

Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial

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Abstract

Background Uremic pruritus as a symptom that affects hemodialysis (HD) patients can decrease the quality of life and increase morbidity in these patients. The aim of this study was to evaluate the effects of turmeric on uremic pruritus in HD patients.

Subjects and methods This was a double-blind placebo-controlled trial conducted on 100 HD patients suffering from pruritus. Patients (mean age 53.3 ± 15.8 years) were randomized into two groups: turmeric and placebo. The pruritus score and biochemical determinants including high-sensitivity C-reactive protein (hs-CRP) were compared before and at the end of the study between the two groups.

Results The mean decrease in hs-CRP was significantly higher in the turmeric than the placebo group (-0.8 ± 2.6 vs. 0.4 ± 8.7 mg/l, $p = 0.012$). Also reduction of pruritus scores was greater in the turmeric than the placebo group (13.6 ± 2.6 vs. 7.2 ± 2.6 , $p = 0.001$). No side effect was observed during the study due to the use of turmeric.

Conclusions This study demonstrates the possible efficacy of turmeric in decreasing hs-CRP and uremic pruritus

in end stage renal disease patients. Future studies are needed to further evaluate the efficacy and safety of turmeric.

Keywords Clinical trial · End stage renal disease · Hemodialysis · Turmeric · Uremic pruritus

Introduction

Uremic pruritus (UP) is one of the most common and bothersome symptoms affecting patients with end stage renal disease (ESRD) [1]. The prevalence of UP varies from 50 to 90 % in various studies [2]. Chronic pruritus can be persistent and distressing, with significant impact on quality of life and physical comfort with potential psychological, functional, and social impact and increased morbidity [3]. The pathogenic molecular basis of pruritus in chronic renal failure remains elusive, which limits the use of effective treatments. Treatments currently used for UP are oral antihistamines, gabapentin, ondansetron, thalidomide, naltrexone/nalbufine, ultraviolet (UV) light, and topical tacrolimus [4–10]. Unfortunately, the results of different studies are not concordant and most of the mentioned treatments have had limited success.

Many hypotheses have been proposed to clarify the reasons for its occurrence, including xerosis and hypohidrosis, the presence of pruritogenic cytokines (histamine, kallikrein, interleukin (IL)-2, acetylcholine, and other substances that are released by histamine-mediated mast cell stimulation), secondary hyperparathyroidism and immune-inflammatory reactions [2, 11]. Previous studies have verified that inflammation is mainly associated with UP in ESRD patients. Patients with severe UP have higher high-sensitivity C-reactive protein (hs-CRP) levels [12].

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On the other hand, several inflammatory cytokines promote the genesis of uremic pruritus, such as IL-2 [13].

Turmeric, a powder of the rhizomes of *Curcuma longa* L. (Zingiberaceae), commonly used as a dietary spice, is also used in Asian and Iranian medicine ordinarily for treatment of inflammation and skin wounds [14]. Curcumin (diferuloylmethane), the most active and non-toxic component of turmeric, is a polyphenol [15] that has been extensively studied for its therapeutic benefit, such as anti-inflammatory activities [16, 17]. Turmeric appears to be non-toxic to humans even at high doses [18]. However, there is a paucity of information on the effect of turmeric on hemodialysis (HD) patients. We, therefore, conducted this study to determine if there was any beneficial effect of turmeric on pruritus in HD patients.

Materials and methods

This study was a parallel, double-blind placebo-controlled trial carried out between August 2011 and June 2012. The trial was approved by the ethics committee of Shiraz University of Medical Sciences and carried out in accordance with the Declaration of Helsinki. The trial was registered at clinicaltrials.gov (NCT01037595).

In accord with the convenience sampling method, all HD patients ($n = 255$) attending the Ebrahimi HD center in Shiraz were enrolled in this study. Inclusion criteria were: adults over 18 years of age who had been suffering from pruritus during the previous 6 weeks but did not respond to anti pruritic drugs, and who signed the informed consent. Patients with dermatologic, liver or metabolic diseases associated with pruritus and serum parathyroid >300 pg/ml were excluded. One hundred and one patients who met the study criteria were enrolled in the study. One patient before the start of the study dropped out due to renal transplantation. The remaining 100 patients were randomized into two groups: the trial group ($n = 50$) and the controls ($n = 50$); a factorial block randomization was used for allocation sequence (each block has equal numbers of A for trial and B for control). Our statistical consultant assigned by a table of random numbers a number 0 to 4 to AB block and 5–9 to BA block. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment.

Each patient in the trial group received a safe dose of turmeric (one capsule with each meal containing 500 mg turmeric, of which 22.1 mg was the active ingredient curcumin, 3 caps/day for 8 weeks) while the control group received starch capsules for the same 8-week period. The

type and dose of the individualized drugs remained unchanged during the study. Each patient was given an order number and received the medications in the equivalent pre-packed bottles. All drugs and placebo tablets were similar in size, shape, weight and color. Drug compliance was evaluated by tablet counts. The membrane and general dialysis prescription were similar for all patients. Any medications with antipruritic effect were discontinued 1 week before the study.

All the patients were visited by a trained dermatologist who evaluated the pruritus complaint. The pruritus measurement was performed by the same person throughout the study (at the start, during, and end). The data collection technique was based on observation and interview. We evaluated patients in weekly visits at the dialysis center for side effects but the pruritus score was calculated before and at the end of the study. To assess pruritus, we used the Detailed Pruritus Score proposed by Duo [19], based on a combined score of severity and distribution of pruritus and sleep disturbance. Severity was scored as follows: sense of itching with no need to scratch = 1 point; scratching a few times without excoriation = 2; frequent need to scratch = 3; scratching with excoriation = 4; an itch that led to continuous unrest = 5 points (maximum daily score of 10 points—5 in the morning, 5 in the afternoon). Distribution of the pruritus was scored: 1 point for pruritus in less than two areas; 2 points for pruritus in more than two areas; and 3 points for widespread pruritus. The scores for severity and distribution were multiplied separately for the morning and afternoon. The maximum daily score was 30 points. Sleep disturbance was scored: 2 points for each wakeup because of pruritus (with a maximum of 10 points); and 1 point for each scratching with excoriation during the night (with a maximum of 5 points). 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.

Turmeric rhizome was obtained from the Indian market and powdered rhizomes were encapsulated by Medical and Natural Products Chemistry Research Center of Shiraz University of Medical Sciences, using hard gelatin capsules. Also starch capsules were made by the same Center. Curcumin as standard was obtained from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile, methanol and acetic acid were high pressure liquid chromatography (HPLC)-grade (Merck, Darmstadt, Germany). Reagent grade water (Purelab[®] UHQ, ELGA, High Wycombe, UK) was used throughout the study. Curcumin level of turmeric was measured by methods described elsewhere [20].

Blood samples from HD patients in a fasting state were collected from the arterial line immediately before the mid week dialysis session before heparin administration, and they were centrifuged and frozen at -70 °C before the

Table 1 Demographic data of patients according to group allocation (placebo vs. turmeric)

Variable	Placebo (n = 50)	Turmeric (n = 50)	p
Age (years), mean \pm SD	51.0 \pm 16.6	55.6 \pm 14.7	0.147
Sex (male), n (%)	27 (54.0)	33 (66.0)	0.154
Dialysis duration (months), mean \pm SD	6.4 \pm 4.8	3.5 \pm 2.6	0.001
KT/V, mean \pm SD	1.5 \pm 0.3	1.6 \pm 0.3	0.113

n number, *SD* standard deviation

measurements. Biochemical determinations included levels of serum albumin (Alb), lipid profile, blood urea nitrogen (BUN), serum creatinine (cr), calcium (Ca), phosphorus (P) before starting the study, and hs-CRP at the start and end of the study was measured. All measurements were performed at the Gastrohepatology Research Center Laboratory of Shiraz Medical University. The levels of hs-CRP were assayed with the nephelometric method.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software, version 15.0 (SPSS Inc, Chicago, IL, USA). Association between categorical variables was analyzed using the Chi square test. Quantitative data were presented as mean \pm standard deviation and compared by independent-samples *t* test in the two groups. Data variations were performed before and after administration of turmeric by paired-samples *t* test. Other tests were used as appropriate. All the tests were two-sided, and *p* values <0.05 were considered as significant.

Results

All dialysis patients attending the Ebrahimi HD referral center in Shiraz between August 2011 and June 2012 were assessed for eligibility. One hundred and one patients fulfilled the inclusion criteria and were randomized in double-blind fashion into two groups. One patient dropped out due to renal transplantation leaving a total of 100 patients (60 males and 40 females) who participated in this research project, randomized into the trial (turmeric) group (*n* = 50) and controls (placebo) (*n* = 50). The mean age of patients was 53.3 years \pm 15.8 (standard deviation, SD). Average duration of HD treatment was 4.9 \pm 4.1 months. Characteristics of the two groups are presented in Table 1.

Tables 2 and 3 present a comparison of the measured parameters between the two groups (turmeric vs. controls). Mean hs-CRP in the turmeric group changed from 10.8 \pm 9.7 mg/l at baseline to 7.0 \pm 8.9 (*p* = 0.003) while

Table 2 Comparison of some parameters between placebo and turmeric groups

Variable	Placebo (n = 50)	Turmeric (n = 50)	p
CRP, mg/l			
Before trial	9.4 \pm 8.4	10.8 \pm 9.7	0.428
After trial	9.6 \pm 9.5	7.0 \pm 8.9	0.173
p-value	0.831	0.003	–
Mean decrease	0.4 \pm 8.7	–0.8 \pm 2.6	0.012
BUN, mg/dl			
Before trial	71.6 \pm 20.0	70.9 \pm 17.7	0.870
After trial	64.2 \pm 18.4	66.7 \pm 15.4	0.475
p-value	0.0001	0.067	–
Mean decrease	–7.3 \pm 14.6	–4.3 \pm 16.1	0.322
Creatinine, mg/dl			
Before trial	9.5 \pm 3.9	9.6 \pm 2.6	0.949
After trial	10.0 \pm 8.4	8.7 \pm 3.1	0.333
p-value	0.721	0.028	–
Mean decrease	0.4 \pm 8.8	–0.8 \pm 2.6	0.323
Total pruritus score			
Before trial	23.1 \pm 1.9	23.9 \pm 2.6	0.168
After trial	15.9 \pm 2.1	10.3 \pm 1.6	0.0001
p-value	0.0001	0.0001	–
Mean decrease	7.2 \pm 2.6	13.6 \pm 2.6	0.001

CRP C-reactive protein, BUN blood urea nitrogen

Table 3 Comparison of some parameters between placebo and turmeric groups

Variable	Placebo (n = 50)	Turmeric (n = 50)	p
PTH	274.4 \pm 348.8	291.1 \pm 314.0	0.802
Calcium	8.1 \pm 2.2	7.9 \pm 1.5	0.673
Phosphorus	5.2 \pm 2.1	4.8 \pm 1.2	0.269
Ca \times Ph	41.5 \pm 16.9	38.8 \pm 12.8	0.374

PTH parathyroid hormone

it changed from 9.4 \pm 8.4 to 9.6 \pm 9.5 mg/l (*p* = 0.831) in the placebo group. Mean decrease of hs-CRP was significantly higher in the turmeric group -0.8 ± 2.6 mg/l vs. 0.4 ± 8.7 in the placebo group (*p* = 0.012).

Mean pruritus scores in both groups at baseline and subsequent follow-up visits are shown in Table 2. The mean pruritus score between the two groups did not differ significantly at baseline (*p* = 0.068), but after treatment the mean reduction in pruritus score of the group treated with turmeric was significantly greater than that of the placebo group (*p* = 0.01); the mean difference in pruritus scores before and after treatment in the turmeric group at 8 weeks was 13.6 \pm 2.6 vs. 7.2 \pm 2.6 in the placebo group. Spearman's correlation showed no significant correlation between the severity of pruritus and hs-CRP (*p* > 0.05).

Due to a possible role of dialysis duration, sex, and age as a confounding factor and their effect on response, after univariate analysis of variance these variables were controlled (dialysis duration with p-value: 0.293, sex with p-value: 0.749, age with p-value: 0.633) and the group variable still was significant (p-value 0.001).

Based on repeated interviews during the study, the patients mentioned no minor or major complaints attributable to the use of turmeric.

Discussion

Our findings revealed that turmeric reduces pruritus in patients with UP. Even though the decrease in symptoms was seen in both the turmeric and placebo groups, there was a significant difference between the pruritus scores in the two groups at the end of the study, indicating that turmeric is significantly more effective than placebo.

Previous studies showed that besides metabolic factors and dialysis clearance [21, 22], inflammation is the factor mainly associated with UP in HD patients [12]. UP has been shown to be associated with high levels of C reactive protein and inflammatory cytokines such as IL-2 or IL-6 [12, 13, 23]. Narita et al. [24] showed that higher β 2-microglobulin independently predicts UP. And chronic inflammation stimulates the accumulation of β 2-microglobulin in dialysis patients [25].

Our study showed that the hs-CRP level decreased significantly in ESRD patients who received turmeric as compared to placebo. hs-CRP has been confirmed to be one of the most reliable markers of inflammation in ESRD patients, independently predicting their overall mortality [26, 27]. Besides hs-CRP, ESRD patients with moderate/severe UP have a worse survival [12]. The skin of ESRD patients with UP has an increased number of mast cells, and these cells can release a variety of substances such as histamine, tumor necrosis factor (TNF) and IL, common markers of inflammatory processes [28, 29].

Fallahzade et al. [23] demonstrated the significantly higher serum levels of IL-2 in HD patients with UP compared to those without UP. Impairment of T helper (TH) cells balanced with TH1 predominance seems to be a main provider for systemic inflammation in UP [13]. TH1 cells produce inflammatory cytokines such as interferon (IFN) that engage and trigger leukocytes; consequently, the over-activity of TH1 cells results in an inflammatory response. Alternatively, TH2 cells produce anti-inflammatory cytokines such as IL-4 and are correlated with allergic responses [30].

As a result, any prescribed medication, by decreasing the inflammatory cascade in ESRD patients, might be effective in the modulation of UP. Previous research indicates curcumin may have potential as a therapeutic

agent in inflammatory diseases such as arthritis, pancreatitis, inflammatory bowel disease and chronic anterior uveitis [31]. Curcumin (diferuloylmethane), a component of turmeric (*Curcuma longa*) that is inexpensive, orally bioavailable, and very safe in humans, has been shown to be able to block TNF- α action and production in in vitro and in vivo studies [32].

Hanai et al. reported the efficacy of curcumin in suppression of induced inflammatory bowel disease and promoting changes in cytokine profiles from the pro-inflammatory Th1 to the anti-inflammatory Th2 type. Curcumin has inhibitory effects on major inflammatory mechanisms like COX-2, TNF- α , IFN- γ , and nuclear factor (NF)- κ B [33]. Curcumin-mediated inhibition of IL-12 production led to the inhibition of Th1 and a possible enhancement of Th2 cytokine synthesis in CD4+ T cells. The mechanism by which curcumin inhibits IL-12 production appears to be in the course of the down-regulation of NF- κ B-mediated activation. NF- κ B activation is considered to play a major role in the regulation of pro-inflammatory gene transcription; consequently, curcumin may inhibit early steps of inflammation and modulate up-regulation of multiple proinflammatory genes [34].

Although in our study there was no statistical association between hs-CRP and pruritus severity, this trial supports the idea that turmeric can be used to reduce pruritus and hs-CRP as a major inflammatory marker in patients with ESRD. No adverse reactions were seen on general health and biochemical marker tests. Turmeric is an inexpensive drug and has very few side effects [35]. In contrast to gabapentin that has been established to be useful for the treatment of CKD-associated pruritus, turmeric has less adverse effects [36].

Thus, it seems that turmeric is a safe medication in this population. However, the safety of turmeric therapy in ESRD patients should be further evaluated in larger trials with longer duration of therapy. The main limitations of our study and of the interpretation of its results are the small sample size and short duration of the treatment phase.

In conclusion, to the best of our knowledge, this is the first randomized, double-blind, clinical trial that demonstrates the possible efficacy and safety of turmeric in attenuating UP and hs-CRP in ESRD patients. Future multicenter randomized trials with larger sample size and longer treatment duration are necessary to further confirm the long-term efficacy and safety of adding turmeric in the HD population.

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Conflict of interest The authors declare that they have no conflict of interest.

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