Original Article

Comparison of exogenous melatonin versus placebo on sleep efficiency in emergency medicine residents working night shifts: A randomized trial

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BACKGROUND: Sleep deprivation resulting from night shifts, is a major cause of burnout among physicians. Exogenous melatonin may improve sleep quality in night-shift workers. The study aims to compare the effectiveness of melatonin versus placebo on sleep efficiency in emergency medicine (EM) residents.

METHODS: A randomized, double-blind, replicated crossover trial was performed on EM residents. This study consisted of 4 phases within a month with intervention periods of 2 nights and washouts of 6 days. In our study, EM residents had nine-hour shifts on 6 consecutive days, 2 mornings, 2 evenings and 2 nights and then 2 days off. At the end of shifts' cycle, 24 EM residents were given 3 mg melatonin or placebo (12 in each arm of the study) for 2 consecutive nights after the second night shift with crossover to the other arm after a six-day off drug. This crossover intervention was repeated for two more another time. Finally, we created 48 cases and comparisons in each arm. Different items related to sleep quality were assessed and compared both within the same group and between the two groups.

RESULTS: In the melatonin group, daytime sleepiness (calculated by Karolinska Sleep Scale) had a significant reduction after taking the second dose of drug ($P=0.003$) but the same result was not observed when comparing the 2 groups. Mood status (calculated by Profile of Mood States) showed no remarkable difference between the 2 groups.

CONCLUSION: Melatonin might have a limited benefit on sleep quality in EM residents working night shifts.

KEY WORDS: Melatonin; Placebo; Emergency medicine; Night shift; Sleep

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INTRODUCTION

Rotating clinical shifts from mornings to nights can affect emergency physicians' function due to the changes in sleep circadian rhythm. This can also lead to sleep disorders and fatigue during clinical shifts. Night-shift work is accompanied by deleterious physical and psychological problems including insomnia,^[1] hypertriglyceridemia,^[2] hypertension,^[3] coronary artery

disease,^[4] depression,^[5] alcohol or drug abuse^[6] and gastrointestinal disorders.^[7] Sleep deprivation can have a bad effect on physician gestalt and patient safety. Thus, offering an appropriate strategy to decrease sleep related difficulties, can have a good impact on physicians' professional activity.

The Accreditation Council for Graduate Medical Education has developed the newest work-duty hour

standards and emphasized that use of night float rotation would provide daytime residents with the opportunity of some rest during the nights on call.^[8]

Exogenous administration of the pineal hormone, melatonin, may be a promising treatment for improving daytime sleep in night time workers. Some of the melatonin important roles are: falling asleep, sleep maintenance and keeping the balance of circadian rhythm.^[9,10] Side effects are usually minimal and rare,^[9,10] with similar symptoms occurring in subjects taking placebo. Treatment trials of melatonin to induce and augment phase-shifted circadian rhythms, have been successfully studied in travelers experiencing jet lag^[11] and in individuals with blindness^[12-14] or pinealectomy.^[15] Moreover, many studies have showed that melatonin treatment can accelerate adjustment to an inverted activity-sleep cycle.^[16]

Melatonin publicity as a drug for reestablishment of normal sleep patterns, has been validated in a variety of sleep disorders since long ago.^[17,18] Preliminary studies have also suggested that exogenous melatonin may improve sleep quality and alertness in night-shift workers.^[19,20] A recent review concluded that, there is an adequate evidence in the medical literature to support the contention that "melatonin has a hypnotic effect in humans".^[21]

There are few yet scientific studies about melatonin efficacy and most of them have used objective data like polysomnography or actigraphy to evaluate sleep parameters. This seems to be inadequate. Thus, in this study we decided to use subjective self-report data and our objective was to determine whether there were measurable beneficial effects from using exogenous melatonin on sleep quality of emergency medicine (EM) residents after intermittent night shifts.

METHODS

Participants and drug administration

Inclusion criteria

Twenty-four EM residents of Tehran University of Medical Sciences (TUMS) with 9-hour shifts and meeting our inclusion criteria, were enrolled in our study within a month. They were first randomly allocated into two groups, 12 in each, whether the placebo (group A) or the melatonin (group B) group.

Residents entered their group based on the code in block randomization and only the triage nurse and the chief investigator were aware of their randomization.

Our residents' shift program consisted of 2 days off

following 6 consecutive shifts: 2 mornings (from 7:00 am to 4:00 pm), 2 evenings (from 3:00 pm to 12:00 pm) and 2 nights (from 11:00 pm to 8:00 am). The study was approved by the Ethics Committee of TUMS and it was registered in www.irct.ir with the trial number of IRCT2015112925286N1. All residents were required to read informed consent letter and signed it, if they accepted to participate in our study.

Exclusion criteria

We excluded residents with any other shift's model, residents with alcohol or drug abusing behaviors or any psychological problems, who were on some sedative-hypnotic drugs, and also pregnant or lactating residents.

Consenting participants were randomized to one of the two sequences: placebo followed by melatonin or melatonin followed by placebo. Our triage nurse provided residents with specific drug and its appropriate dose. An emergency physician who was blinded to the study, collected all the data and followed participants. None of the residents were aware of the group specified.

The treatment phase of each sequence (arm of the study) consisted of taking a 3-mg tablet of either melatonin or placebo about 1 hour before habitual nighttime sleep (both drugs had the same shape, size and color). We evaluated 27 EM residents at the beginning of the study; 3 were excluded: 1 was pregnant, 1 had major depression and 1 was on tranquilizers.

Study design and randomization

This was an interventional randomized, placebo-controlled, double-blind study. Our study was designed to evaluate the effect of melatonin on EM residents' sleep quality at Imam Khomeini hospital during one month (from 19th May to 19th June) in 2016.

In order to randomize cases in the best way, before the study was started, we rolled dice and made 6 groups of 4 characters as followed: AABB, BBAA, BAAB, ABBA, ABAB and BABA. Thus, all 24 EM residents had a code (character) before entering into the study. Whoever was in the melatonin group would then crossover to the placebo group and vice versa. This study was designed in a way that each EM resident was evaluated and followed four times in 4 different phases. Six consecutive shifts following 2 days off, comprised a phase. By reaching the end of each phase, residents had a crossover, so that all residents were given the intervention two times (Figure 1). By means of this crossover design we finally could assess 48 comparisons in each group.

Melatonin was administered as 3 mg tablets made by

the Nature Made factory in the united states of America (USA). Pharmacology department of TUMS provided us with the placebo exactly the same as 3 mg melatonin tablets.

The triage nurse gave all EM residents the specific drug and 2 questionnaires at the end of their second night shift. She guided residents about how to take tablets and how to answer the questionnaires. Two tablets (either melatonin or placebo) were given to each resident. Residents were required to take the first tablet one hour before their night-time sleep at their first night off and answer one of the questionnaire given to them, the morning after. On the second night off, the second tablet of either drug was taken and the questionnaire was filled one more time. If by taking the first tablet they couldn't sleep, they were advised to take another tablet and ask for extra doses by calling the nurse. The triage nurse reminded taking the second tablet by sending a message to all residents.

The questionnaire included items like: sleep onset delay or problems in falling asleep, night mares, the length of time participants slept the night before, night awakening, early awakening, feeling drowsy, tiredness, mood status and drug side effects.

The subjects completed the Karolinska Sleep Scale for drowsiness (KSS; a 9-point scale ranging from "extremely alert" to "extremely sleepy—fighting sleep")^[22] and a 100-mm visual analogue scale (VAS) designed to assess the current level of tiredness ("extremely sleepy; difficult to stay awake" to "wide awake; not at all sleepy"). The

Profile of Mood States (POMS) survey^[23] was completed to assess behavior and mood. The POMS consists of 65 adjectives, each rated on a 5-point scale, serving to assess 6 fluctuating affective states consisting of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Our primary endpoint was comparison of KSS and POMS scores between the 2 arms. Our secondary endpoints were comparison of other sleep quality variables between the 2 arms.

Statistical analysis and sample size calculation

We finally performed our intervention on 24 EM residents in this study. Crossover was done on them 3 times thus we created 48 comparisons in each arm of the study. All 24 cases participated in both arms of the study.

The data are presented as mean values (mean standard deviation [SD]) or proportions, and differences in these values are presented with accompanying 95% confidence intervals (95% CIs). We used Wilcoxon signed rank and Mann-Whitney U tests for analyzing and comparing non-normally distributed continuous and quantitative data. McNemar, Chi-square and Fisher exact tests were used for analyzing and comparing qualitative data. We applied repeated measure analysis of variance in order to see the changes of quantitative data along the study. All data were analyzed by SPSS v.22. As previously mentioned, we had multiple comparisons of the same individuals and our data was highly intercorrelated. We performed the replicated crossover design 3 times on the same sample

Figure 1. Study design.

size. Thus, *P*-value's true level of acceptance, to be statistically significant, was considered <0.0125 .

RESULTS

Twenty-seven EM residents were enrolled in our study. Three were excluded by the exclusion criteria. Finally, 24 EM residents fit the eligibility criteria. In this interventional randomized clinical trial, 10 of our residents were females and 14 of them were males. By means of replicated crossover design, we finally performed both drugs' intervention on all 24 cases and thus we created the possibility of assessing 48 comparisons in each arm of the study. The mean age of our participants was 31.21 ± 5.23 years old.

Table 1 shows the comparison of qualitative data in our study. In the melatonin group, night awakening on the first night was less than the placebo group ($P=0.020$). Daytime drowsiness decreased by taking the second dose of melatonin ($P=0.021$). However, these values were not significant.

Table 2 shows the comparison of quantitative data in our study. In the melatonin group, drowsiness calculated by KSS score on the first night, was more than the placebo group ($P=0.020$), yet melatonin could significantly reduce this rate on the second night ($P=0.003$) within its group.

The most common side effects observed in group

A were: lightheadedness (20.8%), abdominal cramps (12.5%) and some other minor adverse events (20.8%). Conversely 11 residents (45.8%) reported no side effects.

The most common side effects observed in group B were: headache (16.7%), lightheadedness (12.5%), nausea (8.3%), vomiting (8.3%), abdominal cramps (8.3%) and some other minor adverse events (4.2%). Conversely 10 residents (41.7%) reported no side effects. Finally, Chi-Square analysis showed no significant difference in adverse events between the 2 groups ($P=0.069$).

By using repeated measure analysis of variance, we found no significant differences in the mean sleep hours, KSS, VAS and POMS scores' changes between the two groups along the study ($P=0.766, 0.405, 0.651$ and 0.903 respectively).

DISCUSSION

Working night shifts can change normal circadian rhythm. The effects of sleep deprivation on emergency staff and physician performance have been reported in the literature.^[24,25] Melatonin has been prescribed in sleep disorders and jet lag from long ago.^[26-28]

Most articles studying melatonin are not very recent. Some of them evaluated melatonin administration in emergency staff and physicians.^[9,29,30] These studies were all placebo-controlled and double-blind trials and applied

Table 1. Evaluation of study qualitative variables

Variables	Melatonin			Placebo			<i>P</i> -value ²	<i>P</i> -value ³
	First night	Second night	<i>P</i> -value ⁰	First night	Second night	<i>P</i> -value ¹		
Delay in falling asleep (extra doses needed)	1 (4.2%)	5 (20.8%)	0.219	2 (8.3%)	2 (8.3%)	1.00	0.551	0.416
Night mare	2 (8.3%)	4 (16.7%)	0.625	4 (16.7%)	3 (12.5%)	0.981	0.666	0.683
Night awakening	7 (29.2%)	11 (45.8%)	0.219	16 (66.7%)	9 (37.5%)	0.039	0.020	0.770
Early awakening	4 (16.7%)	7 (29.2%)	0.453	7 (29.2%)	5 (20.8%)	0.625	0.494	0.740
Drowsiness on the following day	16 (66.7%)	8 (33.8%)	0.021	11 (45.8%)	11 (45.8%)	1.00	0.244	0.556

P-value⁰: calculated by McNemar test to compare within the melatonin group changes along the study; *P*-value¹: calculated by McNemar test to compare within the placebo group changes along the study; *P*-value²: calculated by Chi-square test to compare between group changes on the first night; *P*-value³: calculated by Chi-square test to compare between group changes on the second night.

Table 2. Evaluation of study quantitative variables

Variables	Melatonin				Placebo				Mean difference (95% CI) Between groups on first night	<i>P</i> -value ²	Mean difference (95% CI) Between groups on second night	<i>P</i> -value ³
	First night	Second night	Mean difference (95% CI)	<i>P</i> -value ⁰	First night	Second night	Mean difference (95% CI)	<i>P</i> -value ¹				
Sleep hours	7.68±1.15	6.81±1.24	0.87 (0.07, 1.67)	0.231	7.91±2.32	6.79±1.58	1.12 (0.06, 2.18)	0.315	0.22 (-0.83, 1.29)	0.826	-0.20 (-0.84, 0.80)	0.916
KSS score (drowsiness)	4.54±2.06	3.13±1.75	1.41 (0.56, 2.27)	0.003	3.33±1.20	3.67±1.12	-0.33 (-0.74, 0.07)	0.106	-1.20 (-2.19, -0.22)	0.020	0.54 (-0.31, 1.40)	0.056
VAS score (tiredness)	6.67±3.00	7.54±2.48	-0.87 (-1.77, 0.02)	0.049	6.79±3.07	6.71±2.86	0.08 (-0.66, 0.83)	0.958	0.12 (-1.64, 1.89)	0.802	-0.83 (-2.39, 0.72)	0.268
POMS score (mood status)	119.29±67.37	122.71±36.90	-3.41 (-12.53, 5.69)	0.210	115.58±35.95	123.92±36.53	-8.33 (-16.88, 0.21)	0.119	-3.70 (-25.10, 17.69)	0.812	1.20 (-20.12, 22.54)	0.721

P-value⁰: calculated by Wilcoxon Signed Rank test to compare within the melatonin group changes along the study; *P*-value¹: calculated by Wilcoxon Signed Rank test to compare within the placebo group changes along the study; *P*-value²: calculated by Mann-Whitney U test to compare between group changes on the first night; *P*-value³: calculated by Mann-Whitney U test to compare between group changes on the second night.

KSS for analyzing drowsiness and POMS for mood status. Their results showed no significant difference in the final outcome.

Reviewing all the study results, we found no significant differences in the prevalence of night awakening, night mare, early awakening, tiredness, mood status or the mean sleep hours between melatonin and placebo. We only observed that melatonin effectively decreased KSS score on the second night within its group ($P=0.003$).

Katherine et al^[31] in 2001, prescribed melatonin 1.8 mg to night shift staffs prior to their daytime sleep and the results were the same as ours. Jorgenson et al^[29] in 1998, studied melatonin 10 mg in emergency physicians and found no improvement in sleep quality.

Based on our study it seemed that melatonin had no effect on physician's mood. This was the same as Jockkovich and Katherine studies.^[30,31] Similar to other studies, the most common side effects observed in ours were headache, lightheadedness and nausea and there was no significant difference between the two groups.^[27,30]

The most recent study comparing melatonin versus placebo in night-shift-work nurses, was conducted by Sadeghniai-Haghighi et al^[32] in 2008 and they concluded that sleep onset latency was significantly reduced in the melatonin group.

Limitations of the study

The lack of benefit or adverse results might not be due to sample size but rather a situation in which there was really no effect. Given that this was not a study predicated on a predetermined required sample size based on prior study information, we should emphasize that the intervention had no beneficial effect.

Further clinical trials with larger sample sizes and longer follow-ups are recommended to be performed to support our results. The limitation was that the age range of our participants was young adults and we evaluated a population of physicians with the worst and most inorganized circadian rhythm. More studies about melatonin effects on different insomnia parameters and different samples of society are recommended.

CONCLUSION

Melatonin might have a limited benefit on sleep quality in EM residents working night shifts. In our study, we observe that melatonin could significantly decrease drowsiness (KSS score) within its group however this value had no significant difference between the two groups.

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