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Efficacy of topical cromolyn sodium 4% on pruritus of uremic nephrogenic patients; a randomized double blind study on 60 patients

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Key words
Cromolyn sodium 4% – pruritus – uremic patients

Abstract. Background: Chronic kidney disease (CKD)-associated pruritus is a significant clinical symptom affecting more than 50% of patients on hemodialysis. The availability of effective therapeutic options for management of CKD-associated pruritus remains a treatment challenge. Objective: The aim of this study was to compare cromolyn sodium cream 4% with placebo for the treatment of renal pruritus. Methods: A randomized, double-blind, prospective, 4-week study was designed. 60 patients with ESRD in our dialysis ward were randomly allocated to cromolyn sodium cream 4% or placebo. All of them completed the study period and their pruritus levels were evaluated 5 times (before the start of the study and at the end of each week for 4 weeks) using a Visual Analogue Scale (VAS). Results: The average pruritus score before administration of the drug in cromolyn sodium 4% and placebo group had been 2.5 ± 1.1 and 2.7 ± 1.3, respectively. In the cromolyn sodium 4% group the average score of pruritus gradually reduced to 0.3 ± 1.3 and in the placebo group it gradually decreased to 1.3 ± 1.4 at the end of Week 4. Method of t-test repeat analytical measurement indicated that there is no significant difference between reduction of pruritus in cromolyn 4% and placebo groups in the first and second week of the study, but in third and fourth week there were significant differences in reducing pruritus in favor of cromolyn sodium 4% ($p < 0.04$). Conclusion: According to our study cromolyn sodium cream 4% was more effective than placebo in reducing pruritus in uremic patients. We suggest to our colleagues to consider this treatment when facing a patient suffering from this symptom.

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Introduction

During the last decades a high number of substances were considered to be etiologic factors in uremic patients (UP), and an even higher number of therapeutic substances appeared with promising potentials and conflicting results in the course of their use [1]. The main reason for this controversy is the lack of sound evidence on the pathogenetic mechanisms that may potentiate UP [1]. Some probable mechanisms include: xerosis, [2], hypervitaminosis A [3], increasing in number of skin mast cells [4, 5], immunologic impairment [6], hyperparathyroidism [5, 7] and increasing of BUN [8] and substance P [9].

Notably, dermal mast cells and afferent C neuron terminals may play an important role in the mediation of pruritus because these structures are very close together [10]. It has been shown that in the skin of CKD patients with pruritus there is a greater number of mast cells [4, 11] and also an increased plasma histamine level compared to those without pruritus [12, 13]. But interestingly, there is no relationship between plasma histamine and pruritus score in patients undergoing dialysis [9]. Nevertheless mast cells release many other mediators that may be responsible for CKD-associated pruritus. Accordingly perhaps cromolyn sodium (CS) as a mast cell stabilizer is effective in the treatment of patients undergoing dialysis. The advice of CS as a treatment for UP was first

Table 1. Comparison of efficacy of CS 4% with placebo in a 4 week study.

p-value	Placebo	cromolyn sodium 4% cream	Weeks of treatment
	Mean ± SD	Mean ± SD	
0.588	3.1 ± 7.2	1.1 ± 5.2	Before treatment
0.948	1.2 ± 9.1	2.1 ± 8.1	First week
0.081	6.1 ± 7.1	4.1 ± 2.1	Second week
0.042	5.1 ± 6.1	2.1 ± 0.1	Third week
0.038	4.1 ± 3.1	3.1 ± 3.0	Fourth week

There is no significant difference between reduction of pruritus in cromolyn 4% and placebo groups in the first and second weeks of the study, but in the third and fourth weeks there were significant differences in reducing pruritus in favor of CS 4% ($p < 0.04$).

described by Rosner [11], who showed 2 patients with disabling uremic pruritus refractory with multiple interventions who showed significant improvement in pruritus severity as assessed by a visual analogue scale when they were treated with the mast cell stabilizer CS [11]. We decided to conduct this placebo-controlled clinical trial to evaluate the antipruritic effect of topical CS on hemodialysis (HD) patients.

Patients and methods

The study was conducted at the dialysis ward, Department of kidney disease Jundishapur University of Medical Sciences, Ahvaz, Iran between January 2010 and July 2010. The eligible patients had to meet the following criteria: (i) known cases of end-stage renal disease (ESRD) patients treated with HD; (ii) ages between 18 and 60 years; (iii) At least 6 weeks history of pruritus; and; (iv) no systemic or topical treatment for the pruritus.

Exclusion criteria included: (i) pregnant and breast feeding women; (ii) a known hypersensitivity to cromolyn sodium ; (iii) suffering from other known skin diseases, liver disorders, metabolic disorders, any other condition except for ESRD causing pruritus; (iv) any serious systemic diseases;(v) usage of antihistamines or other anti pruritus drugs in the last 3 months. The study was approved by the ethics Committee of the Faculty of Medicine before the trial started, and all patients gave written informed consent. Notably all patients were treated 3 times per week by HD, and in none of them the HD regimen was changed during the observation period.

Study design

The study employed a randomized, comparative, doubled-blind design. Randomization was performed by using a simple random table, and the patients were randomly allocated to one of the two arms of the study: study group (topical CS 4% 2 times a day starting immediately after dialysis) or control group (topical placebo). The placebo was formulated by a pharmacist to have a similar base with the drug but not containing the active ingredient and stored in a tube without any labeling. A similar tube was used to store CS 4% to make both creams to look physically identical.

The medications used were not revealed to their physicians. The patients were instructed to apply the medication to all affected parts of the body surface area 2 times a day for 4 weeks and were prohibited from using any other treatments for pruritus during the study. They were allowed to use their routine medications, e.g. antihypertensive agents. Each patient was visited 5 times in total, 1 time at the beginning of treatment and weekly for 1 month. They also received needed warnings like not using the drug on or near any scar or eyes and washing their hands after usage. At each visit patients were oriented on how to interpret their pruritus based on the Visual Analogue Scale (VAS) numbers from 0 to 5 (0: no pruritus and 5: the worst pruritus). Patients then were asked to indicate their pruritus level based on VAS. Additionally they were also asked to report any side effects.

Statistical analysis

In a pilot study on 12 patients, sample size was calculated by two mean comparisons (Alpha: 0.05 and Beta: 0.2) as 60 and the patients screened consecutively.

$$n = \frac{(Z_{(1-\beta)} + Z_{(1-\alpha/2)})^2(\delta_1^2 + \delta_2^2)}{(\mu_1 - \mu_2)^2}$$

The reduction of patients pruritus scores based on VAS in CS 4% group was compared with those of the placebo group. The test between the groups was carried out using repeated measure analyses χ^2 t-test and reported as (mean value ± SD). A p-value of

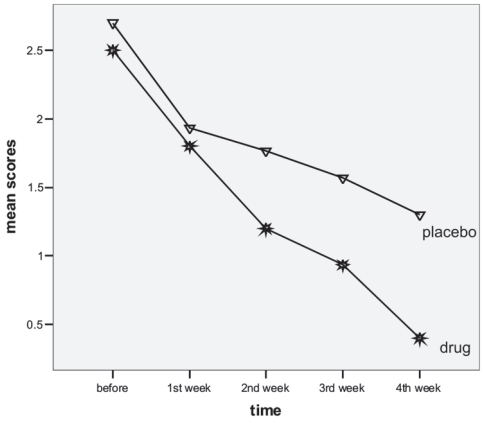

Figure 1. Comparison of efficacy of CS 4% with placebo in 4-week study. There is no significant difference between reduction of pruritus in cromolyn 4% and placebo groups in the first and second weeks of the study but in the third and fourth weeks there were significant differences in reducing pruritus in favor of CS 4%.

< 0.05 was required for a result to be considered statistically significant. Findings were analyzed using SPSS software version 17.

Results

After the 4-week course of treatment, all of the patients completed the study. The patients' mean age was (53 ± 11.4) years, with the sex distribution of 38 (63%) male and 22 (37%) female. The average dialysis time before treatment was 18 months. At the beginning of the study, treatment groups were not significantly different with respect to age, duration of disease before treatment and male-female ratio. 30 patients in the CS 4% group and 30 patients in placebo group were evaluated for efficacy. The average pruritus score before administration of the drug in the CS 4% group and in the placebo group had been 2.5 ± 1.1 and 2.7 ± 1.3 respectively. In the CS 4% group the average score of pruritus gradually decreased to 0.3 ± 1.3 at the end of Week 4. Notably the reduction of pruritus in these consecutive weeks was statistically significant in just the third and fourth week ($p < 0.04$). In the placebo group, the average pruritus score in control group was 2.7 ± 1.3 before the placebo administration and 1.9 ± 2.1 1 week after the start of placebo administration. Pruritus gradually decreased to 1.3 ± 1.4 in this group the end of Week 4. Interestingly the decline was also statistically significant only in the third and fourth week of the study ($p < 0.04$).

Repeated analytic t-test-measurements revealed that there is no significant difference between reduction of pruritus in cromolyn 4% and placebo groups in the first and second week of the study but in third and fourth week there were significant differences in reducing pruritus in favor of CS 4% ($p < 0.04$).

In the group receiving CS, 6 patients reported a burning sensation which gradually subsided during the course of treatment and completely disappeared in all patients at the end of Week 4. Overall patient's compliance of both creams was good. No other side effects were reported by patients in the case or control groups.

Discussion

Uremic pruritus is still one of the most vexing and disabling symptoms in chronic renal failure afflicting up to 50% of patients on dialysis [14]. Uremic pruritus causes skin damage, discomfort, sleeping disorders and diminished quality of life. Pathophysiology of pruritus in chronic renal diseases is not clearly understood and different theories are being suggested. Autoimmune reactions, uremic skin, mast cell proliferation, atrophy of adipose cells, secondary hyperparathyroidism, skin pH changes, electrolyte imbalances, anemia, peripheral neuropathy, hypervitaminosis A, and finally high concentration of bile acids have been suggested as causes of pruritus in these patients [15]. Considering the wide variety of probable causes of pruritus in HD patients [16], several treatments like erythropoietin [17], gabapentin [16] skin moisturizing creams [11] and ultra violet light [18] have been suggested but none of these treatments is known as the treatment of choice for this condition. It has been shown that skin of CKD patients with pruritus has a greater number of mast cells [4, 11] and also increased plasma histamine level compared to those without pruritus [12] so it is logical to use the mast cell stabilizing CS in the treatment of renal pruritus. The introduction of oral CS as a treatment of renal pruritus [11], so one double-blind placebo-controlled trial has been performed on this subject by Vessal et al. [10]. They showed

that oral CS 135 mg 3 times daily significantly reduced the severity of pruritus in HD patients and confirmed the first report [10]. In comparison to a later study, which revealed that the absolute oral bioavailability of CS is less than 5% [19], a clinically useful benefit of topical skin lotion of CS has been shown in children with moderately severe atopic dermatitis [20]. We decided to use topical CS 4% cream in our HD patients.

Interestingly we found out that in the third and fourth week of the study CS 4% cream was more effective in reducing pruritus than placebo. The randomized double blind clinical trial with CS 4% cream carried out in this study, even though not exactly in line with the previous study by Vessal et al. [10], confirms the results of the latter study. Few differences between the results of these studies may be due to the differences of methods used. Thus our trial for the third time demonstrates the favorable clinical response of patients with renal pruritus to CS even in topical form. In conclusion, we think that CS can be regarded a new therapeutic option in the treatment of renal pruritus even in the form of a topical formulation. Thus, given the safety and effectiveness of CS, we suggest to our colleagues to consider this treatment when facing a patient suffering from this symptom.

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