Evaluation of Antipruritic Effect of Melatonin on Hemodialysis Patients with Uremic Pruritus, A Double-Blind, Randomized, Crossover Trial

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Original Paper

Introduction. Uremic pruritus (UP) is one of the major complaints in hemodialysis patients without specific treatment. Considering the antipruritic effect of melatonin in atopic dermatitis (AD) and similarities in mechanism between pruritus in AD and UP, this randomized clinical trial designed to evaluate the antipruritic effect of melatonin on hemodialysis patients with UP.

Methods. This multicenter double-blind randomized clinical trial was conducted among the hemodialysis patients with UP. Adult patients were randomly assigned to receive two capsules of melatonin 5 mg /d for a 2 weeks period, undergoing a 1 week washout period, and then two capsules of placebo for another 2 weeks period, or the reverse sequence. Visual Analogue Scale (VAS), % affected Body Surface Area (%BSA) and 12-Pruritus Severity Scale questionnaire (12-PSS) were measured before and after each of the three periods. A crossover analysis of variance adjusted by treatment, period and carryover effect was performed by STATA 14.

Results. Thirty-nine patients under hemodialysis (mean age of 55.08 ± 12.34 years) completed the study. Mean changes in VAS, 12-PSS, and %BSA after the interventions (melatonin vs. placebo, mean ± SD) were as follows, respectively: -3.21 ± 3.33 vs. -1.38 ± 2.23, -4.59 ± 5.22 vs. -2.08 ± 4.35, and -19.10 ± 30.31 vs. 4.64 ± 29.11 ($P < .05$). However, the statistical significance of the treatment effect from melatonin was observed, carryover and period effects were not significant ($P > .05$) for any of the main variables.

Conclusion. Based on to the preliminary results of this study, melatonin can be introduced as an effective drug for management of pruritus in uremic patients.

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INTRODUCTION

Uremic pruritus (UP) with a prevalence of 20 to 50% is one of the major complaints in patients who are undergoing hemodialysis.[1] The symptoms of UP are more disturbing at night.[2] UP has a negative effect on mood, sleep and daily functioning[3,4] besides correlates with poor outcome in survival of patients undergoing chronic hemodialysis.[5] Many mechanisms have been hypothesized to explain the unknown pathophysiology of UP, such as an increased C-reactive protein and other inflammatory cytokines (immune hypothesis), formation of calcium phosphate crystals, peripheral neuropathy,[6,7] and accumulation of

advanced glycation end products (AGES) in the stratum corneum.[8] Many pharmacological and non-pharmacological therapies have been used for UP relief, however, a curative treatment for UP has not been achieved so far.[9-11] Melatonin plays an important role in the regulation of the circadian rhythm and body temperature.[12] Another physiological effects are also defined for melatonin including antioxidant,[13] immune modulatory,[14] and analgesic effects.[15-7] Endogenous melatonin rhythm was increasingly compromised in relation to the degree of chronic kidney disease as a result of the suppression of serotonin *N*-acetyltransferase (NAT) synthesis (the main enzyme involved in the production of melatonin).[18] Additionally, based on animal studies, melatonin has the protective effect on renal mesenchymal cells against p-Cresol, a uremic toxin with cytotoxic effects by induction of autophagy actions.[19] Some clinical trials have showed that the administration of melatonin has anti-inflammatory effects and can decrease pruritus in atopic dermatitis and improve the quality of sleep in pediatric population.[20,21] Another study reported that melatonin may have a positive role in treatment of nocturnal pruritus by immunomodulatory effect.[22] Alongside this effect, the safety profile of exogenous melatonin has been accepted in a systematic review.[23]

Finally, because of similarities in the pattern and mechanism between induced pruritus in atopic dermatitis and UP, also melatonin positive consequences on neuropathy, endothelial progenitor cells against AGE,[24] inflammatory reaction, uremic toxin, sleep disorder experienced by uremic patients, it is hypothesized that melatonin can subside UP. The aim of this randomized clinical trial was to evaluate the antipruritic effect of melatonin on hemodialysis patients with UP.

MATERIALS AND METHODS

Participants and Study Design

This multicenter randomized controlled clinical trial was performed as a "two treatments – two periods" (2 × 2) double-blind crossover study from July 20th 2018 through January 30th 2019. Participants were hemodialysis patients with UP that referred to the Dialysis Department of Imam Khomeini Hospital and Ghiasi Hospital Specialty Center affiliated with Tehran University of Medical Sciences (TUMS), Labbafinezhad Hospital affiliated with Shahid Beheshti University of Medical Sciences (SBUMS) in Tehran, Iran. All hemodialysis patients who enrolled in this study were 18 years and older with at least a history of hemodialysis (trice weekly) for more than 3 months. The exclusion criteria included lactation and pregnancy, a history of seizure, using anticonvulsant, anticoagulant and / or immunosuppressant medications,[25] having a skin condition with pruritus, liver diseases that cause pruritus,[26,27] cancer, mean arterial pressure < 65 mmHg, and hypersensitivity to melatonin.[28,29] A signed written consent was obtained from all participants. The study protocol was approved by the medical ethics committee of TUMS (IR.TUMS.TIPS.REC.1397.040) and the trial was registered in the Iranian Registry of Clinical Trials (IRCT20180714040462N1).

Allocation and Blinding

Participants were allocated to receive treatment in the sequence of placebo / melatonin or melatonin / placebo using block randomization with a block size of 4. Both patients and researchers were blinded to the order and treatment received in each period. The shape, appearance, size and package of melatonin and placebo capsules were the same. The drug and placebo were coded into A and B by the executer.

Intervention

Three periods were designed in this study. In the first period, eligible patients were randomly assigned to two sequences; melatonin / placebo (AB) or placebo / melatonin (BA). In this period, each patient in the AB group received two soft gel capsules of 5mg melatonin[15] (made by NUTRALAB, Canada and filled into soft gel capsules by Zahravi Pharmaceutical Company, Iran) after dinner, and the BA group received two soft gel capsules of placebo (order by Zahravi Pharmaceutical company, Iran) after dinner. The second period included a washout period of 1 week and in the third period, patients who had received melatonin or placebo switched to the other intervention. The duration of the first and second periods was 2 weeks. During this study, baseline antipruritic medications taken by patients were continued the same as before without any change. The flowchart of patients' recruitment and assignment is shown in Figure 1.

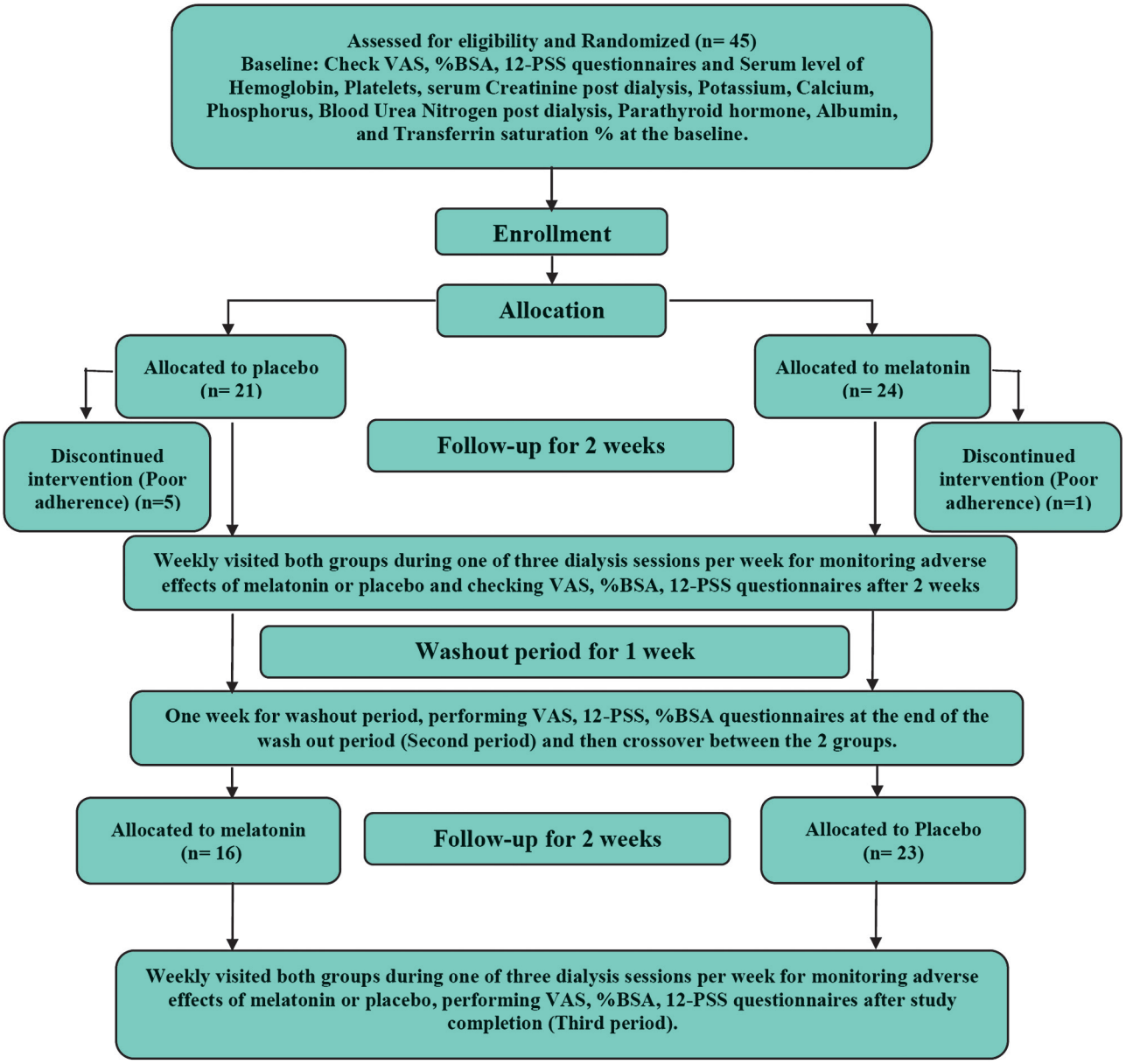

Figure 1. Flowchart of Participant Recruitment and Assignment

Outcomes

The status of pruritus was determined by three different tools including a Visual Analogue Scale (VAS),[30,31] affecting Body Surface Area (%BSA)[32] and 12-Item Pruritus Severity Scale (12-PSS).[33]

The 12-PSS questionnaire has five domains including pruritus intensity (PI), pruritus effect on mood (POM), scratching assessment as a response to pruritus (SA), pruritus extent (PE) as well as frequency and duration of pruritus (FRP). Sleep quality as a qualitative outcome was evaluated by question 9 of the 12-PSS questionnaire, deciding whether patients had frequent awakening episodes during their sleep hours.[33] The 12-PSS questionnaire was not translated to Farsi (Persian) before this study. According to Beaton's intercultural adaptation principles, the validity and reliability of the confirmed Farsi questionnaire were investigated.[34]

The internal consistency (Cronbach's alpha) of the 12-PSS was found to be 0.88.

Another outcome to evaluate the patient's pruritus status was the %BSA based on the severity scoring of atopic dermatitis (SCORAD).[32] Patients were asked to report any new or adverse events that could

be due to complications of melatonin or placebo. Reported complications were evaluated using the Naranjo adverse drug reaction probability scale.[35] Compliance with medication regimens was defined as at least 80% adherence to therapy.[36] Periodic visit of patients (at least twice per week for dialysis sessions), social media applications (e.g., telegram and WhatsApp without compromising confidential patient information), as well as phone calls / text messages were used to follow up patients during and following completion of each treatment period.

Baseline Characteristics

At the baseline, patients' demographic data including age (year), sex, weight (kg) and patients clinical conditions consisted of dialysis duration and quality (kt/v),[37] type of medication and other related illnesses were recorded. In addition, laboratory factors including serum levels of hemoglobin, platelets, post dialysis serum creatinine and blood urea nitrogen, potassium, calcium, phosphorus, parathyroid hormone, albumin and transferrin saturation percent at the baseline were measured.

Statistical Analysis

Sample size was calculated based on a statistical power of 90% and a type one error rate of 5% for detecting at least an effect size of 2 for VAS as the study's main outcome. We predicted a 10% drop out rate, which was calculated to be 45. Normality of continuous data was evaluated using the Kolmogorov–Smirnov test and a Q-Q plot. Continuous data were reported as mean ± standard deviation (SD) with categorical data as frequency (percentages). Baseline characteristics between the two sequences were compared using a chi-square test for qualitative variables and a two-sample independent t-test or ranked Mann-Whitney test for quantitative variables. These statistical tests were conducted using SPSS 20.

To investigate treatment effects on pruritus reduction, changes in outcomes (VAS, %BSA and 12-PSS score and its domains) in the first period from baseline and in the second period from the 3rd week (after washout) were considered as response variables. The effect of melatonin was compared with placebo in a 2 × 2 crossover analysis of variance approach including period and carryover (treatment-by-period interaction) effects. A separate analysis was done for each outcome. A crossover analysis was conducted by STATA14 (Stata Corp. 2015. The effects of sex and medication history on melatonin effect were analyzed in a crossover analysis of variance which included interaction effects of these variables by treatment. Mean changes of VAS score in different categories of baseline VAS as pruritus severity were also compared using one sample t- test. Laboratory factors at baseline and the end-of-the study were compared using paired sample t-test. Sleep quality before and after the intervention was compared using the McNemar test between placebo and melatonin groups. We also investigated the effectiveness of melatonin on decreasing the severity of pruritus measured by VAS through performing an equivalence test and calculating the number needed to treat (NNT) index.[38] A minimum reduction of 2 units in VAS score was considered as an efficient response to treatment by melatonin[39] and a .05 significance probability was considered for all analyses.

RESULTS

Subject Disposition

During this study, six participants discontinued the trial and were excluded from the study due to poor compliance. Overall, 23 participants remained in the melatonin/placebo sequence and 16 participants remained in the placebo/melatonin sequence and completed the study. More details are presented in the flow diagram depicted in Figure 1.

Subject Characteristics

The mean age of participants was 55.08 ± 12.34, ranging from 30 to 70 years. All baseline characteristics of participants are summarized in Table 1.

VAS, %BSA, and 12-PSS

In the performed crossover analysis, treatment effect was adjusted for period and carryover effect. Carryover effect and period effects were not statistically significant in any of the performed models for measuring pruritus, including VAS, %BSA, and 12-PSS ($P > .05$), however the treatment effect of melatonin was significant for mentioned variables (Table 2).

Figure 2 illustrates the mean changes in the main outcomes before and after interventions.

Based on the equivalence paired t-test, on average, melatonin significantly decreased VAS

Table 1. Baseline Characteristics of Participants Assigned to the Two Sequences of Intervention

Variable	Sequence 1	Sequence 2	*P*
	Melatonin / Placebo	Placebo / Melatonin	
Number (%)	23	16	
Age, y	54.52 ± 13.00	55.88 ± 11.70	> .05[c]
Sex			
Female	16 (69.20)	2 (12.50)	< .001[c]
Male	7 (43.75)	14 (87.50)	< .001[c]
Baseline of Visual Analogue Scale	8.56 ± 2.00	6.63 ± 1.93	< .001[a]
Mild (≤ 3)	1 (4.30)	2 (12.50)	> .05[c]
Moderate (4 to 6)	5 (21.70)	7 (43.80)	
Sever (7 to 8)	2 (8.70)	4 (25.0)	
Very Sever (9 to 10)	15 (65.20)	3 (18.80)	
Baseline of Body Surface Area (%)	36.61 ± 25.39	45.65 ± 36.69	> .05[a]
Baseline of 12- Pruritus Severity Scale	14.18 ± 2.21	12.31 ± 3.55	> .05[a]
Dialysis Durations, y	3.89 ± 4.06	10.00 ± 10.13	> .05[a]
One of ESRD Etiology			
Hypertension	15 (62.50)	8 (56.50)	> .05[c]
Diabetes Mellitus	13 (56.50)	5 (31.30)	> .05[c]
Other Causes	4 (17.40)	9 (56.30)	< .05[c]
Baseline Anti-pruritus Medicine			
Gabapentin	5 (21.70)	3 (18.80)	> .05[c]
Hydroxyzine	0	1	> .05[c]
Sertraline	1 (4.3)	0	> .05[c]
Ketotifen	1 (4.3)	0	> .05[c]
Hemoglobin, g/dL	11.00 ± 1.17	10.44 ± 1.41	> .05[a]
Platelets, 1000/μL	218.87 ± 50.32	180.44 ± 87.09	> .05[a]
Serum Creatinine, mg/dL	8.52 ± 2.35	7.19 ± 3.60	> .05[a]
Potassium, meq/L	5.26 ± 0.69	5.13 ± 0.89	> .05[b]
Calcium, mg/dL	8.22 ± 0.52	8.56 ± 0.96	> .05[b]
Phosphorus, mg/dL	5.78 ± 1.13	6.19 ± 1.87	> .05[b]
Blood Urea Nitrogen, mg/dL	41.39 ± 10.22	44.00 ± 9.87	> .05[a]
Albumin, g/dL	3.83 ± 0.39	4.06 ± 0.25	> .05[b]
Parathyroid Hormone, pg/mL	490.52 ± 327.94	382.13 ± 267.82	> .05[b]
Iron, μg/dL	68.57 ± 40.23	48.88 ± 15.14	> .05[b]
Total Iron-binding Capacity, μg/dL	270.78 ± 49.05	250.31 ± 142.21	> .05[a]
Transferrin Saturated (%)	24.61 ± 11.70	22.50 ± 9.11	> .05[a]
Kt/v	1.17 ± 0.39	1.38 ± 0.50	> .05[a]

Mean ± SD for quantitative variables, number (%) for qualitative variables
[a] Resulted from Two Sample Independent t-test
[b] Mann -Whitney rank test
[c] Chi-square test

score by at least 2 units ($P < .05$). In contrast, this was not observed with placebo ($P > .05$).

The NNT obtained was 3.32 (CI 95%: 1.67 to 166.76), denoting that approximately one out of 3 patients will benefit from treatment with melatonin.

The study outcomes (VAS, %BSA and 12-PSS) were not influenced by the baseline antipruritic medications ($P > .05$).

There was no statistically significant difference in the magnitude of antipruritic response seen in patients with mild to moderate VAS scores (-1.50 ± 4.37) compared to those with severe to very severe baseline VAS scores (-4.41 ± 3.39) ($P > .05$). The study power to detect a 2 units differences of VAS score was 96%.

Sleep Quality

An improvement in sleep quality was found in 55% (11/20) of patients after melatonin intake. In contrast, 18.8% (3/16) of patients reported an improvement in their sleep quality after treatment with placebo ($P < .05$).

Sex Disparities in Treatment Effect

The interaction effect of treatment and sex on

Table 2. Comparative Effects of Melatonin and Placebo on Measures of Pruritus

	Mean Difference (SD) in Sequence 1 (Melatonin / Placebo)		Mean Difference (SD) in Sequence 2 (Placebo / Melatonin)		*P*		
	Period 1 (Melatonin)	Period 2 (Placebo)	Period 1 (Placebo)	Period 2 (Melatonin)	Period Effect	Melatonin Effect	Carryover Effect
VAS	-3.65 ± 3.80	-1.30 ± 2.36	-1.50 ± 2.10	-2.56 ± 2.50	> .05	< .05*	> .05
%BSA	-18.65 ± 32.68	-9.30 ± 33.01	-2.06 ± 21.62	-19.75 ± 27.56	> .05	< .001*	> .05
12-PSS	-5.43 ± 5.81	-1.43 ± 4.67	-3.00 ± 3.79	-3.38 ± 4.10	> .05	< .05*	> .05
PI	-1.87 ± 2.18	-0.39 ± 1.50	-0.94 ± 1.39	-1.38 ± 1.59	> .05	< .05*	> .05
POM	-1.17 ± 1.19	-0.74 ± 1.21	-0.44 ± 0.81	-0.44 ± 0.73	> .05	> .05	< .05
SA	-0.78 ± 1.65	-0.09 ± 1.44	-0.63 ± 0.96	-0.69 ± 1.08	> .05	> .05	> .05
PE	-0.70 ± 0.76	0.00 ± 1.17	-0.50 ± 0.89	-0.44 ± 0.73	> .05	> .05	> .05
FRP	-1.00 ± 1.04	-0.22 ± 0.67	-0.50 ± 0.73	-0.44 ± 0.96	< .05	> .05	> .05

*Significant at the level of .05.
Abbreviations: SD, standard deviation; VAS, visual analogue scale; %BSA, %body surface area; 12-PSS,12-item pruritus severity scale; FRP, frequency and duration of pruritus (question 1 from 12-PSS); PE, pruritus extent (question 11 from 12-PSS); PI, pruritus intensity (sum of questions 9 and10); POM, pruritus effect on mood (sum of questions 2, 3, 4 and 5); SA, scratching assessment as a response to pruritus (sum of questions 6, 7, 8 and 12).

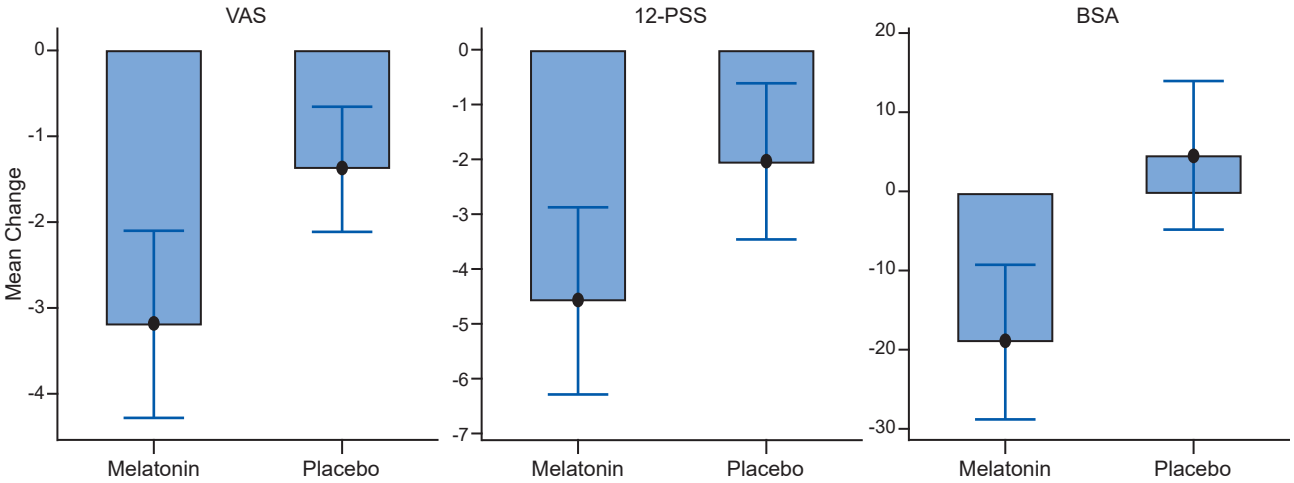

Figure 2. Mean changes (95% CI) in VAS, 12-PSS score, and %BSA after the interventions (melatonin vs. placebo, mean ± SD) were as follows; respectively: -3.21 ± 3.33 vs. -1.38 ± 2.23, -4.59 ± 5.22 vs. -2.08 ± 4.35, -19.10 ± 30.31 vs. 4.64 ± 29.11 (P < .05). (Abbreviations: VAS, visual analogue scale; %BSA, %body surface area; 12-PSS: 12-pruritus severity scale)

Table 3. Mean of Changes of Outcomes by Sex Groups Before and After of Intervention

	Females		Males		*P* for Interaction *
	Melatonin	Placebo	Melatonin	Placebo	
VAS	-4.78 ± 2.88	-1.44 ± 2.62	-1.86 ± 3.15	-1.33 ± 1.91	< .05
%BSA	-18.28 ± 32.9	-3.61 ± 10.24	-19.81 ± 28.71	11.71 ± 37.52	< .05
12-PSS	-6.78 ± 5.28	-1.72 ± 4.97	-2.71 ± 4.48	-2.38 ± 3.84	> .05

*Significant at the level of .05.
Abbreviations: SD, standard deviation; VAS, visual analogue scale; %BSA, %body surface area; 12-PSS, 12-pruritus severity scale.

pruritus is reported in Table 3.

Safety Report (Adverse Events / Drug Reactions)

Adverse events were reported during treatment with melatonin which included hot flashes in 2 male patients with a Naranjo Casualty as possible, decreased libido in 1 male with a Naranjo Casualty as doubtful, and Nightmare in 1 female with Naranjo Casualty as possible. No adverse events were observed with placebo intake. No adverse events lead to withdrawal from the study.

DISCUSSION

Based on the aforementioned mechanisms that may explain the antipruritic effects of

melatonin,[16,24,40] this pilot clinical trial was designed to investigate its use in patients with UP. According to our search in PubMed and Scopus, there were no published animal or human studies on this subject, therefore we could not compare and contrast our results to similar studies.

Antipruritic Effect

This trial's results showed a beneficial and significant decrease in itching intensity, severity, extension and duration with melatonin compared with placebo by reducing VAS score, %BSA and 12-PSS in patients with UP ($P < .05$).

The results showed that melatonin alleviated VAS score by 3.21 ± 3.33 units compared to 1.38 ± 2.23 units in the placebo arm, with 26 (66.7%) of patients achieving the study goal (a decrease of at least 2 units in VAS score).

Many studies have investigated the efficacy of drugs with different mechanism of action on UP in hemodialysis patients, including, Gabapentin,[41] Desloratadine,[39] Pregabalin, Doxepin,[42] Naltrexone,[43] Sertraline,[44] and Montelukast.[45] These trials were crossover[39,43] or parallel[42,44,45] in design, and shared the use of VAS for evaluating the severity of itching and therapeutic response, which is similar to our study. Based on the results of the equivalence test from our study, the VAS score decreased by an average of at least 2 units after taking melatonin as the goal of study ($P < .05$). In contrast, this response was not noted in the placebo group ($P > .05$). Only in the crossover study conducted by Marquez *et al.*, a 2 units decrease in VAS score was considered as a measurement of therapeutic response, which was found to be significant for Desloratadine ($P < .05$), but not for Gabapentin ($P > .05$).[39] Although the treatment periods in other crossover or parallel studies referenced above were between 1 to 8 weeks, a 2-week study duration was considered for each sequence in this study with a 1-week washout period, giving us a total study duration of 5 weeks. Given that the period effect was not significant ($P > .05$) for any of the main variables in the modeling of this study (VAS, %BSA and 12-PSS), the adequacy of the crossover design time can be confirmed.

However, in our study, the statistical significance of the treatment effect from melatonin was evaluated by adjusting for period and the carryover effects. The carryover effect in this model was not significant ($P > .05$) for any of the main variables studied (VAS, %BSA and 12-PSS), which could possibly be explained by the sufficient washout period considered for clearing the effect of melatonin from the first period – a predictable result given the half-life of melatonin.[12] Based on the onset of treatment effect for melatonin,[12] we expected to see a therapeutic response within two weeks or even less. This is one of the advantages of melatonin compared with other slow-acting medications such as Sertraline, which has demonstrated antipruritic effects after 4 weeks.[44] The average change in the 12-PSS with melatonin was -4.59 ± 5.22 units, which is a significantly larger decrease compared with placebo (-2.08 ± 4.35). This effect was also significant on PI which is one of the 12-PSS domains ($P < .05$), however, the impact of melatonin on other domains of the 12-PSS questionnaire was not statistically significant ($P > .05$).

It is worth noting that relief from itching should be accompanied by a concurrent decrease in the affected area.(46) Melatonin decreased %BSA by an average of 19.10 ± 30.31, while the %BSA score with placebo was increased by an average of 4.64 ± 29.11. The %BSA and 12-PSS scores were not reported for other antipruritic agents studied for UP.[39,41-45] Another result from our data showed that patients with more severe baseline itching according to the VAS score did not experience significant reduction in their mean VAS score following melatonin intake compared with mild and moderate itching ($P > .05$). Therefore, the severity of baseline pruritus does not pose any limitations in using melatonin as an antipruritic agent. Among previous studies investigating UP which were mentioned earlier, none have considered the effect from the severity of baseline pruritus on the effectiveness of antipruritic agents.

Sleep Quality

In this study, melatonin resulted in a 55% decrease in waking periods during the night, which was significant ($P < .05$) compared to placebo (18.8%). Melatonin is known as an effective medicine for improving the onset, quality and duration of sleep.[47] In one study, it was shown that melatonin has a positive effect on the treatment of nocturnal pruritus and sleep quality, especially in the elderly.[22]

The Melody study examined the effect of a 3-mg daily dose of melatonin on sleep and quality of life

in hemodialysis patients compared with placebo, which demonstrated the short-term positive effects of melatonin on these outcomes.[48] These findings support our results. One explanation for this observation is that melatonin alleviated the intensity of itching during the night; therefore, prescribing a medication that could target both sleep pattern and pruritus would be favorable.

None of these studies independently noted evaluation of treatment effect from antipruritic medications on sleep quality, however, in the study by Tol *et al.*, the treatment effect of Gabapentin on pruritus, quality of life and sleep were assessed in hemodialysis patients. In this crossover study which was conducted on 14 patients, the severity of pruritus was assessed by using VAS and sleep quality was evaluated with the Post Sleep Inventory (PSI) questionnaire, where the PSI score significantly decreased from 5.3 ± 3.8 to 1.8 ± 1.8 following treatment completion.[49]

Sex Disparities in Treatment Effect

In our study, the effect of melatonin on relieving pruritus based on the VAS score was significantly higher in women (-4.78 ± 2.88) compared to men (-1.86 ± 3.15) ($P < .05$). Mean changes in %BSA showed that placebo significantly worsened the status of pruritus in men compared to women) -3.61 ± 10.241 vs. 1.71 ± 37.52, $P < .05$). Other outcomes showed no significant difference in the effect of melatonin between the two sexes ($P > .05$).

The greater efficacy of melatonin observed in the women from this study can be explained by considering the results of a review article on antipruritic medications from 2019.[50] In the studies reviewed in this article, plasma levels of a number of medications with antipruritic properties are reported to be higher in women compared to men. In explaining this observation, differences in epidermal tissues, distribution of sex-dependent receptors, and reduced expression of P-glycoprotein in women are noted.

This is while a narrative review has not shown any differences in the pharmacokinetic and pharmacodynamic properties of drugs between the two sexes while evaluating the effect of medications in the treatment of pruritus associated with chronic kidney disease. Furthermore, the efficacy of gabapentin was found to be equal in men and women, while the incidence of adverse events with pregabalin (e.g., drowsiness, dizziness, and constipation) was higher in female patients under age 50 compared to others.[50]

Safety Report (Adverse Events / Drug Reactions)

During this study, 4 out of 39 patients (10.26%) experienced adverse events, which decreased with the continued use of melatonin with the exception of nightmares. The main safety concern was daytime drowsiness considering the dose of melatonin, which was fortunately not reported in our patients.

Given the prevalence of adverse effects from melatonin in our study (which was comparable to its previously reported safety profile),[23] as well as its comparison to adverse effects from other antipruritic agents used for UP,[10] melatonin can be recommended as a safe medication for this indication (UP).

CONCLUSION

Finally, the results of this study revealed that melatonin has a positive effect on UP in patients undergoing hemodialysis, in addition to improvement the patient's quality of sleep. Given its acceptable safety profile, melatonin can be introduced as an effective pharmacological agent for the management of UP, however, further clinical trials with larger sample size are necessary to confirm this novel effect of melatonin.

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REFERENCES

1. Scherer JS, S.A. Combs, and F. Brennan,. Sleep disorders, restless legs syndrome, and uremic pruritus: diagnosis and treatment of common symptoms in dialysis patients. American Journal of Kidney Diseases,. 2017;69:9.
2. Prasad P, Kaviarasan P, Nethra T. Kannambal Uremic pruritus-a review. Glob Dermatol. 2015;2:218-24.
3. Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, et al. Pruritus in haemodialysis patients: International results from the Dialysis Outcomes and

Practice Patterns Study (DOPPS). Nephrology Dialysis Transplantation. 2006;21(12):3495-505.

4. Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. Clinical Journal of the American Society of Nephrology. 2010;5(8):1410-9.
5. Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, et al. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. Kidney international. 2006;69(9):1626-32.
6. Mettang T, Kremer AE. Uremic pruritus. Kidney Int. 2015;87(4):685-91. Epub 2014/01/10. doi: 10.1038/ki.2013.454. PubMed PMID: 24402092.
7. Heisig M, Reich A, Szepietowski JC. Is uremic pruritus still an important clinical problem in maintenance hemodialysis patients? J Eur Acad Dermatol Venereol. 2016;30(12):e198-e9. Epub 2015/12/01. doi: 10.1111/jdv.13524. PubMed PMID: 26616469.
8. Attia EA, Hassan AA. Uremic pruritus pathogenesis, revisited. Arab journal of nephrology and transplantation. 2014;7(2):91-6.
9. Mettang T. Uremic itch management. Itch-Management in Clinical Practice. 50: Karger Publishers; 2016. p. 133-41.
10. Simonsen E, et al. Treatment of uremic pruritus: a systematic review. American Journal of Kidney Diseases,. 2017;70:17.
11. Lugon JR. Uremic pruritus: a review. Hemodialysis international. 2005;9(2):180-8.
12. Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, et al. Melatonin: pharmacology, functions and therapeutic benefits. Current neuropharmacology. 2017;15(3):434-43.
13. Sánchez A, Calpena A, Clares B. Evaluating the oxidative stress in inflammation: role of melatonin. International journal of molecular sciences. 2015;16(8):16981-7004.
14. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. Endocrine. 2005;27(2):189-200.
15. Danilov A, Kurganova J. Melatonin in Chronic Pain Syndromes. Pain Ther. 2016;5(1):1-17. Epub 2016/03/18. doi: 10.1007/s40122-016-0049-y. PubMed PMID: 26984272; PubMed Central PMCID: PMCPMC4912970.
16. Negi G, Kumar A, Sharma SS. Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-κB and Nrf2 cascades. Journal of pineal research. 2011;50(2):124-31.
17. Giram PS, Upasani C, Bhusnure OG. Recent and Emerging Trends in Treatment of Diabetic Patients with Peripheral Neuropathic Pain (PNP). 2016.
18. Koch BC, Van der Putten K, Van Someren EJ, Wielders JP, Ter Wee PM, Nagtegaal JE, et al. Impairment of endogenous melatonin rhythm is related to the degree of chronic kidney disease (CREAM study). Nephrology Dialysis Transplantation. 2009;25(2):513-9.
19. Yun SP, Han Y-S, Lee JH, Kim SM, Lee SH. Melatonin rescues mesenchymal stem cells from senescence induced by the uremic toxin p-cresol via inhibiting mTOR-dependent autophagy. Biomolecules & therapeutics. 2018;26(4):389.
20. Chang YS, Lin MH, Lee JH, Lee PL, Dai YS, Chu KH, et al. Melatonin Supplementation for Children With Atopic Dermatitis and Sleep Disturbance: A Randomized Clinical Trial. JAMA Pediatr. 2016;170(1):35-42. Epub 2015/11/17. doi: 10.1001/jamapediatrics.2015.3092. PubMed PMID: 26569624.
21. Boozalis E, Grossberg AL, Puttgen KB, Cohen BA, Kwatra SG. Itching at night: A review on reducing nocturnal pruritus in children. Pediatr Dermatol. 2018;35(5):560-5. Epub 2018/06/27. doi: 10.1111/pde.13562. PubMed PMID: 29943835.
22. Patel T, Y. Ishiuji, and G. Yosipovitch,. Nocturnal itch: why do we itch at night? Acta dermato-venereologica. 2007;87:3.
23. Foley HM, Steel AE. Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. Complementary therapies in medicine. 2018.
24. Jin H, Zhang Z, Wang C, Tang Q, Wang J, Bai X, et al. Melatonin protects endothelial progenitor cells against AGE-induced apoptosis via autophagy flux stimulation and promotes wound healing in diabetic mice. Experimental & molecular medicine. 2018;50(11):154.
25. Papagiannidou E, Skene DJ, Ioannides C. Potential drug interactions with melatonin. Physiology & behavior. 2014;131:17-24.
26. Bunchorntavakul C, Reddy KR. Pruritus in chronic cholestatic liver disease. Clinics in liver disease. 2012;16(2):331-46.
27. Garden JM, Ostrow JD, Roenigk HH. Pruritus in hepatic cholestasis: pathogenesis and therapy. Archives of dermatology. 1985;121(11):1415-20.
28. Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, et al. Melatonin reduces night blood pressure in patients with nocturnal hypertension. The American journal of medicine. 2006;119(10):898-902.
29. Cheng C, Gooneratne NS, Payton C, Keith S, Hafycz J. Abstract P308: Pilot Study: 24 Hour and Daytime Blood Pressure Lowering Effect of Melatonin in Younger and Older Non-hypertensive Adults. Hypertension. 2016;68(suppl_1):AP308-AP.
30. Ständer S, Augustin M, Reich A, Blome C, Ebata T, Phan NQ, et al. Pruritus assessment in clinical trials: consensus recommendations from the International Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. Acta dermato-venereologica. 2013;93(5):509-14.
31. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta dermato-venereologica. 2012;92(5):497-501.
32. Schallreuter K, Levenig C, Berger J, Umbert J, Winkelmann R, Wegener L, et al. Severity scoring of atopic dermatitis: the SCORAD index. Dermatology. 1993;186(1):23-31.
33. Reich A, Bożek A, Janiszewska K, Szepietowski JC. 12-Item Pruritus Severity Scale: Development and Validation of New Itch Severity Questionnaire. BioMed research international. 2017;2017.
34. Gjersing L, Caplehorn JR, Clausen T. Cross-cultural

adaptation of research instruments: language, setting, time and statistical considerations. BMC medical research methodology. 2010;10(1):13.

35. Naranjo C, Busto U, Sellers E, Sandor P, Ruiz I, Roberts E. Naranjo ADR probability scale. Clin Pharmacol Ther. 1981;30:239-45.
36. Verma D, Hashim OH, Jayapalan JJ, Subramanian P. Effect of melatonin on antioxidant status and circadian activity rhythm during hepatocarcinogenesis in mice. Journal of cancer research and therapeutics. 2014;10(4):1040.
37. Hakim R, Depner T, Parker III T. Adequacy of hemodialysis. American journal of kidney diseases. 1992;20(2):107-23.
38. Moore A, McQuay HJ. What is an NNT?: Hayward Medical Communications; 1997.
39. Marquez D, Ramonda C, Lauxmann JE, Romero CA, Vukelic VL, Martinatto C, et al. Uremic pruritus in hemodialysis patients: treatment with desloratidine versus gabapentin. Brazilian Journal of Nephrology. 2012;34(2):148-52.
40. Slomski A. Melatonin to Improve Skin and Sleep in Pediatric Dermatitis. Jama. 2016;315(8):742-.
41. Lau T, Leung S, Lau W. Gabapentin for uremic pruritus in hemodialysis patients: a qualitative systematic review. Can J Kidney Health Dis. 2016;3:14. Epub 2016/03/30. doi: 10.1186/s40697-016-0107-8. PubMed PMID: 27022475; PubMed Central PMCID: PMCPMC4809033.
42. Foroutan N, Etminan A, Nikvarz N, Shojai Shahrokh Abadi M. Comparison of pregabalin with doxepin in the management of uremic pruritus: a randomized single blind clinical trial. Hemodialysis International. 2017;21(1):63-71.
43. Peer G, Kivity S, Agami O, Fireman E, Silverberg D, Blum M, et al. Randomised crossover trial of naltrexone in uraemic pruritus. The Lancet. 1996;348(9041):1552-4.
44. Pakfetrat M, Malekmakan L, Hashemi N, Tadayon T. Sertraline can reduce uremic pruritus in hemodialysis patient: A double blind randomized clinical trial from Southern Iran. Hemodialysis International. 2018;22(1):103-9.
45. Mahmudpour M, Roozbeh J, Raiss Jalali GA, Pakfetrat M, Ezzat Zadegan S, Sagheb MM. Therapeutic Effect of Montelukast for Treatment of Uremic Pruritus in Hemodialysis Patients. Iran J Kidney Dis. 2017;11(1):50-5. Epub 2017/02/09. PubMed PMID: 28174353.
46. Weisshaar E, Gieler U, KUpFER J, Furue M, Saeki H, YOSIpOVITCH G. Questionnaires to assess chronic itch: a consensus paper of the special interest group of the International Forum on the Study of Itch. Acta dermato-venereologica. 2012;92(5):493-6.
47. Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, et al. Effects of exogenous melatonin on sleep: a meta-analysis. Sleep medicine reviews. 2005;9(1):41-50.
48. Russcher M, Koch BC, Nagtegaal JE, van Ittersum FJ, Pasker-de Jong PC, Hagen EC, et al. Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (M elody study): a randomized controlled trial. British journal of clinical pharmacology. 2013;76(5):668-79.
49. Hüseyin T, ATALAY H, GÜNEY İ, GÖKBEL H, ALTINTEPE L, BÜYÜKBAŞ S, et al. The Effects of Gabapentin Therapy on Pruritus, Quality of Life, Depression and Sleep Quality in Pruritic Hemodialysis Patients. Balkan Medical Journal.2010(2).
50. Schmid Y, Navarini A, Thomas Z-RM, Pfleiderer B, Krähenbühl S, Mueller SM. Sex differences in the pharmacology of itch therapies—a narrative review. Current opinion in pharmacology. 2019;46:122-42.

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