Comparison of *Avena Sativa*, Vinegar, and Hydroxyzine for Uremic Pruritus of Hemodialysis Patients

A Crossover Randomized Clinical Trial

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Introduction. Uremic pruritus is a common complication in patients with chronic kidney disease. While its cause is not known for certain, different treatments are currently applied. This study aimed to compare the effects of *Avena sativa*, diluted vinegar, and hydroxyzine on the reduction of uremic pruritus.

Materials and Methods. In this crossover randomized clinical trial, 23 hemodialysis patients with uremic pruritus were randomly divided into 3 groups. The first group was treated with *Avena sativa* lotion, twice a day, for as long as 2 weeks; the second group received diluted vinegar; and the third group took hydroxyzine tablets for the same time span. After 3-day-long washout periods, the therapeutic methods were crossed over. The data were collected by a pruritus scale and a visual analogue scale, which were completed before and after the interventions.

Results. *Avena sativa* lotion significantly decreased the mean scores of pruritus intensity, consequences, and the verbal descriptor, although it did not have a significant effect on the frequency of pruritus and the pruritic surface. Vinegar and hydroxyzine significantly decreased all of the scores.

Conclusions. *Avena sativa*, vinegar, and hydroxyzine were effective in decreasing pruritus. Diluted vinegar and *Avena sativa* can be used as a complement to hydroxyzine, which is itself a common pharmaceutical therapy.

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INTRODUCTION

Uremic pruritus is an unpleasant sensation that has been recognized as a frequent complication in patients with chronic kidney disease.[1,2] It is one of the most common disabling symptoms in patients with end-stage renal disease.[3] It has been found that 15% to 49% of patients with chronic kidney disease and more than 40% of patients undergoing hemodialysis suffer from chronic pruritus.[2,4] Pruritus frequency increases significantly along the deterioration of the disease and the treatment period. It can cause disturbance of day and night rhythm, depression, sleeping disorders, anxiety, and skin complications and can diminish the quality of life.[5] The pathogenesis of pruritus is not fully known in patients with chronic kidney disease. However, there appears to be a relation with hyperparathyroidism, hypervitaminosis A, xerosis, iron deficiency, and elevated levels of histamine, phosphate, magnesium, and calcium in the skin,[1,6-8] as well as mast cells, opioids, allergic sensitization to components in dialysis membranes, and elevated skin surface pH.[9]

Several therapies are in use, yet uremic

pruritus is refractory to them.[1] Phototherapy with ultraviolet B has been the treatment of choice in many centers.[10] Nonetheless, it cannot be openly offered to patients despite its antipruritus effects. It involves purchasing expensive equipment and has complications such as erythema, tanning of the skin, photosensitivity, maculopapular eruption, and potential carcinogenic effects.[2,11] Antihistamine drugs, which are frequently prescribed, yield in disappointing results and are not always effective.[8]

Complementary and alternative medicine is a therapeutic method that has increasingly become popular over the past decades and given rise to a positive attitude on the part of the general public.[12] Here, a mainstay in the treatment of pruritus is a substance called *Avena sativa*,[13] which is commonly known as Oat, Groats, Haber, Hafer, Avena, Straw, and Oatmeal. It is a species of cereal grain grown for its seed.[14] Oatmeal has been used for centuries as a soothing agent to relieve itching in a variety of xeroticdermatoses such as atopic dermatitis, psoriasis, acneiform eruptions, and pruritus during burn wound healing. According to the literature, it seems to be effective when applied for 2 to 8 weeks.[15-18] *Avena sativa* has been approved by the Food and Drug Administration, and clinical studies have not reported any adverse effects associated with its use.[15] Colloidal oatmeal was well tolerated in children and adults for short-term and long-term use.[15,16]

Avena sativa contains various active dermatological compounds that have moisturizing, protective, soothing, antioxidant, and buffering properties[16]; it is also of anti-inflammatory properties.[18] Avenanthramides available in *Avena sativa* reduce histamine release from mast cells,[15,18] and their topical application decreases inflammation and scratching in pruritus-induced models.[16] *Avena sativa* produces a protective moisturizing barrier on the skin which helps to soften and moisten the skin and heal tissue, hence reducing pruritus.[13,16] In addition, patients with kidney failure have an elevated skin surface pH,[19,20] and *Avena sativa* can restore skin pH to within the normal range through its buffering capacity.[15]

In the same line, vinegar has been reported to be useful for the treatment of pruritus.[21-24] By maintaining the acidic pH of the skin surface, vinegar helps to preserve skin barrier function and reduces skin irritation.[20] In general, low-pH topical therapies decrease pruritus by limiting the activity of serine proteases on skin nerve fibers.[25] On the other hand, pruritus is caused by the elimination of urea and sodium through the skin. Diluted vinegar solution can counteract urea crystals and reduce pruritus.[26]

Avena sativa and vinegar can be used for the treatment of pruritus with similar mechanisms, but it is not clear which of is more effective on uremic pruritus of hemodialysis patients in comparison with common antihistamines. The present study was done to compare the effects of these two complementary methods with hydroxyzine as a common pharmaceutical therapy.

MATERIALS AND METHODS

Participants

A convenience sample of hemodialysis patients with pruritus was recruited from hemodialysis units of a general hospital in Birjand, Iran. All the patients who entered the study were on hemodialysis at least twice weekly, and experienced uremic pruritus for at least 2 weeks. The patients did not have a history of dermal or nondermal pruritic diseases such as atopic dermatitis, chronic hepatic disorder, acquired immune deficiency syndrome, and polycythemia vera, according to their charts and examination by specialists. They did not have chronic dermal inflammatory disorders or known allergy records, nor were they pregnant or breast-feeding. Unwillingness to participate in the study, treatment complications such as allergic reaction to vinegar or *Avena sativa*, and kidney transplantation were exclusion criteria. In total, there were 25 participants in the study. Two of them underwent kidney transplantation, and therefore, were excluded from the study.

Ethics Considerations

The study protocol was approved by the Ethics and Research Committee of Birjand University of Medical Sciences (Code, 1391-11-14). First, the researcher explained the objectives and procedure of the study to the participants and ensured them of confidentiality of information and possibility of participants' leaving the study at their own will. Then, the participants provided informed consent.

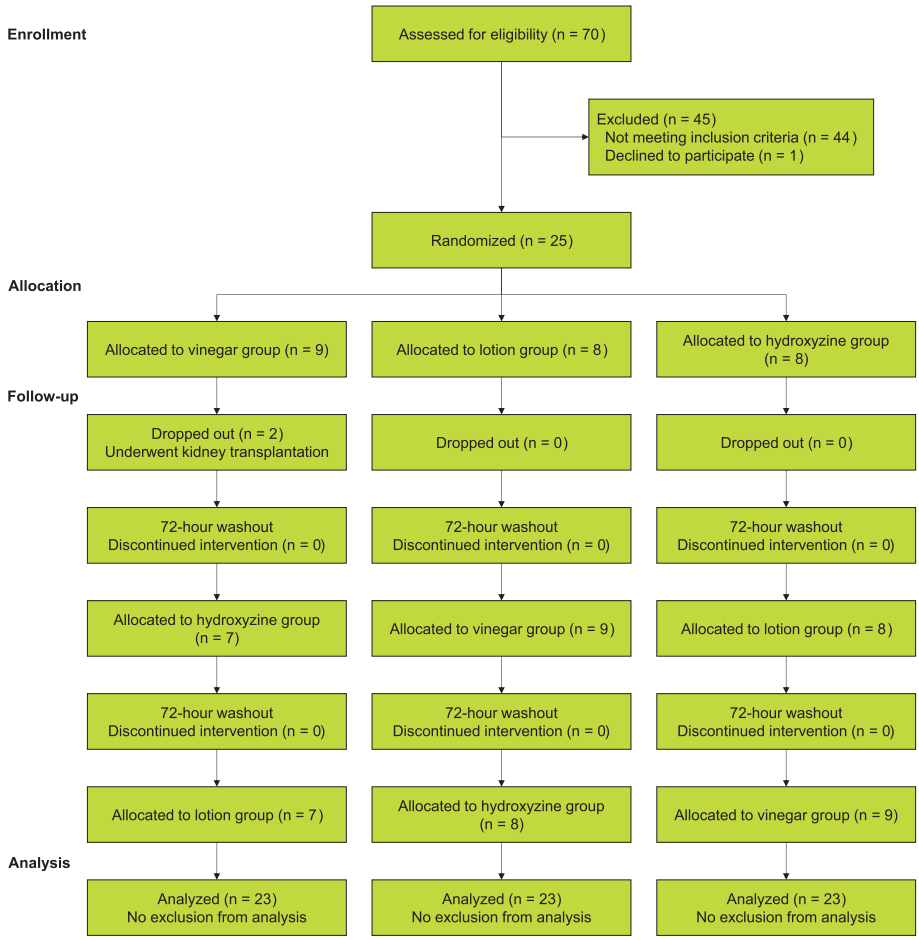
Study Design

In this crossover randomized clinical trial, 25

patients were assigned by random numbers to 3 groups (two with 8 patients and one with 9). The CONSORT flowchart that describes the progress of the patients through the trial is shown in the Figure. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT2013021912525N1).

Pruritus was routinely being treated by hydroxyzine. In light of this and the fact that the terminal elimination half-time for hydroxyzine is approximately 3 to 20 hours in adults,[27,28] the drug was stopped for 24 hours under nephrologist's supervision. Then, group 1 was treated twice daily with *Avena sativa* lotion (Espanol, Spain) on the surface of the pruritic area for as long as 2 weeks.[29] Diluted vinegar was used for group 2 for the same period of time. Vinegar solution (30-mL synthetic white vinegar 5% in 500 ml of water) was used on pruritic areas with a vinegar sponge by the patient twice daily for 2 weeks.[30] Group 3 received routine therapy with hydroxyzine, 10-mg tablets every night, for 2 weeks.

After 2 weeks, a pruritus questionnaire was filled out for all the three groups. After a 72-hour period of washout, groups 1, 2, and 3 received vinegar, hydroxyzine, and *Avena sativa* lotion, respectively, for 2 weeks. Finally, for the third 2-week period, groups 1, 2, and 3 were treated with hydroxyzine, *Avena* lotion, and vinegar, respectively. The duration of the washout period (72 hours) was determined based on the bioavailability of vinegar and *Avena sativa*.[31-33] To ensure full and timely implementation of the intervention by the patient, a self-reported form was developed by the researcher. In the form, the patient recorded the frequency of the use of the therapeutic agent (lotion, vinegar, or hydroxyzine) in a table. In addition, the researcher surveyed and reminded timely interventions to the patients through phone calls and visits to the dialysis ward. All the patients performed the interventions completely. The patients were closely monitored during the study period for adverse effects ad abnormal or unbearable pruritus.



CONSORT flow diagram of the studied participants.

Data Collection

The intensity of pruritus was measured by a visual analog scale (VAS). The VAS was a 10-cm-long line on which 0 referred to no pruritus and 10 showed the most severe pruritus the patient could imagine.[34] In addition, the complementary information was obtained using a set of questions added to the end of the questionnaire. This questionnaire included the frequency of pruritus, the verbal descriptor (eg, tickling, tingling, prickling, stinging, and burning), pruritus consequences (including lesion from scratching, reduced social interaction, disturbed routine activity, disturbed sleep and mood, changes in behavior toward others, and loss of concentration), and the pruritic surface, defined by Land and Browder as a percentage of total body surface area.[35,36] Before and after each intervention period, pruritus questionnaires were completed by each of the groups.

Statistical Analysis

The data distribution was tested to be normal by the Kolmogorov-Smirnov test. The Kruskal-Wallis test was performed to assess the presence of a carryover effect and treatment effect,[37, 38] for which no significant effect was found. The paired *t* test was used to compare the mean scores of variables before and after each intervention, and the Friedman test was applied to compare differences of the mean scores before and after the intervention in the three therapeutic methods. In case the variables' distributions were not normal, the Friedman and Wilcoxon nonparametric tests were used. A *P* value less than .05 was considered significant.

RESULTS

Baseline characteristics of the patients at enrolment in the study are listed in Table 1. The mean age of the patients who completed the study (n = 23) was 57.04 ± 12.20 years. Most of the patients (73.9%) were men. The mean serum phosphorus level and mean KT/V scores were 6.57 ± 0.19 mg/dL and 1.33 ± 0.35, respectively. Most participants (65.2%) had a pruritus history of more than 1 year. From among the patients, 56.5% had not used any method to relieve pruritus.

Table 1. Demographic and Clinical Characteristics of the Participants in the Study (n = 23)

Parameter	Value*
Age, y	57.04 ± 12.20
Sex	
Male	17 (73.9)
Female	6 (26.1)
Kidney disease duration, y	5.19 ± 4.85
Hemodialysis duration, y	3.55 ± 2.78
Frequency of hemodialysis, /wk	2.57 ± 0.51
Serum phosphorus level	6.57 ± 0.19
KT/V	1.33 ± 0.35
Pruritus history	
2 weeks to 6 months	5 (21.7)
6 to 12 months	3 (13.0)
More than 1 year	15 (65.2)

*Values are expressed as mean ± standard deviation or frequency (percentage).

A comparison of the mean scores for the various dimensions of pruritus using the three therapeutic methods are shown in Table 2. Differences in the mean scores for frequency of pruritus and surface of pruritic skin before and after the intervention were significant only in the vinegar and hydroxyzine groups, whereas these scores did not significantly change after receiving *Avena sativa*. However, the mean scores for verbal descriptor of pruritus, pruritus consequences, and intensity of pruritus (on the VAS scale) significantly decreased after intervention in all the three groups.

The differences in the mean scores of frequency, verbal descriptor, consequences, intensity of pruritus, and the pruritic surface were compared between the three groups, which showed no significance, ie, all the three therapies reduced all dimensions of pruritus in similar ways (Table 3).

Table 2. Comparison of Mean Scores for Dimensions of Pruritus Using the Three Therapeutic Methods

	Vinegar			Avena			Hydroxyzine		
Pruritus Scores	Before	After	*P*	Before	After	*P*	Before	After	*P*
Intensity	5.19 ± 1.88	3.73 ± 2.41	< .001	5.21 ± 1.69	4.10 ± 2.34	.01	5.21 ± 1.82	3.56 ± 2.52	< .001
Frequency	1.95 ± 1.06	1.13 ± 0.79	< .001	2.30 ± 1.18	1.70 ± 1.31	.06	2.04 ± 0.92	1.15 ± 0.78	.001
Surface, %	33.86 ± 24.11	27.69 ± 25.85	.04	29.30 ± 23.28	27.42 ± 22.76	.47	29.83 ± 22.32	22.61 ± 22.13	.02
Verbal descriptor	3.82 ± 1.87	2.26 ± 1.45	< .001	4.21 ± 2.43	2.78 ± 2.13	.006	1.71 ± 1.06	1.95 ± 1.55	< .001
Consequences	6.95 ± 5.57	3.65 ± 5.68	< .001	7.26 ± 5.74	4.30 ± 4.77	.008	6.65 ± 5.90	2.82 ± 3.92	< .001

Table 3. Comparison of Changes in Pruritus Dimensions After the Interventions

Pruritus Scores	Vinegar	Avena	Hydroxyzine	*P*
Intensity	1.63 ± 1.45	2.03 ± 1.10	1.51 ± 1.65	.15
Frequency	0.86 ± 0.82	1.42 ± 0.59	1.06 ± 0.88	.83
Surface, %	13.93 ± 6.17	12.40 ± 1.87	14.12 ± 7.21	.06
Verbal descriptor	1.77 ± 1.56	2.27 ± 1.34	1.62 ± 1.78	.59
Consequences	3.12 ± 3.30	4.82 ± 2.95	3.57 ± 3.82	.92

DISCUSSION

The results showed that hydroxyzine significantly reduced all dimensions of pruritus. Khalili and colleagues compared 3 medications in relieving uremic pruritus and revealed that the drug which most decreased the intensity of pruritus was hydroxyzine, followed by chlorpheniramine and ketotifen.[9] We should note that although hydroxyzine has antihistaminic and sedating effects, one of the effects of this drug is its anticholinergic effect,[39] which leads to decreased sweating and increased skin dryness and pruritus. The results from the present study also showed that *Avena sativa* lotion could decrease the mean score of pruritus intensity in a significant way. This is consistent with other studies where *Avena sativa* lotion significantly decreased the mean score of pruritus intensity in patients with burn injuries,[17] patients with dry skin and chronic pruritus,[29] or patients with atopic dermatitis.[40] Although the patients are different, there is similarity in pathogenesis of pruritus in these diseases; for example, the level of histamine is high in the skin and in the peripheral blood of several patients with atopic dermatitis. Therefore, it is often suggested that pruritus is partially due to histamine.[39] Histamines release during the inflammatory stage of burn injury healing, so the underlying mechanism of itching is rise in the amount of histamine.[17] Also, plasma levels of histamine have been reported to elevate in uremic patients.[2,41] Another similarity is high skin surface pH that has been noted in xerosis, atopic dermatitis, and uremia.[20]

In addition to reducing the intensity of pruritus, *Avena sativa* lotion decreased significantly the complications of pruritus. This is in line with Pacifico and colleagues' study on 54 patients with pruritus where 10 of them were hemodialysis patients. In that study, all the patients used Aveeno moisturizing lotion; after a 3-week treatment, 96% of all the patients and 80% of hemodialysis patients had significant improvements in skin complications including erythema, scratching, and scaling, and the pruritus of the patients reduced as much as 44.8% within 1 week after the treatment had started.[42] A preclinical study showed that topical application of avenanthramides reduced pruritogen-induced scratching.[43]

Results from the present study also indicated that *Avena sativa* lotion could significantly decrease mean scores of pruritus verbal description. Results from a cross-over study showed that colloidal oatmeal bath in patients with a history of atopic dermatitis led to 50% reduction in pruritus and 67% reduction in burning.[44] It is noteworthy that lotions have softening effects which can relieve skin dryness. This can strengthen antipruritus ability of *Avena sativa* lotion.

As the results of our study indicated, diluted vinegar has a significant effect on decreasing all dimensions of pruritus. The results reported by Oh, who compared the effects of vinegar and tepid sponge bath to relieve uremic pruritus, are consistent with the results of the present study. He reported longer soothing duration in the vinegar group; in general, he considered vinegar bath more effective than tepid bath in relieving pruritus in hemodialysis patients.[22] In a study of comparing skin surface pH of patients with end-stage renal disease with that of healthy persons, skin surface pH was slightly higher in the patients than in healthy controls; nevertheless, the difference was statistically insignificant. In addition, there was no correlation between pruritus and skin pH in patients with end-stage renal disease.[45] Nonetheless, skin surface pH in these patients was reported as significantly higher than that of the healthy persons. The authors concluded that although blood pH was low in hemodialysis patients, their skin surface pH was high, adding that there was no relationship between the skin pH and the systemic acid-base balance. In his opinion, the ability of the dermal cells to secrete acid could be affected by the uremic state.[19]

Effects of vinegar on nonuremic pruritus have also been investigated. For example, the application of diluted vinegar and concentrated salt water baths was studied in the treatment of *Trichomonas* vaginitis, where both methods decreased pruritus 1 week after the treatment.[23] Such results verify the antipruritic effects of vinegar as in the present study. Although the patients are different, there is some similarity in factors that have been considered to explain the pathogenesis of pruritus in these diseases; for example, one mechanism by which bacteria may cause itching is the release of endoproteinase and other inflammatory mediators, and hence release of histamine.[46] In addition, it has been proposed that histamine may play an important role in the development of uremic pruritus.[47]

One limitation of this clinical trial was the small size of the study population; the patients referring to the hemodialysis center under study with the inclusion criteria were limited to the ones who participated in the study. This limited the researchers in using placebo for other groups of patients. Another limitation of the study rooted from the difficulty in blinding the study where double blinding was impossible because of the smell of vinegar and the difference in the type of interventions (solution, lotion, and tablet).

CONCLUSIONS

According to this study, diluted vinegar reduced all pruritus dimensions, and *Avena sativa* lotion reduced the three dimensions of intensity, complications, and verbal descriptor of pruritus. Considering the side effects of chemical drugs, these two materials can be used for uremic pruritus. It should be noted that based on the results from the current study, vinegar was more effective than *Avena sativa*. Although the results of this study showed the effectiveness of diluted vinegar and *Avena sativa* lotion in relieving uremic pruritus in hemodialysis patients, generalizability of the results to other pruritic diseases requires more research. It is also recommended that other studies be done with larger sample sizes.

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CONFLICT OF INTEREST

None declared.

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