Therapeutic Effect of Montelukast for Treatment of Uremic Pruritus in Hemodialysis Patients

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Introduction. Uremic pruritus is one of the most common disabling symptoms in patients with end-stage renal disease. We aimed to study the effect of montelukast sodium for the treatment of uremic pruritus lasting more than 3 months in patients undergoing hemodialysis and compare it with placebo.
Methods and Materials. Eighty patients undergoing hemodialysis at 3 centers in Shiraz, Iran, were recruited to a randomized double-blinded controlled trial to receive 10 mg of montelukast or placebo, daily for 30 days. To assess the severity of pruritus, a visual analogue scale and the Detailed Pruritus Score, based on a combined score of severity and distribution of pruritus and sleep disturbance, were used. Sleep disturbance, severity, and distribution scores were added up to calculate the patients' final score at the start and the end of the study.
Results. The mean reduction of visual analogue scale score was significantly greater in the montelukast group (2.73 ± 2.03) compared to that in the placebo group (5.47 ± 2.37, $P < .001$). Mean reduction in Detailed Pruritus Score was also greater in the montelukast group (3.24 ± 2.2 versus 6.44 ± 3.25, respectively, $P < .001$). The mean high-sensitivity C-reactive protein in the montelukast group decreased from 5.48 ± 3.86 µg/mL to 3.86 ± 3.58 µg/mL, while it increased in the placebo group from 6.69 ± 4.49 µg/mL to 8.14 ± 5.20 µg/mL.
Conclusions. Montelukast can be an add-on therapy in uremic pruritus, especially when pruritus is refractive to other treatments.

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INTRODUCTION

Uremic pruritus is one of the most common disabling symptoms in patients with end-stage renal disease. Although pruritus was a very common problem in the early days of dialysis treatment, afflicting up to 85% of patients, its incidence declined to 50% to 60% in the late eighties.[1] In most patients, pruritus begins through the dialysis session and in 25%, it is persistent both along dialysis sessions and between those.[2] In Iran, pruritus was found in 41.9% of hemodialysis patients, and pruritus intensified in 31.4% during and after dialysis.[3]

There are different pathologic pathways that cause uremic pruritus. The correlation between mast cells and severity of pruritus has been studied, and it seems the patients' symptoms are due to histamine release from the mast cells.[4] Nevertheless, the perception of pruritus in the central nervous system is related to opioid receptors, which

introduce the use of opioid antagonists in the management of pruritus.[5] Of the other causes, skin contact to some antigens sensitive to leukotriene B4 should be mentioned.[6,7]

At present, different therapeutic modalities are used that consist of keeping the optimum adequacy of dialysis (Kt/V > 1.2), ultraviolet B radiation, antihistamines, opioid antagonists, erythropoietin, topical capsaicin, evening primrose oil, gabapentin, heparin, cholestyramine, doxepin, thalidomide, charcoal, gamma-linolenic acid, cromolyn sodium, loratadine, ondansetron, nalfurafine, and alternative medicine (acupuncture and massage).[4,5,8-21] Leukotriene B4 has been suggested to induce scratching behavior in mice. Furthermore, substance P-induced scratching may be mediated by release of leukotriene B4 from keratinocytes. Furthermore, sphingosine phosphorylcholine-induced pruritus was in part explained by synthesis and secretion of leukotriene B4 from keratinocytes, as scratching behavior was diminished by the 5-lipoxygenase inhibitor zileuton and the leukotriene B4-antagonist ONO-4057.[22]

Montelukast sodium is a leukotriene receptor antagonist that has been used in the treatment of asthma, atopic dermatitis, allergic rhinitis, and idiopathic urticarial.[23-26] We studied the effect of montelukast in patients on hemodialysis with uremic pruritus lasting more than 3 months, and compared it with placebo.

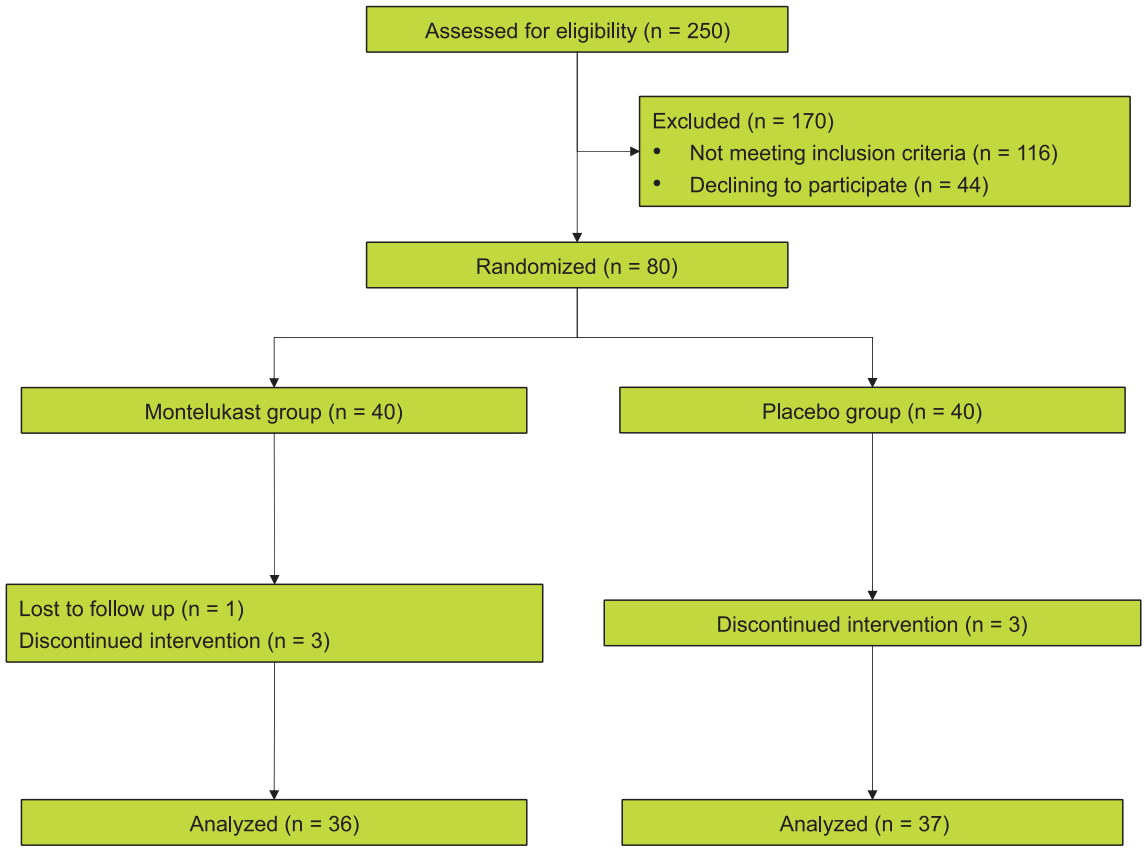
MATERIALS AND METHODS

This study has been registered with the Clinical Trials.gov (NCT02559388). This was a randomized double-blinded placebo-controlled trial conducted between April and August 2015. The study protocol was approved by the ethics committee of Shiraz University of Medical Sciences. All hemodialysis patients attending the three major dialysis centers in Shiraz were evaluated. All patients were on dialysis with bicarbonate hemodialysis with polysulfone membranes, and heparin was used for anticoagulation. Eligible paricipants were adults aged over 18 years who were suffering from pruritus during the past 3 months that, despite consumption of antipruritic medications, had not experienced proper response to medications. Patients who had less than 3 months history of pruritus, Kt/V less than 1.2, dermatologic diseases, malignancies, cholestatic diseases, active infection or infection with hepatitis B or C virus, and hemoglobin less than 10 g/dL were excluded from the study, as well as those who took corticosteroids or were hospitalized during the course of study.

Medications with antipruritic effects were discontinued 1 week before the study. Eighty patients who met the study criteria were enrolled in the study and based on block randomization method, were randomized into 2 groups of 40 participants. Of these, 4 patients in the control group left the study due to nonadherence to medication and 1 patient in trial group dropped out due to hospitalization and 2 patients in trial group dropped out due to nonadherence (Figure). Montelukast (Aerokast) and placebo were prepared as 10 mg tablets (Dr Abidi's Pharmaceutical Company, Tehran, Iran). All medication and placebo tablets were similar in size, shape, weight, color, and package. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment and code breaking was done at the end of study. Each patient in the montelukast group received 10 mg (1 tablet) of montelukast, while the control group received 1 tablet placebo, daily for 30 days. To assess severity of pruritus we used a visual analogue score and the Detailed Pruritus Score (DPS) proposed by Duo (Table 1),[27] based on a combined score of severity and distribution of pruritus and sleep disturbance. Sleep disturbance and severity/distribution scores were added up to calculate the patient's final score at the start and the end of the study. Blood sample from patients were collected from arterial line before starting dialysis and were centrifuged and frozen at -70°C before the measurement at the start and end of study. Biochemical determination included level of serum creatinine, blood urea nitrogen, serum sodium, serum potassium, serum calcium, hemoglobin, serum phosphorus, serum parathyroid hormone, high-sensitivity C-reactive protein (HSCRP), and tumor necrotizing factor-α before starting the study and HSCRP and tumor necrotizing factor-α at the end of study. Dialysis efficacy was calculated using urea kinetics model and expressed as Kt/V.

Data Analysis

All continuous variables were reported as the mean ± standard deviation and were compared using the independent Sample *t* test. Multivariable



Flowchart of patients' recruitment and assignment with excluded cases

Table 1. Detailed Pruritus Scale Score

Pruritus Characteristic	Score
Severity of pruritus	
Mild need for scratching	1
Need for scratching without excoriation	2
Need for scratching with excoriation	4
Frustrating pruritus	5
Distribution of pruritus	
Less than 2 sites	1
More than 2 sites	2
Generalized	3
Sleep disturbance as a result of pruritus	
Waking up of pruritus	1 for each time per night, up to 10
Scratching during night with excoriation	1 for each time per night, up to 5

repeated-measure analysis of variance was used for overall comparison of the montelukast and placebo groups during the study. All data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, IL, USA) and *P* values less than .05 were considered significant.

RESULTS

All dialysis patients attending the three hemodialysis referral centers in Shiraz between April and August 2015 were assessed for eligibility. Eighty patients fulfilled the inclusion criteria and were randomized into the montelukast (n = 40) and placebo (n = 40) groups. The mean age of the patients was 53.3 ± 15.8 years. Characteristic of the two groups are presented in Table 2.

Table 3 presents the comparison of measured parameters between the two groups. The mean visual analogue scale score was comparable between the two groups at baseline ($P = .39$), but the mean reduction of the score after treatment was significantly greater in the montelukast group (2.73 ± 2.03) than in the placebo group (5.47 ± 2.37; $P < .001$). Mean DPS did not differ significantly between the groups at baseline ($P = .07$), while the mean DPS at the end of the study was significantly lower in the montelukast group (3.24 ± 2.2) than that in the placebo group (6.44 ± 3.25; $P < .001$). The mean HSCRP in the montelukast group changed from 5.48 ± 3.86 µg/mL to 3.86 ± 3.58 µg/

Table 2. Patient Demographic and Laboratory Data of Montelukast and Placebo Groups at the Beginning of Study

Variable	Montelukast	Placebo	*P*
Body weight, kg	66.53 ± 12.98	67.22 ± 12.07	.81
Blood urea nitrogen, mg/dL	64.55 ± 13.53	61.92 ± 22.07	.54
Serum creatinine, mg/dL	8.16 ± 2.18	7.97 ± 2.43	.72
Serum calcium, mg/dL	5.44 ± 0.61	5.35 ± 1.03	.64
Serum phosphorus, mg/dL	7.27 ± 2.35	5.21 ± 1.38	.19
Parathyroid hormone, pg/mL	569.18 ± 514.40	640.08 ± 827.01	.66
Hemoglobin, g/dL	12.12 ± 1.85	12.18 ± 1.80	.89
Kt/V	1.46 ± 0.20	1.42 ± 0.14	.38
Visual analogue scale score	6.43 ± 2.36	6.00 ± 1.94	.39
Detailed Pruritus Scale score	8.89 ± 4.78	7.17 ± 3.15	.07
High-sensitivity C-reactive protein, µg/mL	5.46 ± 3.86	6.69 ± 4.49	.22

Table 3. Comparison of Measured Parameters Before and After Study Between Montelukast and Placebo Groups

Variable	Montelukast	Placebo	*P*
Visual analogue scale			
Before trial	6.43 ± 2.36	6.00 ± 1.94	
After trial	2.73 ± 2.03	5.47 ± 2.37	< .001
Detailed Pruritus Scale			
Before trial	8.89 ± 4.78	7.17 ± 3.15	
After trial	3.24 ± 2.20	6.44 ± 3.25	< .001
High-sensitivity C-reactive protein, µg/mL			
Before trial	5.48 ± 3.86	6.69 ± 4.49	
After trial	3.81 ± 3.58	8.14 ± 5.20	< .001

mL, while it increased from 6.69 ± 4.49 µg/mL to 8.14 ± 5.2 µg/mL in the placebo group. The mean HSCRP reduced significantly in the montelukast group, while it increased in the placebo group ($P < .001$).

DISCUSSION

Our findings revealed that montelukast reduced uremic pruritus in hemodialysis patients. While there was a mild decrease in pruritus severity score (DPS) in the placebo group, a significant decrease in the DPS happened in the montelukast group at the end of the study, indicating that montelukast was significantly more effective than placebo for symptom relieve in uremic pruritus.

There are different mechanisms responsible for uremic pruritus such as perception of pruritus via opioid receptors in the central nervous system, pruritogenic effects of parathyroid hormone and histamine, xerosis, and mast cell activity. More recent research points to micro-inflammation on the skin and probably at systemic level, as an etiopathologically relevant factor in uremic pruritus.[1] Elevated levels of CRP were observed in serum of hemodialysis patients with chronic pruritus.[28,29] Furthermore, relatively increased pro-inflammatory relevant to T helper 1 cells and raised interleukin-6 concentrations could be detected in these patients.[29] Compared with patients with moderate pruritus or no pruritus, patients with more severe pruritus tended to have higher serum CRP and lower serum albumin levels.[30]

In general, substances that cause pruritus include kinins, serotonin, proteases, neuropeptides, leukotrienes, and other chemicals. Leukotrienes are mediators with pro-inflammatory properties generated from arachidonic acid, an essential fatty acid found in the membrane of all cells. A synthesis pathway whose key enzyme is 5-lipoxygenase provides all known leukotrienes. Their cellular origin is reflected by 5-lipoxygenase expression and essentially restricted to various myeloid cells such as neutrophils, monocytes/macrophages, B lymphocytes, and mast cells. The contribution of leukotrienes to the pathophysiology of inflammatory diseases, in particular asthma, is well established, whereas their role in the pathogenesis of pruritus is still a subject of debate. However, intradermally injected leukotriene B4 was demonstrated to provoke scratching in mice, and high urinary leukotriene

E4 levels could be correlated to nocturnal itch. An increased abundance of leukotrienes could therefore account for itch induction.[31]

Increased intradermal amount of substance P can lead to pruritus.[1,32] Montelukast can lead to significant decrease of inflammation and inflammatory mediators like substance P and neurokinin A.[33] Since substance P can act as a neurotransmitter in uremic pruritus,[32] one mechanism that can explain the antipruritic effect of Montelukast is reduction of substance P and inflammation.

In our study, the mean amount of HSCRP decreased significantly in the montelukast group. Hadi and colleagues also showed that montelukast could lead to significant reduction of HSCRP.[34] This finding also confirms anti-inflammatory effects of montelukast as a mechanism to explain anti-pruritic effect of that.

Nasrollahi and associates also showed that montelukast at a dose of 10 g/d in hemodialysis patients can improve uremic pruritus severity.[35] Based on all these data, it is proposed that montelukast can be introduced as an add-on therapy in uremic pruritus, especially when pruritus is refractive to other traditional therapies. It should be mentioned that main advantages of this drug are renal adjustment is not required, single daily dose is enough, patients have good compliance, there are no specific interactions with other medications used in end-stage renal disease, and there is no serious side effect associated with this medication. Hence, montelukast overall can be included as new drug for uremic pruritus.

CONCLUSIONS

Based on all these data it is proposed that Montelukast can be introduced as an add-on therapy in uremic pruritus, especially when pruritus is refractive to other traditional therapies. In order to confirm the effectiveness of montelukast, we recommend other randomized double-blinded controlled trials in larger scales and compare it with other traditional medications for uremic pruritus. Since we did not enroll peritoneal dialysis patients in this study, it is recommended to perform other studies on these patients, too.

CONFLICT OF INTEREST

None declared.

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