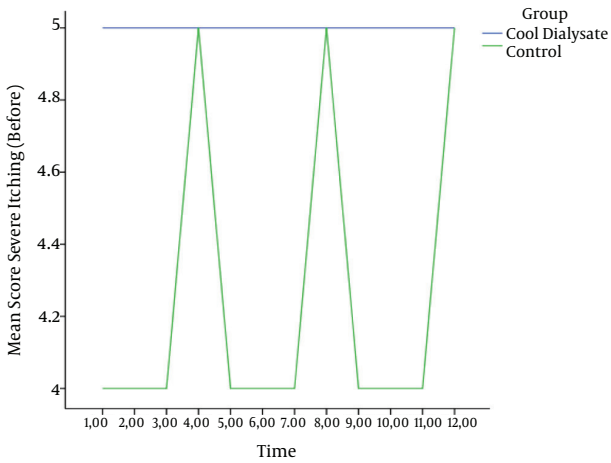

Figure 2. Comparison of the Pruritus Scores (VAS) of Each Group Prior to the Intervention at Different Times

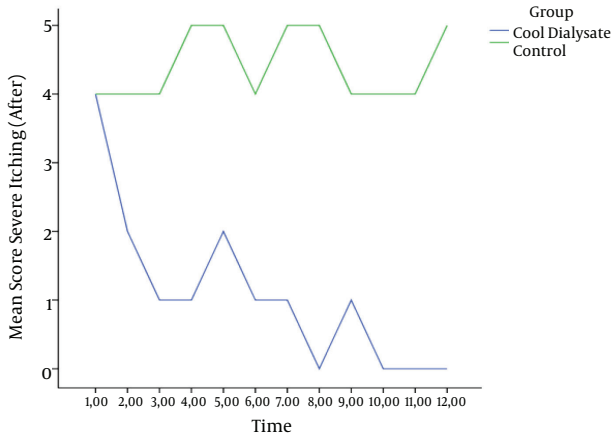

Figure 3. Comparison of the Pruritus Scores (VAS) of Each Group After the Intervention at Different Times

5. Discussion

This study assessed the impact of cool dialysate on the severity of pruritus during hemodialysis in patients with chronic renal failure. Cool dialysate can exchange heat between the blood and the dialysis solution, which prevents increases in body temperature. The results showed that cool dialysate during dialysis significantly reduced the severity of pruritus after the intervention.

Parker et al. showed that cool dialysate reduced the stimulation of the sympathetic nervous system and improved the skin temperature of hemodialysis patients (15).

The present study used a nondrug approach. Nakhaee et al. (3) reported that the local use of vinegar reduced the severity of pruritus but that the use of vinegar required dilution, dose adjustments, and special tools. According to Nakhaee et al., patients experience acute and unpleasant complications, such as hypotension, headaches, dizziness, nausea, vomiting, muscle cramps, chest and back pain, and fever, during dialysis (2). Thus, the use of topical vinegar to relieve pruritus during dialysis is not always possible and faces limitations, such as a lack of acceptance by patients. In contrast, cool dialysate requires no dose adjustment and is easily performed during dialysis. In addition, various studies have shown that the use of cool dialysate during dialysis has positive effects. For example, blood pressure was more stable during dialysis with cool dialysate, and hypotension occurred significantly less frequently, as compared to dialysis using a standard solution temperature. The incidence of nausea and dizziness with cool dialysate was also lower (12). Aromatherapy is a nonpharmacological approach (as in this study). The results of Curcani and Tan study confirmed its effect on uremic pruritus (16), whereas the systematic review by Posadzki et al. reported mild to severe adverse effects of aromatherapy, with dermatitis mentioned as the most common side effect. Mortality was reported in another study (17). In contrast, no allergic reactions or deaths have been reported thus far with the use of cool dialysate. In addition, cool dialysate was found to be an effective therapeutic intervention for all dialysis patients, especially elderly patients over 55 years, patients with cardiovascular diseases, patients with poor physical strength, and women (18). Acupuncture is another effective method of treating uremic pruritus, as confirmed by Kilic Akca et al. (19), although a systematic review by Ernst et al. reported complications, such as pneumothorax, infection, and in some cases, mortality in pa-

Table 3. Estimating the Regression Coefficients of Correlated Data of Itching Severity Using the GEE Test

Parameter	Estimates (ß)	Std. Error	Confidence Interval	Z	P Value
Constant coefficient	-1.07	0.12	(-1.79 - -0.36)	-2.93	0.003
Duration of dialysis therapy	0.04	0.02	(0.01 - 0.071)	2.41	0.02
Duration of chronic renal failure	-0.02	0.01	(-0.05 - 0.00)	-1.74	0.09
Age	0.003	0.003	(-0.009 - 0.004)	-0.81	0.42
Sex	0. 05	0.06	(-0.08 - 0.17)	0.75	0.45
Group	1.14	0.12	(0.91 - 1.36)	9.83	< 0.0001

tients treated with acupuncture (20). Unlike acupuncture, cool dialysate is associated with no complications. Furthermore, studies showed that it had positive psychosocial and physical effects on patients (12, 13).

The application of capsaicin ointment is a therapeutic intervention that acts on the nervous system. Makhlough et al. confirmed its ability to reduce the severity of pruritus in dialysis patients (21). However, the same study reported irritation of the skin during the use of this drug and the need to use preventive measures, including avoiding contact with the eyes, mucous membranes, and affected or wounded skin areas. In contrast to capsaicin ointment, cool dialysate does not have these side effects.

In addition to the aforementioned treatments, oral antihistamines and gabapentin have been used in the treatment of uremic pruritus. Nakhaee et al. demonstrated the effectiveness of hydroxyzine in reducing the severity of pruritus in dialysis patients (3), However, due to anticholinergic effects and drowsiness, the therapeutic use of antihistamines is not acceptable.

Cheikh Hassan et al. studied the effect of gabapentin on relieving pruritus in dialysis patients (22). However, its use in dialysis patients requires accurate dose adjustments, and various studies have shown that neurotoxicity and coma occur in the absence of precise gabapentin dosing (23, 24).

Cool dialysate lacks the side effects of antihistamines (anticholinergic effects and drowsiness) and gabapentin (neurotoxicity and coma). The results of various studies in this area have shown that the application of cool dialysate during dialysis was effective in reducing patient fatigue. After dialysis with cool dialysate, patients were reported to have more energy, which significantly improved their general health. It has also been reported that the majority of patients have demanded dialysis with cool dialysate (13). The use of cool dialysate in dialysis is a simple, cheap, and nonmedicinal approach, which does not have the negative and undesirable consequences of pharmacological interventions. It has a positive impact on the severity of pruritus during dialysis. It can also reduce the duration of dialysis and thus improve the effectiveness of dialysis, ultimately improving the sleep and life quality of patients.

The strengths of the present study are its randomized, triple-blinded, parallel design and the unique strengths of the analyses. As we know, the effect of cool dialysate on pruritus has not been investigated yet. The limitation of this study is the lack of sample size.

5.1. Conclusions

According to the results of this study, the use of cool dialysate during dialysis can reduce the severity of pruritus, although additional studies are needed to confirm its effectiveness.

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Footnote

Authors' Contribution: Analysis and interpretation of the data: Mohammad Hasan Rakhshani; drafting of the manuscript: Elahe Jaghouri; critical revision of the manuscript for important intellectual content: Mostafa Rad; statistical analysis: Mohammad Hasan Rakhshani; administrative, technical, and material support: Mostafa Rad; study supervision: Farzaneh Sharifipour.

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