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Research Article

Melatonin for Sleep Quality and Occupational Cognitive Performance in Shift Workers with Low Sleep Quality: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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About one-third of the workers have irregular working hours, subsequently putting them at risk of sleep disorders. It also has negative impacts on employee performance. Sleep disorders and executive performance have been attributed to melatonin dysregulation due to long-term exposure to artificial light. This study investigates melatonin effects on sleep quality and cognitive performance in employees with sleep disorders following shift work. Seventy-two patients with sleep disorders following shift work were equally assigned to melatonin (5 mg before sleep at night after shifts) or matched placebo groups in a randomized, parallel-group, double-blind, placebo-controlled design. Patients were assessed using the short Pittsburgh Sleep Quality Index (shortPSQI), Occupational Cognitive Failure Questionnaire (OCFQ), and adverse events at baseline and weeks 1 and 4. Data from 65 patients were analyzed. Baseline characteristics were comparable between the groups (p values >0.05). The melatonin group showed a greater reduction in total shortPSQI score from baseline to the first (p value = 0.018) and fourth (p value = 0.001) weeks, as well as in total OCFQ score to the fourth week (p value <0.001). In addition, the time-treatment interaction effects on total scores of shortPSQI (p value = 0.004) and OCFQ (p value <0.001) were significant. The only different adverse event between the two groups was fatigue, which was higher in the placebo group (p value = 0.042). Melatonin was safely and tolerably superior to placebo in treating patients with sleep disorders following shift work in the short term. Evidence also shows its effects on improving occupational cognitive performance in the medium term. The study protocol was registered and published prospectively in the Iranian registry of clinical trials (registration number: IRCT20090117001556N153).

1. Introduction

The economy and social services of countries and societies, including medical services, electricity and power supply services, and military and police forces, depend on 24-hour work cycles. A report in the United States showed that about 27 percent of full-time employees are employees with shift and flexible working hours [1], and also, about a third of the workforce in Canada, like many other industrialized countries, has irregular working hours [2]. Shift workers are exposed to numerous health problems, including gastrointestinal problems, cardiovascular complications, increased chances of type 2 diabetes, reproductive issues, and psychiatric disorders, including sleep disorders [3].

A subset of shift workers suffers from shift work disorder, a condition caused by circadian misalignment that leads to insomnia or excessive sleepiness [4–6]. These individuals experience significant adverse health consequences

and reduced quality of life [7]. The principle of treating sleep disorders is first to find the cause of the sleep disorder and treat the accompanying conditions that cause the sleep disorder. If satisfactory treatment for the underlying condition is unavailable or does not resolve the problem, treatment should be directed at the specific sleep disorder [8]. A common strategy that people with sleep disorders consider is pharmacotherapy, which in many cases is arbitrary with benzodiazepines and zolpidem [9].

Shift work can have a negative impact on the productivity and executive performance of employees and it reduces the productivity of employees by increasing fatigue [10–12]. A study on mine workers showed that shift work negatively affects their level of sleepiness and fatigue, and the number of accidents in them was more than that of daytime workers [13]. Another study in a sugar factory also showed that the level of fatigue and occupational accidents was significantly higher in shift workers [14]. Studies on police officers in Italy and the United States have shown that fatigue and shift work are associated with preventable occupational accidents [15, 16]. The association between shift work and the reduction of executive performance of employees can be indirect, caused by sleep disorders. Sleep quality is generally associated with cognitive performance, and poor subjective sleep quality is associated with lower cognitive performance, particularly in executive function, increasing the risk of work injuries and reduced performance [2, 17, 18]. Objective measures of sleep quality appear to have a consistent relationship with cognitive performance. In this regard, intermediate sleep duration and higher sleep efficiency have been associated with better cognitive functioning [19]. In one study, sleep quality was associated with the incidence of minor errors [20]. Despite the importance of the correlation between sleep parameters and cognitive and occupational performance outcomes, few studies have directly investigated the relationship between sleep quality and quantity and cognitive outcomes [2]. The relationship may be influenced by various factors, including cross-cultural differences, the measures being subjective or objective, the cross-sectional rather than longitudinal nature of most studies, age differences, and socioeconomic status [17, 19, 21, 22].

Sleep disorders, followed by a decrease in executive and cognitive performance of shift workers, have been attributed to melatonin hormone dysregulation due to long-term exposure to artificial light at unusual hours [2, 23–25]. This hormone plays a significant role in regulating the circadian rhythms. Changes in its secretion in shift workers are diverse and unpredictable. In some shift workers, the peak of melatonin secretion continues at night, while in others, this peak occurs during daytime sleep [26–29]. High melatonin levels during work hours can cause drowsiness and reduce productivity and cognitive ability [30, 31]. Exogenous melatonin has been shown to be beneficial in treating primary sleep disorders. A meta-analysis found that melatonin significantly reduced sleep onset latency by an average of seven minutes compared to placebo [32]. In addition, the evidence suggests melatonin may be preferable to traditional sleep medications for managing insomnia, as it does not appear to negatively impact cognition [33] and even improves cognitive function [34]. A meta-analysis examined the effects of melatonin on cognitive function in patients with Alzheimer's disease and insomnia. The results showed that melatonin supplementation improved cognitive function in patients with Alzheimer's disease [33].

It can be assumed that adjusting the peak of melatonin to be secreted during shift workers' sleep may be helpful and affect the quantity and quality of their sleep, thereby reducing errors and improving performance. To the best of our knowledge, no study has evaluated the effects of melatonin on sleep quality and executive performance in shift workers with valid questionnaires. This study aimed to investigate the effects of melatonin during nighttime sleep after shifts on sleep quality and occupational cognitive performance in people with low sleep quality following shift work in a randomized, double-blind, placebo-controlled manner.

2. Materials and Methods

2.1. Study Design and Setting. This study is a randomized, double-blind, placebo-controlled clinical trial with two parallel groups of shift workers with sleep disorders receiving melatonin or placebo at Roozbeh Hospital, a large-scale academic psychiatry hospital, from July 2023 to November 2023. After ethical approval by the institutional research ethics committee (approval number: IR.SBMU.TEB.POLICE.REC.1402.009), the study protocol was published in the Iranian registry of clinical trials (https://www.irct.ir; registration number IRCT20090117001556N153).

The study was conducted based on the seventh revision of the Declaration of Helsinki, as revised in Brazil in 2013 [35] and Consolidated Standards of Reporting Trials guidelines (Appendix 1) [36]. As shift workers may be more vulnerable to feeling coerced or pressured to participate due to their demanding schedules and potential fatigue, researchers ensured the informed consent process was robust and that participants truly understood the risks and voluntarily chose to participate. Also, since the participants were all physicians, this helped strengthen this consideration. Also, the trial design minimized additional burdens on shift workers, such as extra time commitments or disruptions to their schedules. In addition, researchers closely monitored the trial to ensure the ongoing safety and well-being of participants and were prepared to stop the trial if the risks outweighed the benefits.

2.2. Participants. Inclusion criteria in this study were (i) being a resident physician with night shift work, (ii) age between 25 and 55 years, (iii) working at least seven night shifts in the past month before entering the study, (iv) having a schedule to work at least seven night shifts during the study month, and (v) complaining about sleep disturbance after shift work and poor sleep quality, defined as a short Pittsburgh Sleep Quality Index (shortPSQI) total score of 5 or higher [37].

The names of the shift workers who had the required number of shifts were specified in the hospital schedule. It was changeable according to people's personal plans, which

is why people themselves were also asked. They were also called through announcements. Then, the shortPSQI was used to identify shift workers with low sleep quality. Patients with (i) pregnancy, breastfeeding, or intention to become pregnant in female participants, (ii) history of sensitivity or side effects after taking melatonin and its agonists, and (iii) history of thyroid, cardiovascular, kidney, and endocrine diseases and psychiatric disorders (except for sleep disorders) were not included. In addition, a small flexibility was made due to the possibility of changes in the initial planning of the participants. Regarding item iv of the inclusion criteria, if the patient had worked at least six night shifts during the study month, they were not excluded from the study. Severe side effects led to exclusion.

2.3. Sample Size. The sample size was calculated using the SigmaPlot 12 sample size calculator (SYSTAT Software Inc., San Jose, CA, USA). Based on a previous institutional pilot study and several studies we performed in the past, a sample size of 72 participants, 36 in each arm, was estimated to be enough for detecting a between-group difference of 2 in reducing shortPSQI total scores assuming a standard deviation (SD) of 2 using a two-tailed *t*-test of difference between the means with 90% power and a 5% level of significance considering a dropout rate of 15% increasing the generalizability of the results.

2.4. Randomization, Allocation Concealment, and Blinding. Random distribution of the participants was performed by the block method using a computer random number generator (blocks of 4, with a ratio of 1 : 1). The generation of randomization codes was performed by an independent person who was not involved in any other part of the study. Distribution to participants was performed using numbered, sealed, opaque, and stapled envelopes. Independent people were responsible for the randomization and distribution of samples. Participants, study investigators, and raters were all unaware of group allocation. Melatonin and placebo were specially produced for this trial by Jalinous Pharmaceutical Company and were identical in size, shape, color, smell, and taste.

2.5. Interventions. Participants were equally assigned to the two study arms. The first group received immediate-release melatonin tablets with a dose of 5 mg for night sleep after each shift work 30 minutes before the desired time for the person to sleep, and the other group received placebo tablets under the same conditions for one month. Free medicine was provided to them. Adherence to the medication was checked by patient reports with regular telephone follow-ups. Noncompliance was defined as >30% of reported instances of forgetting to take tablets. The use of antidepressants, antihistamines, diuretics, other hypnotics, benzodiazepines, and narcotics was prohibited during the study month due to their effects on sleep quality [38].

2.6. Outcomes and Tools. At the beginning of the study, demographic data, including gender, age, smoking, marital status, occupational field, number of cups of tea and coffee consumed per day, and number of monthly shifts, were collected.

PSQI is the most widely used questionnaire to assess sleep quality with a valid and reliable Persian version (Cronbach's alpha = 0.73) [39]. Its short version with improved application consists of seven questions, one of which is the seven-part. PSQI has already been used in clinical trials on Iranian participants [34], and its shortened version by removing some items is also used in clinical studies [40]. There is a high correlation between the global scores of the original questionnaire and the shortPSQI (rho = 0.94), and when the global score is defined as good or poor sleep, the agreement is strong (kappa = 0.83). Five components are obtained from the questions, including sleep latency, sleep duration, sleep efficiency, sleep disturbances, and daytime dysfunction, each rated from 0 to 3 based on severity. As a result, the final score range of each questionnaire will be between 0 and 15 [37]. Patients were evaluated in this regard at baseline and weeks 1 and 4.

Occupational Cognitive Failure Questionnaire (OCFQ), with high validity and reliability, contains 30 items. The OCFQ has already been used in clinical studies on Iranian participants [41]. It is valid (content validity index = 0.7), reliable (Cronbach's alpha = 0.96), and repeatable (intraclass correlation coefficient = 0.996). This questionnaire evaluates the dominant cognitive deficits that occur in the workplace. Each item is scored on a five-point Likert scale from 1 to 5. It includes memory, attention, motor function, and comprehension error items. Its total score ranges from 30 to 150 [42]. This questionnaire was filled by patients at baseline and weeks 1 and 4.

Adverse events were assessed using a checklist [43] in which the side effects of melatonin, such as drowsiness, headache, and dizziness [44], were reported, and the participants could report other adverse events that were not included in it. Except for weeks 1 and 4, when patients filled out this checklist, they could also report by phone whenever they experienced a complication using a 24-hour hotline.

All questions were answered by self-report. How to answer the questions was explained to the participants at baseline. Also, the researchers were available for further questions throughout the study.

The primary outcome was the difference in mean changes for shortPSQI total scores from the baseline to the end point between the study arms. The secondary outcomes included differences in mean changes for OCFQ total scores from the baseline to the endpoint, the treatment response rates per shortPSQI and OCFQ in steps of 25% reductions, the remission rates per shortPSQI (a total score of 4 or less [37]), and the frequency of adverse events between the two groups. To obtain the percent reduction in OCFQ scores, 30 points were first subtracted from the total score due to the use of a 1–5 scoring system [45].

2.7. Statistical Analysis. Statistical analysis was performed using IBM® SPSS® Statistics version 27. A p value of less than 0.05 was considered significant. By applying a Bonferroni correction for the two-tailed student's t-test that was used to compare the average scores at each time point and their changes from baseline to each time point between the groups, p values less than 0.025 were considered significant due to the presence of two follow-up sessions. Bonferroni correction was applied not only to the primary outcome (mean changes in shortPSQI total score from baseline), but also to mean changes in OCFQ total score from baseline.

The main population for the efficacy analyses was the full analysis set that included randomized patients who completed the study or prematurely withdrew after week 1 using last-observation-carried forward, a form of intention-to-treat approach. The safety analysis was performed in the safety set that included randomized patients who received at least one dose of the study medication or placebo.

The normality of distribution was tested using the Shapiro–Wilk test and probability graphics. The distributions of continuous variables do not differ significantly from the normal distribution. To check the homogeneity of variances assumptions for t-tests, Levene's test for equality of variances was used. In nonspherical cases, in general linear model (GLM) repeated-measures analyses, if Mauchly's test of sphericity was significant when the estimated epsilon (ε) was less than 0.75, the results of this analysis were corrected with the Greenhouse-Geisser test and when ε was higher, with Huynh-Feldt.

Qualitative variables, including some baseline data (including gender, marital status, smoking, and occupational field), shortPSQI components, response and remission rates, and adverse events were presented as the number and percentage (n, %) of subjects with nonmissing data per category and were compared using the chi-square test. Some baseline variables, which were continuous, were reported as mean ± standard deviation and compared using an independent samples t-test.

The two-tailed student's t-test was used to compare the average scores of shortPSQI and OCFQ at each time point and their changes from baseline to each time point between the groups. The difference between the score changes of the groups was reported as the mean difference (MD) with a 95% confidence interval. Effects of time and time-treatment interaction on shortPSQI and OCFQ scores were evaluated using GLM repeated-measures analyses as they were recorded in three timepoints by considering intervention arms as between-subject factors and study time points as within-subject factors. To address the potential impact of dropouts, GLM repeated measures were repeated by placing the worst value of shortPSQI scores in both groups for missing values in the melatonin group and the best value in both groups for missing values in the placebo group for each dropout participant. These imputations were applied to participants who dropped before week 1. The significance of the results did not change. Pearson's correlation was used to check the correlation between shortPSQI reduction and OCF reduction.

The effect size for the independent samples t-test was reported as Cohen's d, with the results of 0.2, 0.5, and 0.8 indicating small, medium, and large sizes, respectively [46]. The effect sizes for one-way GLM repeated-measures analyses were reported as partial eta squared (η_p^2), with small, medium, and large sizes equal to 0.0099, 0.0588, and 0.1379, respectively [46].

3. Results

3.1. Participants. Figure 1 shows the process of inclusion of patients in the trial based on the CONSORT flowchart. Among 123 people with shift work who were screened, 51 people were not included due to not meeting inclusion criteria ($n = 26$), meeting exclusion criteria ($n = 9$), and refusal to participate ($n = 16$), and subsequently, 70 patients participated and were randomly assigned to melatonin and placebo groups. Of these, five people did not participate in the first follow-up. After participating in the first follow-up, three from the melatonin group and two from the placebo group withdrew their consent. No participant dropped out because of side effects or the study being time-consuming. Consequently, data from 33 patients in the melatonin group and 32 in the placebo group were analyzed, and 30 from each group completed the study. There were no significant differences in baseline characteristics between the groups regarding gender, age, smoking, marital status, occupational field, daily tea and coffee cups, and number of night shifts (Table 1).

3.2. Short Pittsburgh Sleep Quality Index. There was no difference between the two groups regarding the components of the shortPSQI questionnaire at the baseline (p values >0.05). The two groups differed in terms of the second component in the first ($p = 0.010$) week, and there was no difference in other pairwise comparisons in the follow-up sessions (p values >0.05).

As shown in Table 2, there was no difference between the groups in terms of total scores of the shortPSQI at baseline, but the differences in the first and fourth weeks were statistically significant. The interaction effect of time-treatment on shortPSQI total scores was significant ($F = 8.78$, $df = 2.000$, p value = 0.004, $\eta_p^2 = 0.091$) (Figure 2), which indicated a difference in dynamics. Affirmatively, the melatonin group showed more decreases in shortPSQI total scores from baseline to the first and fourth weeks.

Table 3 divides the response to treatment into four domains and compares it between the two groups in the first and fourth weeks. As seen, there is a statistically significant difference in response to treatment in terms of sleep quality between the two groups; that is, the melatonin group responded better to the treatment.

By the first week, 18 (54.5%) of the patients in the melatonin group achieved remission in terms of shortPSQI, which was higher than 9 (28.1%) of the patients in the placebo group (p value = 0.044). By the fourth week, this number reached 25 people (75.8%) in the melatonin group and 11 (34.4%) in the placebo group (p value = 0.001).

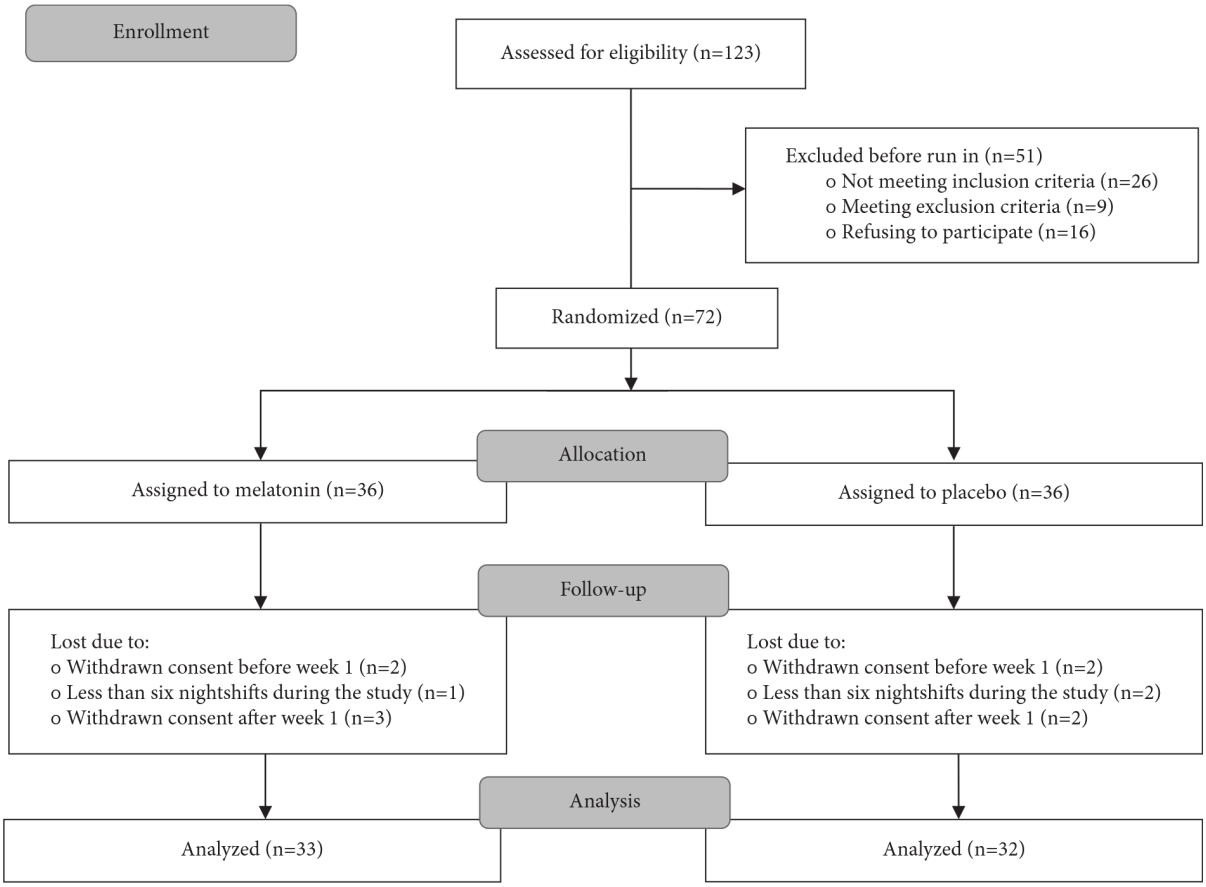

Figure 1: Flowchart showing participant selection for the study program.

Table 1: Baseline characteristics of the patients.

Variable		Melatonin ($n = 33$)	Placebo ($n = 32$)	p value[#]
Gender, n (%)	Male Female	17 (51.5%) 16 (48.5%)	18 (56.3%) 14 (43.8)	0.805[a]
Age, mean years ± SD		29.12 ± 5.18	28.28 ± 3.00	0.429[b]
Smoking, n (%)	Yes No	5 (15.2%) 28 (84.8%)	5 (15.6%) 27 (84.4%)	1.000[a]
Marital status, n (%)	Single Married	22 (66.7%) 11 (33.3%)	22 (68.8%) 10 (31.3%)	1.000[a]
Occupational field, n (%)	Emergency Anesthesia Surgery Internal medicine	19 (57.6%) 3 (9.1%) 6 (18.2%) 5 (15.2%)	17 (53.1%) 5 (15.6%) 4 (12.5%) 6 (18.8%)	0.780[c]
Daily tea and coffee cups, mean ± SD	Last month Study month	3.79 ± 2.23 3.61 ± 1.87	3.53 ± 1.74 3.72 ± 1.95	0.608[b] 0.813[b]
Number of night shifts, mean ± SD	Last month Study month	8.67 ± 1.78 7.97 ± 1.91	9.19 ± 2.25 8.91 ± 2.65	0.306[b] 0.109[b]

[#]No p values were significant. [a]Fisher's exact test. [b]Two-tailed independent sample t-test. [c]Pearson's chi-square. SD, standard deviation.

3.3. Occupational Cognitive Failure Questionnaire. As shown in Table 4, there was no difference between the groups regarding total OCFQ scores at baseline. Also, there was no difference in the results of the first and fourth weeks and the changes from baseline to the first week. The interaction effect of time-treatment on the total OCFQ score was significant ($F = 17.806$, $df = 1.374$, p value < 0.001, $\eta_P^2 = 0.220$) (Figure 2), which indicated a difference in dynamics. Affirmatively, the melatonin group showed a more substantial decrease in terms of the total OCFQ scores from baseline to the fourth week.

Table 2: Short Pittsburgh Sleep Quality Index total scores at baseline and each follow-up session and its changes from baseline.

Item	Melatonin ($n = 33$), mean ± SD	Placebo ($n = 32$), mean ± SD	MD (95% CI)	t	p value[a]	Cohen's d
Baseline	6.33 ± 1.65	6.34 ± 1.06	−0.010 (−0.702, 0.681)	−0.030	0.976	0.007
Week 1	4.45 ± 1.17	5.28 ± 1.57	−0.827 (−1.513, −0.141)	−2.408	0.019*	0.597
Week 4	3.82 ± 1.38	5.03 ± 1.51	−1.213 (−1.930, −0.496)	−3.379	0.001*	0.838
Changes from baseline to week 1	−1.88 ± 1.38	−1.06 ± 1.31	−0.816 (−1.487, −0.145)	−2.431	0.018*	0.603
Changes from baseline to week 4	−2.52 ± 1.34	−1.31 ± 1.51	−1.203 (−1.912, −0.493)	−3.386	0.001*	0.840

[a]Two-tailed independent samples t-test. *A significant p value. SD, standard deviation; MD, mean difference; CI, confidence interval.

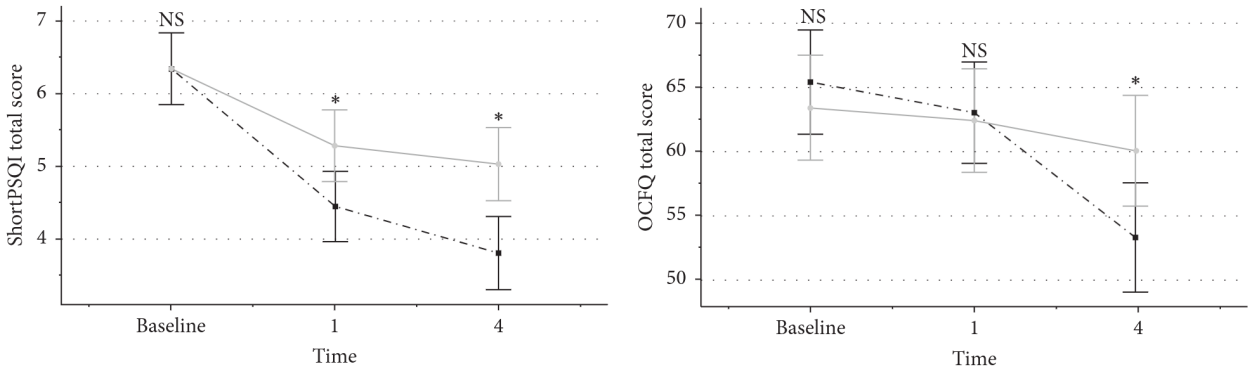

Figure 2: Repeated-measures analysis for comparison of effects of melatonin (black) and placebo (gray) on the short Pittsburgh Sleep Quality Index (a) and Occupational Cognitive Failure Questionnaire (b) mean scores during the study. Error bars represent ±2 standard errors. * and NS show significant and nonsignificant p values obtained from the independent sample t-test comparing the scores of each time point between the groups.

Table 3: Comparison of responder rates in steps of 25% and remitters between the groups in weeks 1 and 4 in terms of short Pittsburgh Sleep Quality Index (shortPSQI) and Occupational Cognitive Failure Questionnaire (OCFQ).

Outcome	Week	Group	<25% reduction, n (%)	25–49.9% reduction, n (%)	50–74.9% reduction, n (%)	≥75% reduction, n (%)	P value[a]
ShortPSQI	1	Melatonin	14 (42.4%)	17 (51.5%)	2 (6.0%)	0	0.157
		Placebo	20 (62.5%)	9 (28.1%)	3 (9.4%)	0	
	4	Melatonin	5 (15.1%)	19 (57.6%)	8 (24.2%)	1 (3.0%)	0.003*
		Placebo	19 (59.4%)	9 (28.1%)	4 (12.5%)	0	
OCFQ	1	Melatonin	31 (93.9%)	2 (6.0%)	0	0	1.000
		Placebo	31 (96.9%)	1 (3.1%)	0	0	
	4	Melatonin	11 (33.3%)	11 (33.3%)	10 (30.3%)	0	<0.001*
		Placebo	28 (87.5%)	2 (6.2%)	2 (6.2%)	0	

[a]Pearson's chi-square. *A significant p value.

Table 4: Occupational Cognitive Failure Questionnaire total scores at baseline and each follow-up session and its changes from baseline.

Item	Melatonin ($n = 33$), mean ± SD	Placebo ($n = 32$), mean ± SD	MD (95% CI)	t	p value[a]	Cohen's d
Baseline	65.36 ± 13.11	63.38 ± 9.89	1.989 (−3.784, 7.761)	0.688	0.494	0.171
Week 1	63.00 ± 12.97	62.38 ± 9.41	0.625 (−5.008, 6.258)	0.222	0.825	0.055
Week 4	53.27 ± 13.22	60.06 ± 11.07	−6.790 (−12.847, −0.733)	−2.240	0.029	0.556
Changes from baseline to week 1	−2.36 ± 2.97	−1.00 ± 4.27	−1.364 (−3.199, 0.472)	−1.497	0.139	0.371
Changes from baseline to week 4	−12.09 ± 8.42	−3.31 ± 6.62	−8.778 (−12.541, −5.016)	−4.663	<0.001*	1.157

[a]Two-tailed independent samples t-test. *A significant p value. SD, standard deviation; MD, mean difference; CI, confidence interval.

Table 3 compares the response to treatment between the groups in the first and fourth weeks. As seen, there is a statistically significant difference in treatment response in terms of OCFQ at week 4; that is, the melatonin group responded better within four weeks of treatment.

3.4. Correlations. Table 5 shows the pairwise correlation of OCFQ reduction percentage and shortPSQI reduction percentage up to weeks 1 and 4.

3.5. Adverse Events. Table 6 compares the frequency of adverse events in groups. None of the patients reported a severe complication. No patients were noncompliant. Fatigue was the only adverse event statistically different between the groups, which was more common in the placebo group (34.4% versus 12.1%). Respectively, 23 patients (63.6%) and 16 patients (50.0%) from the melatonin and placebo groups had at least one adverse event, although this difference was not statistically significant using Fisher's exact test.

4. Discussion

In this clinical trial with a randomized, double-blind design, by studying 72 patients and analyzing the data of 65 of them, it was shown that melatonin is superior to placebo in a safe and tolerable manner for shift workers with subsequent sleep disorders in terms of increasing sleep quality in the short term and reducing cognitive in the medium term.

Melatonin helps regulate the body's internal clock by promoting the release of melatonin at the appropriate time. This can help align the body's natural sleep-wake cycle with the shift work schedule, leading to better sleep quality and reduced sleep disorders [25, 32].

Melatonin can improve occupational cognitive performance by improving sleep quality [33, 34]. Also, it has antioxidant properties, which help protect the brain from oxidative stress and inflammation caused by sleep deprivation. This can improve cognitive performance and reduce the negative effects of sleep disorders on executive functions [47]. In addition, melatonin can enhance the function of neurotransmitters such as serotonin, dopamine, and acetylcholine, which are involved in attention, memory, and mood regulation. This can lead to improved cognitive performance and reduced fatigue in shift workers [48]. Moreover, it can promote neuroplasticity, which is the brain's ability to adapt and change in response to new experiences. This can improve cognitive flexibility, problem-solving, and memory in shift workers [47].

The participants of this trial were all resident physicians. Medical services are one of the most essential needs of today's 24/7 society, but this continuous provision of services harms the health and performance of the providers [49]. Various solutions have been proposed for this problem, and a simple and inexpensive one was investigated in this study. This study found that pharmacotherapy for nighttime sleep after shifts, and not every night, was beneficial for sleep quality and performance. Studying exclusively resident physicians had the advantage of the similarity of the characteristics of the participants and reducing the effects of side factors, but it is necessary to conduct studies and measures for people with other jobs with different characteristics.

One of the results of this study was the superiority of melatonin over placebo in increasing the sleep quality of patients with sleep disorders following shift work. Exogenous melatonin is well known as a hypnotic medication in patients with sleep disorders and insomnia, and many studies have reported its role in increasing sleep quality in patients with sleep disorders who have nocturnal sleep hours [50–54]. However, the results of melatonin administration to shift workers have been conflicting [55–57]. Regarding this, it should be noted that these three studies, which were published in 1998, 2001, and 2005, have significant limitations, including small sample size, study on healthy participants, short duration of the study, not using a valid questionnaire for evaluating sleep quality, and prescribing melatonin in the daytime. By removing their limitations and designing in line with the mechanism of action of the medication, this study achieved a result similar to the literature indicating the effects of melatonin on the sleep quality of patients with shift work.

One of the questions in the shortPSQI was the time it took the participants to fall asleep. One of the previous studies suggested that melatonin has no effect on this question and this component [58]. In this study, according to the oral administration (prolongation to the onset of effect), the patients with a high educational level were asked to take it half an hour before the desired time to sleep at night, so that this item was reviewed with attention and care. Consequently, in this study as well, no superiority of melatonin over placebo was observed in reducing the latency to fall asleep.

Another important result of this study was the reduction of occupational cognitive failure in the medium term, not the short term. The effects of melatonin on "cognition" have been reported in previous studies [33]. However, it seems that the decrease in OCFQ scores observed in this study is different from them and was caused by the increase in sleep quality because, according to previous reports, executive function impairment can be caused by a decrease in sleep quality [2, 15, 16, 20, 59].

The results showed that the beneficial effects of melatonin on cognitive and executive function may take several weeks to manifest, rather than appearing after just one week of administration. The delayed cognitive improvements seen are likely due to the time required for melatonin to exert its multifaceted effects on the brain [47, 48] and sleep-wake cycle [25, 32]. Melatonin's effects on the brain and cognitive function are mediated through complex neurochemical and neurophysiological pathways. It can take time for melatonin to exert its influence on neurotransmitter systems, circadian rhythms, and neuroplasticity, all of which contribute to improved cognitive performance [60, 61]. Melatonin has neuroprotective properties, helping to reduce oxidative stress, inflammation, and apoptosis in the brain. These neuroprotective effects may accumulate over time, leading to gradual improvements in cognitive function rather than immediate changes [61].

Table 5: The pairwise correlation of OCFQ and shortPSQI reduction percentages up to weeks 1 and 4.

Variable		ShortPSQI until week 1	ShortPSQI until week 4	OCFQ until week 1	OCFQ until week 4
ShortPSQI until week 1	Correlation	1	0.435	0.116	0.263
	P value[a]	—	<0.001*	0.359	0.035*
ShortPSQI until week 4	Correlation	0.435	1	0.083	0.291
	P value[a]	<0.001*	—	0.510	0.019*
OCFQ until week 1	Correlation	0.116	0.083	1	0.397
	P value[a]	0.359	0.510	—	0.001*
OCFQ until week 4	Correlation	0.263	0.291	0.397	1
	P value[a]	0.035*	0.019*	0.001*	—

[a]Pearson's correlation. *A significant *p* value. ShortPSQI, short Pittsburgh Sleep Quality Index; OCFQ, Occupational Cognitive Failure Questionnaire.

Table 6: Frequency of mild adverse events in the groups.

Adverse events	Melatonin ($n = 36$), *n* (%)	Placebo ($n = 36$), *n* (%)	*P* value[a]
Fatigue	4 (11.1%)	11 (30.6%)	0.042*
Drowsiness	9 (25.0%)	6 (16.7%)	0.384
Dizziness	7 (19.4%)	5 (13.9%)	0.527
Headache	9 (25.0%)	7 (19.4%)	0.571
Irritability	3 (8.3%)	3 (8.3%)	1.000
Abdominal cramps	10 (27.8%)	5 (13.9%)	0.147

[a]Pearson's chi-square. *A significant *p* value.

One of the results of this study was the correlation of OCFQ reduction during four weeks with shortPSQI reductions during one week and four weeks. Shift workers often experience disruptions in their sleep patterns due to their nontraditional work schedules. The correlation between sleep quality and cognitive function is well established. Sleep quality is a critical factor in maintaining cognitive performance, and sleep disruptions can negatively impact cognitive abilities such as attention, memory, and reaction time. Melatonin, a hormone that regulates sleep-wake cycles, can improve sleep quality and, in turn, enhance cognitive function [33, 62]. The correlation between the reduction in PSQI and OCFQ during different durations of melatonin treatment suggests that the effects of melatonin on sleep quality and cognitive function may vary depending on the duration of treatment. This could be due to the different mechanisms by which melatonin affects sleep and cognitive function over different periods [25, 32, 33, 47, 48]. The correlation between shortPSQI and OCFQ reduction during different durations of melatonin treatment has significant clinical implications. It suggests that melatonin treatment can be effective in improving sleep quality and cognitive function in shift workers, particularly when used over longer periods. This could be particularly beneficial for shift workers who experience chronic sleep disruptions and cognitive impairments due to their work schedules.

The significant effects of melatonin on sleep quality and work performance were in medium and large sizes, respectively. Statistically significant results of trials cannot necessarily be judged as having clinical significance [43, 63]. In previous studies, it has been suggested that the range of effect sizes should be corrected towards larger numbers for subjective psychiatric scales [64]; however, no definitive recommendations were found for sleep quality and work performance. It is worth noting that these statistical ambiguities exist even for well-known psychiatric medicines and are not specific to the treatment mentioned in this study [63, 64]. In this regard, in this study, appropriate terms such as better performance/superior to placebo were selected instead of clinical effectiveness; however, considering the burden of the disorder and the difficulties of its treatment, these effects, which were obtained in only one week to one month in patients, can be of great interest.

In this study, melatonin was safe and well tolerated. Adverse events reported by patients in the melatonin group, as reported in previous studies, occurred with the same frequency as in the placebo group [65], except for fatigue. Its frequency was higher in the placebo group in this study, although listed as a side effect of melatonin. This result aligns with a previous study reporting the reduction of fatigue after using melatonin [66]. The fact that fatigue levels were lower in melatonin recipients than in placebo recipients suggests that melatonin may have a beneficial effect on fatigue levels, contrary to the expected complication. This could be due to the actual therapeutic effects of melatonin on sleep quality, which may help mitigate fatigue. This is also critical for maintaining high levels of cognitive performance and executive function during long periods of work [48]. The observed difference in fatigue frequencies could also be attributed to methodological factors such as the way fatigue was measured, the duration of the trial, or the population of participants. Fatigue after taking melatonin can be due to its prescriptions with different indications than sleep disorders.

Despite significant advantages, including investigating a literature gap and controversy in the field, a completely novel trial on melatonin for occupational cognitive performance, a randomized, double-blind, placebo-controlled design, and the precise adjustment of baseline demographic and clinical characteristics, this study had some limitations. First, the sample size was small to provide definitive clinical outcomes, although it was sufficiently powered to examine between-group differences, and second, the trial duration was not long.

5. Conclusion

Melatonin was safely and tolerably superior to placebo in treating patients with sleep disorders following shift work. Evidence also showed its effects on improving occupational cognitive performance.

Melatonin supplementation can significantly enhance sleep quality within just one week, which is crucial for shift workers who often struggle with sleep disruptions. The four-week period required for cognitive function improvement indicates that shift workers can expect long-term benefits from melatonin supplementation. By improving sleep quality and cognitive function, shift workers can better adapt to the demands of their work schedule. Healthcare providers can recommend melatonin supplementation to shift workers who struggle with sleep quality and cognitive performance and should educate shift workers about the benefits of melatonin supplementation.

It is recommended that future high-quality studies should carefully examine these effects with larger sample sizes and longer durations, considering the limitations of this study and previous preclinical and clinical studies.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study protocol was approved by the institutional research ethics committee (approval code: IR.SBMU.-TEB.POLICE.REC.1402.009). The protocol followed the ethical principles of the seventh revision of the Declaration of Helsinki, as revised in Brazil in 2013, and was approved by the institutional research ethics committee.

Consent

Informed consent was obtained from all patients while being aware of the possibility of withdrawing from the study at any time without affecting their therapy and relationship with healthcare providers.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

SK conceptualized the study, administered the project, supervised the study, curated the data, performed the formal analysis, wrote the original draft, and edited the manuscript. AS wrote the original draft and visualized the study. SA conceptualized the study, administered the project, supervised the study, and was involved in protocol registration. AAM conceptualized the study, curated the data, wrote the original draft, and provided the software.

Supplementary Materials

Appendix 1: CONSORT 2010 checklist of information in reporting the trial. (*Supplementary Materials*)

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