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Original Article

Anaesthesia Section

Efficacy of 3 mg versus 6 mg Oral Melatonin in Improving Sleep Quality among Intensive Care Unit Patients: A Randomised Controlled Trial

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ABSTRACT

Introduction: Melatonin, a molecule found in nearly all living organisms, plays a vital role in regulating circadian rhythm and sleep, while also influencing immune function, cell growth, and endocrine processes. Its role in improving sleep in Intensive Care Unit (ICU) patients remains under investigation.

Aim: To compare the efficacy and safety of oral melatonin at two different doses (3 mg vs 6 mg) on sleep characteristics in ICU patients.

Material and Methods: This single-centred, double-blinded, randomised controlled trial was conducted in the Department of Anaesthesiology and Critical Care, Pt. B. D. Sharma Pandit Bhagwat Dayal Sharma Postgraduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana, India, on 46 adult ICU patients {≥18 years, Glasgow Coma Scale (GCS) ≥10}. Patients were randomly allocated to receive either 3 mg or 6 mg melatonin orally or via feeding tube at 9:00 pm for three consecutive nights, along with earplugs and eye masks. Sleep parameters were recorded from day 1 to day 3. Agitation was assessed using the Riker Sedation-Agitation (RSA) scale at 10:00 am and 6:00 pm. The length of ICU stay was noted. Data were analysed using Statistical Package for Social Sciences (SPSS) version 20.0, with p-value≤0.05 considered statistically significant.

Results: Baseline demographics and American Society of Anaesthesiologists (ASA) status were comparable between groups. Total sleep time in the 3 mg group: 7.57±2.57 h (day 1) to 8.48±2.92 h (day 3); 6 mg group: 9.48±2.74 h to 9.93±2.55 h with no significant overall difference (p-value=0.780). Night sleep was higher on day 2 in the 6 mg group (p-value=0.009), but no significant overall trend (p-value=0.084). Day sleep, arousals, and RSA scores were non significant between the two groups (p-value>0.05), and the mean ICU stay was 4.35±1.46 days in the 3 mg group and 4.48±1.55 days in the 6 mg group, with no statistically significant difference between the groups (p-value=0.781). Both doses were well-tolerated without major adverse effects.

Conclusion: Higher-dose melatonin (6 mg) significantly improved nocturnal sleep on one study day compared to 3 mg but showed no overall benefit in total sleep time, diurnal sleep, arousals, delirium, or sedation needs. Both doses were safe and well-tolerated.

Keywords: Agitation, Circadian rhythm, Critical illness, Delirium, Sedation, Sleep disorders

INTRODUCTION

Melatonin, first identified in 1958 by Aaron Lerner [1], regulates circadian rhythms, sleep, immune function, and cell growth [2]. About 80% of melatonin is secreted mainly in the pineal gland but also in other tissues like the retina, bone marrow, and gastrointestinal tract [1,3]. Melatonin secretion follows a daily cycle, peaking at night and influenced by darkness through the Suprachiasmatic Nucleus (SCN) [4].

Melatonin plays a cardioprotective role, and lower levels have been linked to myocardial infarction and sudden cardiac death [5-7]. Its synthesis originates from tryptophan metabolism, with Arylalkylamine-N-acetyltransferase (AA-NAT) as the key enzyme. Endogenous release starts in infancy, peaks in childhood, and declines with age [2]. The ICU patients often experience disrupted circadian rhythms, poor sleep, and delirium, exacerbated by environmental factors. While non drug interventions like earplugs and eye masks can help, exogenous melatonin is being explored as a potential treatment [8,9]. Sleep disturbances in critically-ill patients are linked to increased delirium risk, longer hospital stays, and cognitive decline, highlighting the need for better sleep management strategies [4]. However, existing literature lacks robust, comparative data on the optimal dosage of melatonin for improving sleep parameters in ICU patients, highlighting the need for further research [2,4,8,9]. The study aimed to evaluate and compare the efficacy and safety of oral melatonin at doses of 3 mg and 6 mg on sleep patterns in ICU patients. The primary objective was to assess nocturnal and diurnal sleep duration, total sleep time, and the frequency of arousals, while the secondary objective focused on evaluating the level of agitation and the requirement for additional sedation.

MATERIALS AND METHODS

This single-centred, double-blinded, randomised controlled trial was conducted in the Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India, from November 2022 to April 2024. The study was approved by the Institutional Ethics Committee (approval number: EC/NEW/INST/2022/HR/0189). Written informed consent was obtained from all participants.

Sample size calculation: For the sample size calculation, the mean difference of 3.3 and standard deviation of 5.5 were derived from the study by Shilo L et al., (2000), who assessed the effect of melatonin on sleep quality in ICU patients using the Pittsburgh Sleep Quality Index (PSQI) [10,11]. The sample size was calculated with 95% confidence interval, 80% power and an alpha level of 0.05. The total sample size calculated was 45, but to compensate for dropouts, the total sample size taken was 46.

Inclusion criteria: Adults more than or equal to 18 years, sedation with propofol, morphine, alfentanil and dexmedetomidine to

be discontinued, GCS more than or equal to 10, patients who were clinically and biologically stable and passed the weaning screening and were therefore ready to be weaned from mechanical ventilation.

Exclusion criteria: Severe hepatic or renal disease, pregnant and breastfeeding women, history of convulsions, psychiatric, any neurological disease, sleep apnoea, deafness or blindness, severe heart failure, intestinal obstruction, ileus, gastroparesis and other conditions likely to affect the enteral absorption of melatonin, pre-admission treatment of sleep disturbances, drugs that might alter melatonin secretion and decrease plasma levels of melatonin such as benzodiazepines, Nonsteroidal Anti-Inflammatory Drugs (NSAIDS), corticosteroids, beta-blockers, haloperidol and amiodarone.

Study Procedure

All ICU-admitted patients were screened for eligibility. Demographic details such as age and sex, along with clinical diagnosis and co-morbidities, were recorded. Past medical history, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Glasgow Coma Scale (GCS) scores were noted. APACHE II, SOFA and GCS scores were recorded as described in their original publications [12-14]. Clinical and physiological parameters, including vital signs, {Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR)} and routine ICU lab tests {White Blood Cells (WBC), Serum Creatinine (SCr), Blood Urea Nitrogen (BUN), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) were assessed at inclusion. Baseline sleep data, both objective {Total Sleep Time (TST), nighttime and daytime night-time sleep duration, sleep disruptions) and subjective (anxiety levels on a 100 mm scale}, were recorded for three days. Objective sleep quality was measured in terms of TST- the cumulative duration of sleep in 24 hours. The length of sleep at night (9:00 pm - 7:00 am) and during the day (7:00 am - 9:00 pm) [8]. Sleep disruptions-quantified as the number of arousals observed during the monitoring period. Anxiety levels were assessed using a 100 mm Visual Analogue Scale (VAS), with 0 indicating no anxiety and 100 indicating extreme anxiety. Patients or their caregivers marked anxiety at 10 am daily.

Patients received either 3 mg or 6 mg of melatonin at 9:00pm for three nights, administered orally or via a feeding tube if necessary. Earplugs and eye masks were provided.

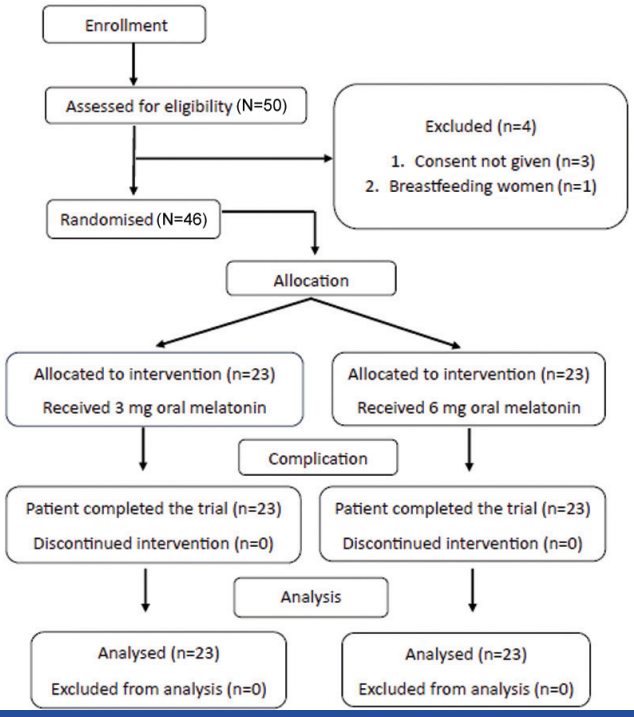
Eligible patients were randomly assigned to one of two groups: Group 1 (3 mg melatonin) or Group 2 (6 mg melatonin). Randomisation followed a computer-generated table and a concealed process using sealed, numbered envelopes. Investigators remained blinded to treatment assignments, which were stored in opaque, sealed envelopes marked only with the randomisation number.

The Consolidated Standards of Reporting Trials (CONSORT) is showing the enrollment, randomisation, allocation, and follow-up of study participants. Of the 50 patients assessed for eligibility, 4 were excluded (3 declined consent, 1 was breastfeeding) [Table/Fig-1]. The remaining 46 participants were randomised equally to receive either 3 mg or 6 mg of oral melatonin.

The primary outcome was to assess nocturnal and diurnal sleep duration, total sleep time, and the frequency of arousals, while the secondary outcome focused on evaluating the level of agitation and the requirement for additional sedation.

STATISTICAL ANALYSIS

For statistical comparisons, continuous variables were analysed using the Student's t-test when normally distributed, and the Wilcoxon Mann–Whitney U test when not normally distributed. Categorical variables were compared using the Chi-square test or Fisher's-exact test (when expected cell counts were <5). The data was coded and entered into a Microsoft Excel spreadsheet. Analysis was done using SPSS version 20.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. The variables were assessed for normality using the Kolmogorov-Smirnov test. Descriptive statistics included computation of percentages, means and standard deviations. The level of significance was set at p-value ≤0.05.



[Table/Fig-1]: CONSORT flow diagram of patient recruitment and allocation.

RESULTS

This research involved 46 ICU patients with a GCS ≥10. Baseline co-morbidities such as hypertension, diabetes, and Chronic Obstructive Pulmonary Disease (COPD) were comparable between the groups, indicating no selection bias [Table/Fig-2].

Co-morbidity	Group A (3 mg) n (%)	Group B (6 mg) n (%)	p-value
Hypertension	8 (34.8%)	7 (30.4%)	0.73
Diabetes Mellitus	6 (26.1%)	5 (21.7%)	0.73
COPD	2 (8.7%)	1 (4.3%)	0.55
Ischaemic Heart Disease	2 (8.7%)	3 (13.0%)	0.63
Chronic Kidney Disease	1 (4.3%)	1 (4.3%)	1.00

[Table/Fig-2]: Co-morbidities in study groups.

Comparisons between groups were made using the Chi-square test. Fisher's-exact test was applied where expected cell counts were <5.

Baseline severity scores are summarised in [Table/Fig-3]. Both groups had similar APACHE II, SOFA, and GCS scores, confirming clinical comparability at study entry.

Score	Group A (3 mg) (Mean±SD)	Group B (6 mg) (Mean±SD)	p-value
APACHE II	13.43±4.58	12.91±4.11	0.687
SOFA	4.57±1.36	4.65±1.39	0.822
GCS	14.13±0.78	14.17±0.75	0.872

[Table/Fig-3]: Baseline score data for APACHE II, SOFA, and GCS.

Baseline clinical and laboratory values are detailed in [Table/Fig-4]. No significant differences were observed in demographic or laboratory parameters, suggesting well-matched study groups. There was no significant difference between the groups in terms of age (years) and gender. Patients in both groups were similar. This ensured that both groups were well-matched at baseline, allowing for unbiased comparison of the clinical outcomes.

Parameters	Group A (3 mg) (Mean±SD)	Group B (6 mg) (Mean±SD)	p-value
Age (years)	46.13±18.36	39.78±19.83	0.173
Gender (M:F)	13:10	13:10	1.000
Pulse rate (beats/min)	95.78±10.78	94.04±10.63	0.537
Respiratory rate (breaths/min)	20.43±2.84	20.52±3.36	0.920
Systolic BP (mmHg)	113.91±7.50	114.08±7.83	0.949
Diastolic BP (mmHg)	75.65±7.83	74.17±6.74	0.471
WBC ($\times 10^9$/L)	11.39±3.80	11.39±4.02	0.999
Serum creatinine (mg/dL)	1.06±0.27	1.01±0.31	0.547
BUN (mg/dL)	19.65±6.56	18.91±6.02	0.655
SGOT (AST) (U/L)	23.78±4.72	24.35±5.22	0.663
SGPT (ALT) (U/L)	26.00±5.84	25.43±5.55	0.710

[Table/Fig-4]: Baseline clinical and laboratory parameters.

Prior sedative exposure is shown in [Table/Fig-5]. The majority of patients had received sedatives like propofol before enrollment, but distributions were comparable across groups.

Sedative used	Number of patients n (%)	Mean duration prior to discontinuation (Hours) (Mean±SD)
Propofol	31 (67.4%)	10.8±2.7
Dexmedetomidine	16 (34.8%)	12.3±3.5
Morphine	12 (26.1%)	8.6±2.1
Alfentanil	6 (13.0%)	6.4±1.8

[Table/Fig-5]: Sedative use prior to study inclusion.

Numbers represent patients who received each sedative before study inclusion. Since, some patients received more than one sedative, the totals exceed 46.

Changes in anxiety scores are shown in [Table/Fig-6]. Anxiety levels decreased gradually over three days in both groups, with no significant differences between doses.

Day	Group A (3 mg) (Mean±SD)	Group B (6 mg) (Mean±SD)	p-value
Day 1	49.78±6.24	50.17±6.31	0.824
Day 2	45.91±6.19	44.96±6.09	0.559
Day 3	42.30±6.25	41.87±6.31	0.779

[Table/Fig-6]: Comparison of anxiety scores (VAS 0–100 mm scale).

A) Total Sleep Time

The overall change in Subjective Sleep Quality: Total sleep time (hours) over time was compared in the two groups using the generalised estimating equations method [Table/Fig-7]. Total sleep time showed a gradual increase over three days in both the 3 mg and 6 mg melatonin groups. However, when comparing between groups, the overall difference in total sleep time was not statistically significant (p-value=0.780).

B) Night Sleep Time

The overall change in Subjective Sleep Quality: Night sleep time (hours) over time was compared in the two groups using the Generalised Estimating Equations method [Table/Fig-8]. Night sleep duration increased steadily in both groups over the three study nights. On day 2, patients receiving 6 mg melatonin had significantly longer night sleep compared to those in the 3 mg group (p-value=0.009). However, the overall trend over time was not statistically significant (p-value=0.084). Within group, analysis showed that the 3 mg group had a gradual increase in night sleep across days (p-value=0.004), while no significant trend was observed in the 6 mg group.

Subjective Sleep Quality: Total Sleep Time (Hours)	Group		p- value for comparison of the two groups at each of the timepoints (Wilcoxon-Mann-Whitney Test)
	3 mg (Mean±SD)	6 mg (Mean±SD)	
Day 1	7.57±2.57	9.48±2.74	0.023
Day 2	8.17±3.52	9.96±2.67	0.059
Day 3	8.48±2.92	9.93±2.55	0.104
p-value for change in Subjective Sleep Quality: Total Sleep Time (Hours) over time within each group (Friedman Test)	0.307	0.861	
Overall p-value for comparison of change in Subjective Sleep Quality: Total Sleep Time (Hours) over time between the two groups (Generalised Estimating Equations)	0.780		

[Table/Fig-7]: Comparison of the two groups in terms of change in subjective sleep quality: total sleep time (hours) over time.

Subjective Sleep Quality: Night Sleep Time (Hours)	Group		p-value for comparison of the two groups at each of the timepoints (Wilcoxon Mann-Whitney Test)
	3 mg (Mean±SD)	6 mg (Mean±SD)	
Day 1	5.22±1.83	6.30±1.96	0.075
Day 2	5.35±2.21	6.87±1.69	0.009
Day 3	6.37±2.11	6.78±1.68	0.465
p-value for change in Subjective Sleep Quality: Night Sleep Time (Hours) over time within each group (Friedman Test)	0.004	0.325	
Overall p-value for comparison of change in Subjective Sleep Quality: Night Sleep Time (Hours) over time between the two groups (Generalised Estimating Equations)	0.084		

[Table/Fig-8]: Comparison of the two groups in terms of change in subjective sleep quality: night sleep time (hours) over time.

C) Day Sleep Time

The overall change in Subjective Sleep Quality: Day sleep time (hours) over time was compared in the two groups using the generalised estimating equations method [Table/Fig-9]. There was no difference in the trend of subjective sleep quality- day sleep time (hours) over time between the two groups (p-value=0.348).

D) Total Number of Arousal

The number of arousals is reported in [Table/Fig-10]. Both doses resulted in a similar frequency of arousals (p-value=0.371), indicating melatonin did not affect sleep fragmentation.

E) Agitation and Sedation Needs

The mean Riker Sedation-Agitation Score was 4.17±0.78 in group A and 4.13±0.75 in group B (p-value=0.872) [Table/Fig-11]. Additional sedation was required in 5 patients (21.7%) in group A and 4 patients (17.4%) in group B (p-value=0.723), and the mean ICU stay was 4.35±1.46 days in the 3 mg group and 4.48±1.55 days in the 6 mg group, with no statistically significant difference between the groups (p-value=0.781).

Subjective Sleep Quality: Day Sleep Time (Hours)	Group		p-value for comparison of the two groups at each of the timepoints (Wilcoxon Mann-Whitney Test)
	3mg	6mg	
	(Mean±SD)	(Mean±SD)	
Day 1	2.35±1.64	3.13±1.58	0.110
Day 2	2.83±2.21	3.07±1.51	0.607
Day 3	2.20±1.70	3.09±1.81	0.112
p-value for change in Subjective Sleep Quality: Day Sleep Time (Hours) over time within each group (Friedman Test)	0.219	0.688	
Overall p-value for comparison of change in Subjective Sleep Quality: Day Sleep Time (Hours) over time between the two groups (Generalised Estimating Equations)	0.348		

[Table/Fig-9]: Comparison of the two groups in terms of change in subjective sleep quality: day sleep time (hours) over time.

Number of arousal	Group		p-value for comparison of the two groups at each of the timepoints (Wilcoxon Mann-Whitney Test)
	3 mg	6 mg	
	(Mean±SD)	(Mean±SD)	
Day 1	1.35±1.23	1.48±1.16	0.597
Day 2	1.26±0.86	1.57±0.84	0.163
Day 3	1.52±1.20	1.30±1.06	0.593
p-value for change in Number of Arousal over time within each group (Friedman Test)	0.615	0.522	
Overall p-value for comparison of change in Number of Arousal over time between the two groups (Generalised Estimating Equations)	0.371		

[Table/Fig-10]: Comparison of the two groups in terms of change in total number of arousal over time.

Parameters	Group A (3 mg) (Mean±SD) /n (%)	Group B (6 mg) (Mean±SD) / n (%)	p-value
Riker Sedation-Agitation Score	4.17±0.78	4.13±0.75	0.872
Patients requiring additional sedation	5 (21.7%)	4 (17.4%)	0.723

[Table/Fig-11]: Comparison of RSA scores and requirement for additional sedation between the two study groups.

DISCUSSION

This present randomised study involved 46 ICU patients (admitted patients with a GCS score ≥10. The aim was to compare the efficacy and safety of oral melatonin (3 mg and 6 mg) on sleep patterns in ICU patients.

In the current study, the comparison of total sleep time between the 3 mg and 6 mg melatonin groups did not show a statistically significant difference over the three days of observation. Although the 6 mg group had slightly longer average sleep durations, the change was not clinically meaningful. This finding aligns with the study by Bellapart J and Boots R, where melatonin use did not significantly impact total sleep time in critically-ill patients [2]. Similarly, Bourne RS et al., reported only modest improvements in sleep with melatonin, which were not statistically robust [9]. In contrast, Chen W et al., observed a significant increase in total sleep time and a greater proportion of Rapid Eye Movement (REM) sleep in ICU patients who received melatonin compared to those using only eye masks or earplugs, suggesting melatonin's potential benefit when combined with environmental controls [3].

This study showed a statistically significant improvement in nocturnal sleep time in the 6 mg melatonin group on day 2, indicating a dose-related short-term benefit. This supports the work of Shilo L et al., who also found that melatonin improved night-time sleep duration in ICU patients [11]. Tordjman S et al., similarly noted improved nocturnal sleep architecture with exogenous melatonin [1]. However, Costello RB et al., found no consistent improvement in nocturnal sleep duration with melatonin, suggesting that its effects may be transient or patient-dependent, possibly influenced by uncontrolled ICU environmental factors [15].

Authors found no significant difference in daytime sleep time between the two groups, suggesting that melatonin, even at higher doses, does not reduce excessive daytime sleep or promote proper circadian sleep-wake patterns in ICU patients. This result was comparable to Zisapel N findings, which emphasised that melatonin may not significantly alter daytime sleep in critically-ill individuals [16]. Contrarily, Richards GA et al., reported some reduction in daytime sleep in patients given melatonin, implying improved circadian regulation, which current study study could not replicate, likely due to environmental confounders such as lighting and routine ICU interruptions [4].

The analysis showed no significant difference in the number of arousals between the two groups throughout the study period. This observation is in line with the findings of Bellapart J and Boots R who also reported that melatonin did not significantly reduce arousal frequency [2]. Besag FMC et al., noted minimal impact of melatonin on sleep fragmentation in ICU settings [17]. However, Kurdi MS and Muthukalai SP found that melatonin significantly reduced night-time awakenings in surgical patients, suggesting that its arousal-limiting effects may be more prominent in non ICU or less critically-ill populations [18].

The study did not show a significant reduction in agitation or the need for extra sedation in either melatonin group. These findings are similar to those of Ameri A et al., who found no impact of melatonin on agitation or sedation scores in severely-ill patients [19]. However, Abbasi S et al., demonstrated a significant reduction in delirium and agitation in melatonin-treated ICU patients, possibly due to different dosing regimens or better environmental control [20]. Burry L et al., also suggested that melatonin might be effective in preventing ICU delirium, though they emphasised that further rigorous studies are needed to confirm its clinical impact [21].

Limitation(s)

Even though patients were provided with eye pads, sunglasses, and earplugs, elevated levels of noise, brightness, and nursing intervention cannot be fully controlled. Sleep parameters were recorded based on patient-reported measures, which are prone to recall bias. The different co-morbidities might have influenced the sleep quality; this factor was not considered.

CONCLUSION(S)

The current study compared the efficacy of 3 mg versus 6 mg oral melatonin in improving sleep quality among ICU patients. Both groups were comparable in baseline characteristics and well-tolerated the intervention. The 6 mg dose significantly improved nocturnal sleep duration on one study day but did not produce a consistent benefit in total sleep time, daytime sleep, arousals, or agitation levels. There were no major adverse effects, and the need for additional sedation or ICU stay length was similar between groups. Thus, melatonin can be considered a safe and effective adjunct to improve nocturnal sleep in critically-ill patients, though larger multicenter studies are required to confirm these findings and establish the optimal dosage.

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