Topical Capsaicin Therapy for Uremic Pruritus in Patients on Hemodialysis

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Introduction. Pruritus is one of the common problems in patients on hemodialysis. There are several causes for pruritus, and different treatment modalities are applied to control it. The aim of this study was to evaluate the therapeutic effect of capsaicin on pruritus, compared with placebo, in patients on hemodialysis.

Materials and Methods. This randomized double-blinded cross-over clinical trial was performed on 34 patients on hemodialysis with uremic pruritus. The patients were divided into 2 groups, one group received capsaicin 0.03% and the other, placebo, for 4 weeks. Treatment was stopped for 2 weeks as washout period and continued as a cross-over technique. Pruritus scores were analyzed and compared.

Results. Thirty-four patients on long-term hemodialysis, 14 men and 20 women with a mean age of 57.0 ± 18.6 years were studied. The mean of pruritus score before capsaicin treatment was 15.9 ± 6.3, which was reduced to 6.4 ± 3.9, 4.7 ± 3.1, 3.2 ± 2.9, and 2.5 ± 2.5 on weeks 1 to 4, respectively ($P < .001$). In the placebo group, pruritus score before treatment was 15.0 ± 6.0 on average, and it was 11.7 ± 5.8, 9.4 ± 5.9, 7.9 ± 5.5, and 7.2 ± 5.5, respectively, on weeks 1 to 4 ($P < .001$). There was no significant difference in pruritus scores before the treatment between the two groups, but after each week, the difference was significant ($P < .001$). Repeated measurement test showed that decreasing in pruritus severity in the capsaicin group was more than that in the placebo group during treatment period ($P < .001$).

Conclusions. Capsaicin is a new safe and effective topical treatment for hemodialysis-induced pruritus in patients with end-stage renal disease.

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INTRODUCTION

Pruritus often constitutes a major problem for patients with end-stage renal disease (ESRD). Unfortunately, dialysis has only a slight improving impact on pruritus. Therefore, it is quite frustrating that an ever-increasing number of patients on hemodialysis, waiting for transplantation, suffer from this tormenting symptom for a long time. According to most sources, more than half of patients undergoing hemodialysis complain of varying degrees of pruritus.[1-5] Different mechanisms have explained this problem; current theories include secondary hyperparathyroidism, histamine release, allergic sensitization, proliferation of skin mast cells, iron deficiency anemia, hypervitaminosis A, xerosis, neuropathy and neurological changes, opioids system involvement, expression of cytokines, serum bile acids, nitric oxide, or some combination of these.[6-10]

Management includes administration of moisturizers, topical steroids, antihistamines, phototherapy (ultraviolet B light), cholestyramine, erythropoietin, and ondansetron. Only a few patients truly benefit from any of these therapeutic regimens.[11-13] Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is an alkaloid naturally found in many botanical species of the night-shade plant family (Solanacea) and has successfully been used

for the treatment of multiple types of pruritus.[13] Evidence suggests that capsaicin exercises an active depressant effect in the synthesis, storage, transport, and release of substance P. Substance P is thought to be an important neuropeptide that acts as a mediator of pain and itching impulses from the periphery to the central nervous system.[14] Few studies have investigated the local effects of topical application of capsaicin in different conditions with pruritus, including ESRD. The aim of this study was to investigate the effect of topical treatment with capsaicin 0.03% on uremic-induced pruritus in patients with ESRD on long-term hemodialysis.

MATERIALS AND METHODS

Study Design

This study was a randomized double-blinded cross-over controlled trial of the effect of topical capsaicin on pruritus in patients on hemodialysis compared with placebo. The study was carried out from July 2007 to February 2008 at Imam Hospital, affiliated to Mazandaran University of Medical Sciences, Sari, Iran. The study protocol was approved by the institutional ethics committee and informed written consent was obtained from all the patients participated in study. The study was conducted in accordance with the Guideline for Good Clinical Practice and the Declaration of Helsinki.

Patients

A total of 34 patients with ESRD on hemodialysis with a Kt/V greater than 1.2 for at least 3 months were included in the study. They suffered from pruritus with no response to common treatment options. All of the patients were on hemodialysis 2 to 3 times per week for 3 to 4 hours. Nonresponsiveness was defined as persistent pruritus after 3 months of treatment with other drugs, reported subjectively by the patients.[12] Patients were excluded from the study if they had a history of systemic therapy for pruritus started in the past month or local therapy started in the past 2 weeks (eg, immunosuppressive drugs, cholestiramine, capsaicin, opioid agonists and antagonists, antiseretionin, glococorticoids, thalidomide, sedative drugs and ultraviolet B) or if they had hepatobiliary diseases (based on history and liver function tests), malignancies, hyperparathyroidism (based on plasma parathyroid hormone), dermatitis, dermatologic diseases (eg, scabies and pediculosis, according to dermatologist consultant), hyperphosphathemia (serum phosphorous level > 5.5 mg/dL and calcium× phosphorous product > 60.[7,13]

Study Procedures

The patients were equally divided and randomly assigned by lottery into 2 groups as following: the study group, in which the patients received Capsian 0.03% ointment (capsaicin 0.03%, Goldaru, Iran), and the control group, in which the patients received placebo (prepared in the Pharmacology Institute of Mazandaran University of Medical Science). The placebo was prepared in a same size and color packages as Capsian 0.03% ointment tubes.

Seventeen patients received capsaicin 0.03% ointment and 17 received placebo ointment, to be rubbed on the pruritus patches 4 times daily for 4 weeks. After this period, the treatment was stopped for 2 weeks as the washout period, and it continued in a cross-over fashion. The patients were evaluated at the beginning of the study and at the end of weeks 1, 2, 3, and 4 of each study period. Each evaluation included a limited physical examination and the assessment of the severity of pruritus. The score was assessed by the same investigator for all patients at each time of the study. For evaluation of itching, we modified a detailed score proposed by Duo.[15,16] The scoring of pruritus was according to the severity of pruritus, distribution of pruritus, and sleep disorder:

Total scoring of pruritus = (severity of pruritus × distribution of pruritus) + sleep disorder scoring[17]

The pruritus severity was monitored as follows: a slight itching sensation without necessity of scratching, 1 point; itching that necessitates scratching, but without excoriations, 2 points; itching that necessitates scratching accompanied by excoriation, 4 points; and pruritus causing total restlessness, 5 points.[17,18] Distribution of pruritus was scored as follows: pruritus in 2 areas of the body or less, 1 point; pruritus in more than 2 areas of the body, 2 points; and generalized pruritus, 3 points. Sleep disorder was scored as follows: every waking up due to pruritus received 2 points (maximum 10 points) and every scratching due to pruritus received 1 point (maximum 5 points).[15-17]

The patients were advised to continue hygienic and drying methods. All of the patients received clinical examinations and were asked about adverse effects and whether they wanted to continue to participate in the study.

Statistical Analyses

Values were expressed as the mean ± standard deviation. The significance of a difference between measurements in a group and two groups was calculated using the *t* test, paired *t* test, and repeat measurement analysis of variance test, where appropriate. A *P* value less than .05 was considered to be significant.

RESULTS

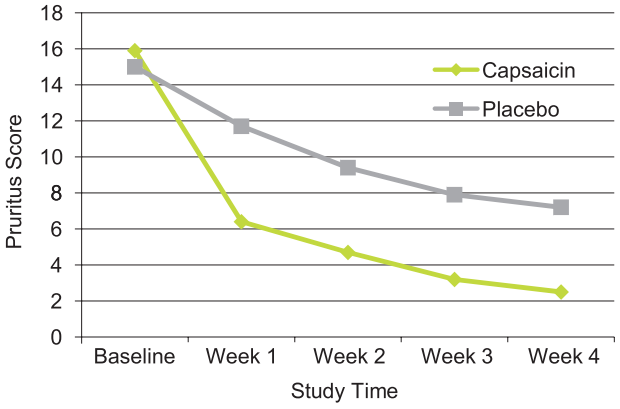
A total of 34 patients with ESRD, 14 men and 20 women, with a mean age of 57.0 ± 18.6 years were enrolled in this study. The mean hemodialysis period was 25 ± 15 months. The mean plasma parathyroid hormone level was 185.0 ± 121.7 pg/mL and the mean serum alkaline phosphatase level was 266 ± 109 IU/L. Causes of ESRD was hypertension in 14 patients (41.2%), diabetes mellitus in 12 (35.3%), glomerulonephritis in 1 (2.8%), urological problems in 1 (2.8%), and unknown in 6 (17.6%).

The mean pruritus scores before and after each week of treatment in the study group were 15.9 ± 6.3, 6.4 ± 3.9, 4.7 ± 3.1, 3.2 ± 2.9, and 2.5 ± 2.5, respectively ($P < .001$), and those were 15.0 ± 6.0, 11.7 ± 5.8, 9.4 ± 5.9, 7.9 ± 5.5, and 7.2 ± 5.5 in the control group ($P < .001$). There was no significant difference in the pruritus score before treatment between two groups, but the scores were significantly different after weeks 1, 2, 3, and 4 of the treatment (Table). Repeated measurement test showed that decreasing in pruritus severity in the study group was more than that in the placebo group during the treatment period ($P < .001$), and there was a linear correlation between pruritus severity and time (Figure).

In the control group, capsaicin 0.03% ointment induced skin burning in all of the patients after the 1st week. Severe skin burning was observed in 1 patient (2.8%), moderate in 10 (29.4%), and mild in 23 (67.6%), but the skin burning severity decreased during next weeks and this decreasing was significant ($P = .01$). No significant complications were observed in the controls.

Mean Pruritus Scores Before and After Each Week During The Treatment Period for Capsaicin and Control Groups

Study Time	Capsaicin	Placebo	*P*
Baseline	15.9 ± 6.3	15.0 ± 6.0	.57
Week 1	6.4 ± 3.9	11.7 ± 5.8	< .001
Week 2	4.7 ± 3.1	9.4 ± 5.9	< .001
Week 3	3.2 ± 2.9	7.9 ± 5.5	< .001
Week 4	2.5 ± 2.5	7.2 ± 5.5	< .001



Pruritus Scores in Capsaicin and Control Groups

DISCUSSION

Pruritus is one of the most prevalent presentations of uremia that occurs in 10% to 85% of patients on hemodialysis.[5,17-19] In this study, we found beneficial effects of topical capsaicin ointment in concentrations of 0.03% on pruritus among patients on hemodialysis. Our study demonstrated that capsaicin can be used successfully to treat pruritus with no serious adverse effect. Patients in this study experienced dramatic itching relief after treatment compared with those who received a placebo. In a case-control study, Weisshaar and colleagues found that capsaicin did not affect pruritus during hemodialysis period in patients with ESRD, and they reported that itching does not vary significantly before and after hemodialysis.[13] They applied capsaicin for 1 week and this result may be due to the short application time of the drug in their study, while we applied capsaicin for 4 weeks and observed good results. This can be explained by the longer time of application in our study. A study by Cho and associates prospectively assessed the role of capsaicin in hemodialysis-induced pruritus and reported that it can reduce the severity of itching in these patients.[20] Breneman and colleagues also observed a good effect of capsaicin 0.025% in improving pruritus with no significant complication in patients on hemodialysis.[21]

Capsaicin is a natural alkaloid extracted from red chili pepper. Its pharmacological action is mainly depletion of substance P from sensory neurons. Capsaicin binds specifically to type C sensory neurons and induces release of substance P, followed by inhibition of synthesis, transport, and storage of this neuropeptide. Topical capsaicin

has been described as a safe and effective medicine for the relief of pain associated with post-herpetic neuralgia, rheumatoid arthritis, and several other pain-related conditions. It has also been shown that capsaicin is effective in the treatment of histamine-induced pruritus, aquagenic pruritus, itching associated with uremia, nodular prurigo, and pruritus related to postmastectomy syndrome.[14,22]

In this study, we observed only a 3% severe complication of the drug, and our patients did not suffer any significant side effect of capsaicin 0.03% ointment. Although appropriate effect of capsaicin in pruritus, the placebo had a good effect in controlling of hemodialysis-related pruritus, our placebo had an emollient property that can be applied to control pruritus.

CONCLUSIONS

In summary, topical administration of capsaicin 0.03% ointment can be a new promising approach to the treatment of hemodialysis-induced pruritus. This concentration of the drug was significantly effective and safe in our patients.

CONFLICT OF INTEREST

None declared.

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