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ORIGINAL ARTICLE

Efficacy and safety of turmeric 1% emollient cream in the control of chronic kidney disease-associated pruritus in hemodialysis patients: A randomized double-blind clinical trial

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ABSTRACT

INTRODUCTION Chronic kidney disease-associated pruritus (CKD-aP) remains a frequent and distressing symptom in hemodialysis patients, further compromising their quality of life. Turmeric, or *Curcuma longa*, is a naturally-occurring, widely available product that inhibits major inflammatory mechanisms associated with CKD-aP.

OBJECTIVES This study aimed to determine the efficacy and safety of turmeric 1% emollient cream versus a bland emollient in the reduction of chronic kidney disease-associated pruritus in hemodialysis patients.

METHODS This study was a randomized, double-blind, controlled trial of the effect of turmeric 1% cream in the reduction of chronic kidney disease associated pruritus in hemodialysis patients compared to a bland emollient. The main outcome measure was the proportion of subjects who demonstrated response to treatment, as well as the incidence of adverse effects.

RESULTS Intention to treat analysis on 106 patients, 53 assigned to turmeric 1% cream and 53 to bland emollient cream, was done. There was a significant difference (P=0.03) in the proportion of patients who achieved treatment success between the turmeric group (66%) and bland emollient group (45%). The mean decrease in pruritus score (VAS) of the group treated with turmeric was significantly greater than that of the bland emollient group (P=0.018). No adverse effects were noted in both groups.

CONCLUSION Among hemodialysis patients diagnosed with CKD-aP, topical application of turmeric 1% cream twice daily for four weeks was superior to that of bland emollient cream based on efficacy and safety outcome measures.

KEYWORDS turmeric, *Curcuma longa*, chronic kidney disease-associated pruritus, uremic pruritus, hemodialysis

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INTRODUCTION

Chronic Kidney Disease (CKD) is one of the most common systemic causes of pruritus, affecting 42% of patients on hemodialysis as reported by the Dialysis Outcomes and Practice Pattern Study (DOPPS).[1,2] CKD-associated pruritus (CKD-aP) is the apt term given to this condition, defined as itching directly related to kidney disease, without the presence of another comorbid condition producing the pruritus.[3,4] It remains a frequent and distressing symptom of CKD.[5] A meta-analysis done by Hu Xinmiao et. al. showed the prevalence of CKD-aP in hemodialysis patients to be 55%.[3] Itching in these patients can impair sleep, interfere with work and social functioning, thus compromising quality of life (QOL).[4,6,7] If left untreated, patients may develop depression.[4] Furthermore, the scratching may lead to skin excoriations that may result to soft tissue infections.[6] These factors contribute to the increased morbidity and mortality among hemodialysis patients.[4,7]

The pathophysiology of CKD-aP is multifactorial but remains incompletely understood. Dry skin or xerosis is suggested to be a major contributor. More current understanding points towards roles for the immune and neurogenic systems. It is hypothesized that CKD-aP is a manifestation of a deranged immune system that results in a proinflammatory state.[8,9]

Despite the high prevalence and increased morbidity of CKD-aP, to date, no drug has been approved by the U.S. Food and Drug Administration (FDA) for this condition. Most patients are not amenable to its definitive treatment, which is renal transplantation. Other therapeutic options are largely empirical, these include moisturizers, antihistamines, gabapentin/pregabalin, kappa-opioid agonists, capsaicin, gamma-linoleic acid, sertraline, mirtazapine, thalidomide, and UVB therapy. Gabapentin is the most studied therapeutic option, however, its side effects and cost limit its usage.[10,11,12] Also, dialysis patients of-

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ten have hesitations in taking oral medications. This highlights the need to explore an efficacious yet safe and readily available topical treatment option.

Curcuma longa, commonly known as turmeric, is one of the most common spices being used today. By tradition, it has been used as a flavoring and medicinal agent.[13,14] Curcumin, its principal active component, has been documented to inhibit major inflammatory mechanisms like lipoxygenase (LOX), cyclooxygenase (COX)- 2, tumor necrosis factor (TNF)- a, interferon (IFN)- λ, and nuclear factor (NF)-κB.[15,16] It has been granted a "Generally Recognized as Safe" (GRAS) status as a food ingredient by the US Food and Drug Administration.[17] A systematic review done by Vaughn et. al. concluded that both oral ingestion and topical application of turmeric/curcumin products may be used in the treatment of a variety of dermatologic diseases such as atopic dermatitis, acne, facial photoaging, alopecia, pruritus, and psoriasis. In a particular controlled study, patients applied either a combination cream containing turmeric, with saffron, sandalwood, and other ingredients, or a bland moisturizer for their pruritus. Both groups showed statistically significant improvement in the participants' subjective rating of pruritus.[18] A local randomized controlled trial done by Guevara et.al. comparing the efficacy and safety of turmeric 1% cream to clobetasol propionate 0.05% cream in the treatment of plaque-type psoriasis showed that topical application of turmeric 1% cream for four weeks reduced both psoriasis assessment severity index and pruritus scores, furthermore, no adverse effects were seen in the turmeric group.[19] The pharmacological efficacy and safety of curcumin makes it an interesting focus for the control of pruritus in hemodialysis patients compared to other drugs which have more side effects.[18,20]

OBJECTIVES

This study aimed to determine the efficacy and safety of turmeric 1% emollient cream versus a bland emollient in the reduction of chronic kidney disease-associated pruritus in hemodialysis patients.

Specifically, it aimed to determine and compare the improvement of chronic kidney disease-associated pruritus in both groups through evaluation of the following:

1. The proportion of patients who responded to treatment.
2. The mean pruritus scores from baseline and after treatment using a visual analogue scale (VAS) for pruritus and the 5D- itch scale.
3. The incidence of patient reported adverse events.

METHODOLOGY

RESEARCH DESIGN AND STUDY SETTING

This study was a randomized, double-blind, controlled trial of the effect of turmeric 1% cream in the reduction of chronic kidney disease associated pruritus in hemodialysis patients compared to a bland emollient (placebo). This study was carried out from September to November 2019 at the hemodialysis unit of Southern Philippines Medical Center (SPMC), Davao City, Philippines. The study was approved by the institution's research ethics committee and written informed consent was obtained from all its participants.

SAMPLING PROCEDURES, RANDOMIZATION, AND BLINDING

The study utilized purposive sampling procedures to select the participants who have chronic kidney disease-associated pruritus from the hemodialysis unit at SPMC. Face-to-face recruitment was done wherein the investigator interviewed and examined all hemodialysis patients to obtain participants for the study. Patients aged 18-75 years old, with pruritus visual analogue scale (VAS) score of more than or equal to 4, were included in the study. Those with hypersensitivity to any ingredients used in the study, use of specific pruritus treatments aside from cetirizine within the last week prior to starting the study, and severe hyperphosphatemia (phosphate levels greater than 14 mg/dL) were excluded from participating in the study.

The participants were randomly allocated to either group A (turmeric 1% emollient cream) or group B (bland emollient cream). Allocation was generated electronically from the website: http://www.randomization.com. The participants and the primary investigator were not aware of the sequence of group allocations done. The research assistant allocated the treatment to the patients following the random numbers in sequence of patients who were seen and evaluated to be eligible for the study. The turmeric 1% emollient cream, and the bland emollient cream were in identical containers labeled as A and B to blind the patients and the primary investigator. Likewise, the creams were similar in consistency, appearance, and smell. The primary investigator recruited and assessed the participants and gathered the data. The gathered data were analyzed by an independent statistician. The treatment allocation was disclosed to the investigator and the patients only at the end of the study.

SAMPLE SIZE COMPUTATION

Sample size for this study was computed using the online sample size calculator from powerandsamplesize.com with the assumption that the mean value of the outcome of group A is 61% +/- 19%. Estimation was done for the study to detect a 19% difference in outcome values between two groups. In the comparison of two means carried out at 5% level of significance, a sample size of 53 per group (total of 106 participants) was needed for the study to have 80% power.

INTERVENTIONS AND COMPARISONS

This study compared the efficacy of turmeric 1% emollient cream versus a bland emollient cream in reducing pruritus in

hemodialysis patients. Any medication with presumed antipruritic effects was discontinued one (1) week before the study. Both turmeric 1% emollient cream and the bland emollient cream was prepared by a local FDA-approved manufacturer compliant with local Good Manufacturing Practices (GMP). For the turmeric cream, the part used for the extract is the root. Purity of extract was ensured prior to compounding of the cream. The appearance, color, consistency, and smell were similar in both groups, and they were repackaged and labelled properly by a pharmacist into uniform 20-gram plastic containers (Figure 1). Cultures of the preparations were obtained to verify sterility of the creams.

Participants were instructed to apply their assigned cream, either turmeric 1% emollient cream or the bland emollient cream, to all involved body surfaces, twice a day, 12 hours apart, for four (4) weeks. Both groups were instructed by the research assistant on how to apply the cream. After application, participants were advised to avoid washing the area where the assigned creams were applied. Participants were instructed to bring the container on each follow-up visit to ensure compliance. The co-investigator inspected and weighed the contents of the containers. The amount that should have been used was evaluated by estimating the surface area involved (rule of hand). This was then used to calculate the number of fingertip units (FTU) that the patient used, in that 2% surface area is equivalent to 1 FTU which corresponds to 0.5 g.[21] The containers were refilled every follow-up as needed.

Participants were given cetirizine 10 mg/tab 1 tab once daily as standard of care for their pruritus. They were instructed to take a bath daily using mild soap and apply the creams after bathing. The same mild soap was given to all patients. Participants were also instructed to neither take nor apply any other medication during the study period.

DATA GATHERING

On day 1 (week 0), baseline demographic and clinical data (age, sex, duration of pruritus, body surface area involved, dialysis duration, dialysis frequency, and Kt/V), VAS, and 5D-itch scale scores were gathered by the primary investigator using a data collection form. Kt/V is a number used to quantify adequacy of hemodialysis treatment, with a level of > 1.2 being adequate. Treatment was started and patients were evaluated by the primary investigator at the end of week 2 and week 4. To assess pruritus, two (2) scoring systems were used, the VAS and the 5D-itch scale, which was obtained from an open-access document with permission to be utilized in this study.

Figure 1. Turmeric 1% emollient cream (A) and bland emollient cream (B).

The visual analogue scale (VAS) is a simple scoring system which uses a 10-cm long line on which the patients denote the intensity of their pruritus by marking the line at the point corresponding to their respective severity of pruritus. The leftmost portion of the scale refers to absence of pruritus (0) and the rightmost to the most severe pruritus imaginable to them (10). The method of categorization by Reich et. al. was used as reference when classifying the VAS score. Severity of pruritus was classified as: < 4 points, mild; ≥ 4 points but < 7 points, moderate; ≥ 7 points but < 9 points, severe; and ≥ 9 points, very severe pruritus.[22]

The 5-D itch scale is used for the multidimensional quantification of pruritus in clinical trials. This scale is sensitive to changes over time. The duration, degree, and direction are single-item domain scores, and is equivalent to the value below the respective response choice (range of 1 to 5). The sleep, social/leisure activities, errands/housework, and school/work domains are part of the disability domain that assess the impact of itching on daily activities. The score for this domain is attained by taking the highest score on any of the four (4) items. For the distribution domain, the number of affected body parts is tallied with a potential sum of 0 to 16. The sum is then sorted into five (5) scoring bins: the sum 0–2 is equivalent to 1, 3–5 is equivalent to 2, 6–10 to 3, 11–13 to 4, and 14–16 to 5. The scores of each of the five (5) domains will then be added together to obtain a total 5-D score. The potential range of 5-D scores is between 5, corresponding to no pruritus, and 25 corresponding to the most severe pruritus.[23]

Presence of adverse events such as pain, erythema, burning, pruritus, and scaling were asked and recorded. Classification of adverse event, if present, are as follows: mild if it results to mild or transient discomfort that does not require intervention or treatment and does not limit or interfere with daily activities; moderate if it is sufficiently discomforting to limit or interfere with daily activities and requires interventional treatment; severe if it results to significant symptoms that prevents normal daily activities and requires hospitalization or invasive intervention.

OUTCOME MEASURES

The primary outcome measure of the study was treatment response, measured by the proportion of subjects who demon-

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strated a reduction of >/= 50% in their VAS scores after four (4) weeks.[24] The secondary outcome measures were reduction in pruritus from baseline to week 4 in terms of mean VAS score per visit and mean 5D-itch scale scores per visit, and incidence of adverse effects (erythema, burning, pruritus, scaling) related to the treatments during the study period.

In case of adverse events, the investigator will give immediate and free medical treatment, and monitor accordingly. These study participants will be considered as withdrawals. But in this study, no adverse events were encountered.

DATA HANDLING AND ANALYSIS

Descriptive statistics was used to summarize the clinical characteristics of the patients. Mean and standard deviation were used to express the continuous variables, and frequency and percentage for categorical data. Comparative analysis among the categorical data was done using Chi-square test. Comparative analysis for two (2) groups was done using t-test for two independent means for continuous data and t-test for two proportion for categorical data. The comparative analysis using VAS and 5D itch scale also made use of t-test for two independent means.

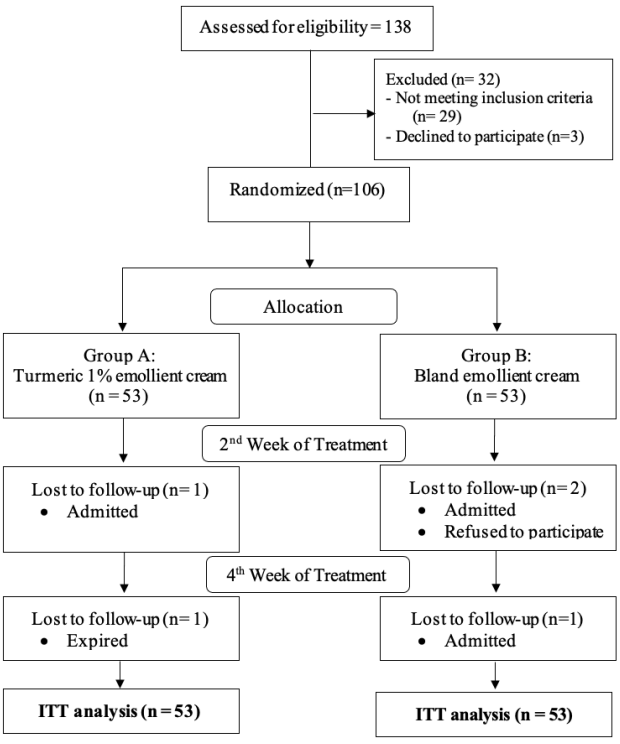

Figure 2. CONSORT diagram to show participant flow in the trial.

RESULTS

STUDY POPULATION

Among 138 hemodialysis patients assessed for eligibility, a total of 106 patients with CKD-aP who signed the consent and satisfied the inclusion criteria were enrolled and randomized into either turmeric 1% emollient cream or bland emollient cream group. Follow-up was done every two (2) weeks for four (4) weeks. Five (5) participants dropped out from the study, producing a drop-out rate of 5%. All participants were included in the analysis. The flow diagram is shown below in Figure 2. The baseline characteristics of the study population are summarized in Table 1. The result shows that in terms of age, sex, duration of pruritus, surface involved, dialysis duration, dialysis frequency, and Kt/V, there is no statistical difference seen, suggesting that both have the same baseline measurements among the parameters identified. Common areas affected reported by the participants were the back and forearms. Mean Kt/V for both groups were > 1.2, roughly indicating adequacy of hemodialysis treatment.

OUTCOME ANALYSIS

Comparison of pruritus scores using VAS in both groups at baseline and subsequent follow-up visits are shown in Table 2. The mean pruritus score between the two (2) groups did not differ significantly at baseline ($p = 0.953$), but after treatment the mean decrease in pruritus score of the group treated with turmeric was significantly greater than that of the bland emollient group ($p = 0.018$); the mean difference in pruritus scores before and after treatment in the turmeric group at four (4) weeks was 4.12 ± 2.17 vs. 3.14 ± 1.46 in the bland emollient group.

Comparative analysis of pruritus scores was also done using the 5D-itch scale as shown in Table 3. The mean pruritus score between the two (2) groups did not differ significantly at baseline ($p = 0.143$). There was a significant difference in 5D-itch scale scores from baseline and week 4 of treatment in the turmeric group (12.15 vs 7.51, $p < 0.01$); the same was also noted for

Table 1. Baseline Demographic Characteristics of Participants.

Characteristics	Turmeric 1% emollient cream	Bland emollient cream	p-value
Mean age ± SD, years	46.77±13.45	49.17±13.21	0.062
Sex, frequency (%)			0.171
Male	27(51%)	32(60%)	
Female	26(49%)	21(40%)	
Duration of pruritus (months), mean ± SD	37.09±27.87	38.47±31.45	0.645
Surface involved (%), mean +_ SD	21.31±6.9	20.21±6.89	0.100
Dialysis duration (months), mean ± SD	49.38±36.06	52.5±35.79	0.371
Dialysis frequency/ week	2.15±0.36	2.19±0.39	0.325
Kt/V, mean ± SD	1.81±0.26	1.77±0.27	0.187

Table 2. Comparison of Pruritus Score using VAS for the 2 Treatments at Week 0 and 4.

Total pruritus score	Turmeric 1% emollient cream	Bland emollient cream	p-value
Before trial	6.79±1.65	6.81±1.63	0.953
After trial	4.44±1.66	4.94±1.93	0.002
p-value	<0.01	<0.01	
Mean decrease VAS	4.12±2.17	3.14±1.46	0.018

Table 3. Comparison of Pruritus Score using 5D-itch scale for the 2 Treatments at Week 0 and 4.

Total pruritus score	Turmeric 1% emollient cream	Bland emollient cream	p-value
Before trial	12.15±2.8	12.77±3.17	0.143
After trial	7.51±1.84	8.9±2.5	<0.01
p-value	<0.01	<0.01	
Mean decrease 5D-itch	4.2±2.11	5.14±4.45	0.468

the bland emollient group (12.77 vs 8.9, $p < 0.01$). The mean pruritus score between the two groups differs significantly at week 4 ($p < 0.01$); however, there was no statistical difference noted in the mean decrease in their pruritus scores ($p = 0.468$).

When the efficacy of each cream was assessed by comparing the proportions of participants who achieved treatment success (>/= 50% reductions in VAS scores), outcomes in the turmeric group were superior to those in the bland emollient cream group. In the turmeric group, 66% (35/53) of participants had successful treatments, while in the bland emollient group, 45% (24/53) of participants improved. The Chi-square test for 2x2 tables revealed that there was a statistically significant difference between the two (2) groups ($p=0.031503$, $p <0.05$) (Table 3).

Computation of the relative risk reduction (RRR) for failed outcomes revealed that turmeric will improve VAS scores 37.93% more (RRR = 0.3793, 95% confidence interval [CI] 0.0283–0.6035) than bland emollient. The absolute risk reduction (ARR) was 20.75%, favoring turmeric (ARR = 0.2075, 95% CI 0.0187–0.3768). The number needed to treat (NNT) revealed that five (5) study participants were required to be treated with turmeric 1% emollient cream for four (4) weeks to demonstrate improvement.

Based on repeated interviews during follow-up in the study, the patients mentioned no minor or major adverse effects to both turmeric 1% and bland emollient cream.

DISCUSSION

CKD-aP is a common and bothersome condition affecting dialysis patients. It has a significant impact on the quality of life and physical comfort of these patients.[1,5] Our results have shown that turmeric 1% emollient cream reduces pruritus in patients with CKD-aP. A decrease in pruritus scores was seen in both the turmeric and bland emollient groups, however, there was a significant difference between the mean decrease in VAS scores

Table 4. Comparison of the therapeutic efficacy of turmeric 1% emollient cream versus bland emollient after 4 weeks (intention-to-treat analysis).

	Treatment success, >/= 50% reduction in VAS score (n, %)	Treatment failure, < 50% reduction in VAS score (n, %)	Total	P-value
Turmeric 1% emollient cream	35(66%)	18(34%)	53(100%)	0.031503
Bland emollient cream	24(45%)	29(55%)	53(100%)	

between the two (2) groups at the end of the study, in favor of turmeric. There was also a significant difference based on the proportion of participants who achieved treatment success, still in favor of turmeric. This study shows that turmeric 1% emollient cream is more efficacious than the bland emollient cream in reducing the severity of CKD-aP. The beneficial effect of turmeric on CKD-aP could be attributed to its anti-inflammatory property.

Xerosis is found in most CKD and dialysis patients, frequently contributing to the severity of their pruritus. This was evident in the patients included in the analysis of this study. The cornerstone of CKD-aP therapy is adequate skin hydration with aqueous cream emollient applied two to four times daily. Unfortunately, pruritus is often resistant to emollient therapy alone.[4,12] Included study participants also attest to this finding.

Several studies have shown that inflammation plays a major factor in the development of CKD-aP in hemodialysis patients. CKD-aP has been reported to be associated with elevated C-reactive protein (CRP) values and high levels of T-helper 1 cells, interleukin-6, and interleukin-2.8.[24,25] Therefore, treatments directed toward inhibiting this inflammatory process may be effective in the reduction of CKD-aP. Curcumin, the active component of turmeric, has been shown to shift cytokine profiles from the pro-inflammatory Th1 to the anti-inflammatory Th2 type. It has inhibitory effects on inflammatory cytokines like TNF-α, IL-1, IL -2, IL-6, IL-8, and IL-12, as well as, LOX, COX- 2, IFN-λ, and NF-κB.[16,18,26] As a result, turmeric may inhibit early steps of inflammation and modulate CKD-aP. In a double-blind placebo-controlled trial using turmeric in 500 mg capsules taken three (3) times a day for eight (8) weeks, Pakfetrat and colleagues found that the pruritus score and CRP values of the dialysis patients in their study significantly improved at the end of the trial with no noted adverse effects.[27] Our study further reinforces the role of turmeric in the treatment of pruritus in hemodialysis patients.

This study supports the idea that addition of a naturally occurring, inexpensive, and safe, anti-inflammatory agent, like turmeric, to a cream emollient can be used to reduce the severity of pruritus in patients with CKD-aP. No adverse reactions were reported in both arms of the study, although the possibil-

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ity that oral cetirizine may have contributed to the attenuation of pruritus that may have been brought about by application of turmeric cannot be excluded.

LIMITATIONS AND RECOMMENDATIONS

To the best of our knowledge, this is the first randomized, double-blind, controlled trial investigating and demonstrating the efficacy and safety of topical turmeric in reducing the severity of CKD-aP in hemodialysis patients. The result of this study adds to the existing literature on the use of medicinal plants in dermatology and serves as a basis to other researchers on conducting further studies on topical turmeric.

A limitation of this study is that although it has a relatively large sample size with adequate power, it was only done in a single center. Future multicenter randomized trials with a larger sample size would better establish the robustness of the results in this study. The 4-week duration of the treatment phase may not be enough to confirm long-term efficacy and safety of turmeric in hemodialysis patients. Extension of the study duration to 8 or 12 weeks is recommended. Lastly, although pruritus is inherently a subjective complaint, it may be prudent to measure biochemical inflammatory markers as well to assess and monitor attenuation of inflammation associated with CKD-aP.

CONCLUSION

Among hemodialysis patients diagnosed with CKD-aP, topical application of turmeric 1% emollient cream twice daily for four (4) weeks is a promising treatment approach in reducing the severity of CKD-aP. No adverse effects were associated with application of turmeric in this study.

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