

Sleep and circadian rhythm disturbances in intensive care unit (ICU)-acquired delirium: a case–control study

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Abstract

Objective: The relationships among sleep, circadian rhythm, and intensive care unit (ICU)-acquired delirium are complex and remain unclear. This study aimed to examine the pathophysiological mechanisms of sleep and circadian rhythm disturbances in patients with ICU-acquired delirium.

Methods: This study included critical adult patients aged 18 to 75 years who were treated in the ICU. Twenty-four-hour polysomnography was performed and serum melatonin and cortisol levels were measured six times during polysomnography. Receiver operating characteristic curves and binomial logistic regression were used to evaluate the potential of sleep, melatonin, and cortisol as indicators of delirium in the ICU.

Results: Patients with delirium ($n = 24$) showed less rapid eye movement (REM) sleep compared with patients without delirium ($n = 24$, controls). Melatonin levels were lower and cortisol levels were higher in the delirium group than in the control group. REM sleep, melatonin, and cortisol were significantly associated with delirium. The optimal cutoff values of REM sleep and mean melatonin and cortisol levels that predicted delirium were $\leq 1.05\%$, ≤ 422.09 pg/mL, and ≥ 212.14 ng/mL, respectively.

Conclusions: REM sleep, and melatonin and cortisol levels are significantly associated with the risk of ICU-acquired delirium. Improved sleep and readjustment of circadian rhythmicity may be therapeutic targets of ICU-acquired delirium.

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Keywords

Delirium, critical care, polysomnography, sleep, melatonin, cortisol

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Introduction

Delirium is an acute disorder of cognition and marked cerebral dysfunction that results in various symptoms. Delirium is common among patients treated in the intensive care unit (ICU) and is associated with poor outcomes, including increased mortality, increased length of hospital stay, cognitive decline, and long-term cognitive impairment.^{1–3}

A core domain of delirium is represented by disruption of sleep. Sleep disturbances impair cognition, resulting in apathy and confusion.^{4–6} Therefore, we hypothesized that sleep disturbances represent a high risk factor for delirium. However, the relationship between sleep disturbances and delirium is unclear.⁷ Patients in the ICU are affected by noise, pain experienced, discomfort, medication, and the mode of mechanical ventilation.⁸ Therefore, assessment of sleep in the ICU setting is difficult. Polysomnography (PSG) is a standard sleep monitoring method that allows for assessment of sleep architecture. Some PSG studies that only monitored nighttime sleep reported that patients in the ICU showed sleep fragmentation,⁹ a severe decrease in rapid eye movement (REM) sleep, and circadian misalignment.¹⁰ Because sleep patterns of patients in the ICU do not follow a normal profile, they may sleep all day and night. Therefore, 24-hour continuous PSG is appropriate and necessary to monitor sleep. However, few studies have used 24-hour continuous PSG to examine sleep disturbances among patients in the ICU.^{11,12}

Melatonin and cortisol levels follow a circadian rhythm, which is believed to be associated with sleep. Our previous study showed that patients with delirium in the ICU had reduced melatonin secretion.¹² Other studies have suggested that increased cortisol levels are associated with a risk of brain dysfunction and postoperative delirium.¹³ However, whether abnormal secretion of melatonin and cortisol can be used as an indicator of delirium among patients in the ICU remains unclear.

We investigated the proposed pathophysiological mechanisms of disrupted sleep and circadian dysrhythmia as possible contributing factors of delirium in the ICU. To verify these hypotheses, we examined 24-hour continuous PSG, and serum melatonin and cortisol levels in patients with and without delirium in the ICU.

Methods**Participants**

In this single-center, prospective case-control study, we recruited patients who were treated in the ICU of an educational hospital with 1903 beds and 22 ICU beds. The study was approved by the Human Research Ethics Committee of Binzhou Medical University Hospital (approval number: 2016-011-01) and was conducted in accordance with the ethical standards stated in the Helsinki Declaration. The study was registered in the Clinical Trials Register (ChiCTR-ROC-16010274). All patients or guardians provided written

informed consent on the day of admission. The inclusion criteria were patients aged 18 to 75 years staying in the ICU during the period of the study (24 hours). The exclusion criteria were as follows: presence of delirium before ICU admission, psychiatric illness or dementia, pregnancy, nervous system disease, auditory or visual impairment, severe liver dysfunction, brain disease, advanced malignancy, and a history of sleep disorders.

All patients were routinely assessed in accordance with the confusion assessment method-ICU once per shift (one shift = 8 hours).¹⁴ Patients showing signs of delirium during the assessment were assigned to the delirium group. At the same time, Patients without delirium who were admitted into the ICU with a similar age (<a 5-year age gap) and the same diseases were selected for the control group at a ratio of 1:1.

Clinical data collection

Clinical and laboratory data were recorded on admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II was used to assess the severity of illness.¹⁵ All patients were monitored in accordance with standard ICU principles. Sedatives and analgesics were prescribed by attending physicians in accordance with the guidelines outlined by the Society of Critical Care Medicine.¹⁶

Peripheral venous blood samples (3 mL) were obtained six times during the 24-hour PSG monitoring period (02:00, 06:00, 10:00, 14:00, 18:00, and 22:00 hours). Each blood sample was poured into a serum separator tube and centrifuged for 10 minutes at 2000×g. The separated serum was collected and stored at -80°C until analysis. Cortisol and melatonin levels were assayed using the Immulite system (KGE008; R&D systems, Minneapolis, MN, USA and RE 54021; IBL International, Hamburg, Germany).

PSG procedure and analysis

Patients in both groups were monitored for 24 hours using a portable PSG device (Siesta 802; Compumedics, Melbourne, Australia). During sleep monitoring, patients underwent two-lead frontal electroencephalography (EEG [F3/M2, F4/M1]), two-lead electrooculography, one-chin electromyography, and one-lead electrocardiography. Standard skin preparation techniques were used. Gold cup EEG electrodes were placed in accordance with the International System.¹⁷ Electrodes were applied by trained technicians. Channels were calibrated before each recording and electrode impedance was kept below 5000 Ω. A notch filter was applied to reject 50-Hz electrical noise. We used a bedside laptop to display real-time monitoring signals, and between recordings, the nurse and technicians viewed the PSG signals and rechecked the electrodes.

Sleep recordings were manually scored by trained sleep technicians in 30-s epochs. PSG data were analyzed by technicians, who were blinded to the patient groups, in accordance with the standards outlined by the American Academy of Sleep Medicine (AASM).^{17,18} Total sleep time was defined as the sum of the total time spent in all sleep stages during the overall monitoring period. Total sleep time was further separated into daytime (06:00–22:00 hours) and nighttime (22:00–06:00 hours the next day) sleep periods. Arousals were defined on the basis of the AASM criteria.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as numbers and percentages. Continuous

variables were compared using the Student's t-test or the Mann–Whitney U-test, as appropriate, and categorical variables were analyzed using the chi-square test. The different time points of excretion levels were assessed by repeated-measures analysis of variance. Peak and mean values of melatonin and cortisol excretion were compared between patients with and without delirium. Receiver operating characteristic curves were generated and the area under the curve was calculated. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed using a binomial logistic regression with delirium as the dependent variable. For all tests, a *P* value of < 0.05 was considered significant.

Results

Characteristics of the patients

Sixty patients were enrolled from December 2017 to November 2018. Four patients with delirium removed PSG electrodes after recording began because of dysphoria. Therefore, these patients were excluded. Two more PSG records of delirium that were unable to be analyzed were excluded. Six patients in the corresponding control group (patients without delirium) were excluded at the same time. Finally, data from 48 patients, 24 who had delirium and 24 who did not have delirium, comprised the final PSG data set for analysis.

The basic clinical characteristics of the two groups are shown in Table 1. There was no significant difference in age or sex between the two groups. The mean APACHE II score was significantly higher in the delirium group than in the control group (*P* = 0.03). Lactic acid levels at the time of enrolment were significantly higher in the delirium group than in the control group (*P* = 0.009).

PSG

There were substantial variations in the predominant background EEG activity in individual patients. Some patients showed suppressed EEG activity or diffuse slow waves. In some patients, PSG recordings showed high levels of alpha activity. Patients in both groups showed abnormal sleep architecture compared with standard normative values, as indicated by an abnormal distribution of sleep stage.¹⁹ Sleep stages 1 and 2 were predominant (23.50% and 53.12%, respectively) (Table 2). All patients showed a low rate of stage 3 and REM sleep, and were accompanied by a high rate of arousal. REM sleep in the delirium group was significantly lower than that in the control group (*P* = 0.002). Eighteen of the patients had no REM sleep. There were no significant differences in other sleep stages between the two groups.

Serum melatonin and cortisol levels

Serum melatonin and cortisol levels over the 24-hour monitoring period are shown

Table 1. Patients' baseline characteristics.

Characteristic	Delirium group (n = 24)	Control group (n = 24)	<i>P</i> value
Age (years)	55.29 ± 14.30	51.88 ± 15.08	0.425
Male/female	18/6	12/12	0.074
APACHE II score	18.42 ± 6.94	14.21 ± 6.08	0.03*
Lactic acid	4.00 (2.93–5.20)	2.25 (1.13–4.15)	0.009 [#]

Values are shown as mean ± standard deviation, number, or median (interquartile range). *t-test; [#]Mann–Whitney U-test. APACHE II, acute physiology and chronic health evaluation II.

Table 2. Sleep characteristics.

Variable	Normal values	All patients (n = 48)	Delirium group (n = 24)	Control group (n = 24)	P value
Total sleep time (minutes)	480	383.50 (241.5–605.0)	369.00 (220.75–894.00)	392.5 (298.00–564.00)	0.837
Total sleep time daytime (minutes)		142.50 (47.25–265.25)	143.00 (62.00–460.13)	125.00 (34.87–194.00)	0.124
Stage 1 (% total sleep time)	4.4	23.50 (15.25–41.25)	27.85 (17.48–53.55)	18.85 (14.2–37.75)	0.161
Stage 2 (% total sleep time)	56.5	53.12±17.54	52.95±19.40	53.30±15.89	0.945
Stage 3 (% total sleep time)	17.7	10.65 (3.60–17.35)	7.1 (3.6–12.93)	13.7 (4.85–22.83)	0.119
REM (% total sleep time)	20.8	1.0 (0.23–4.58)	0.45 (0.005–1.00)	3.15 (0.88–7.15)	0.002 [#]
Arousals per hour		16.84±10.14	14.80±9.91	18.88±10.15	0.165

Values are shown as mean ± standard deviation or median (interquartile range). [#]Mann-Whitney U-test. REM, rapid eye movement.

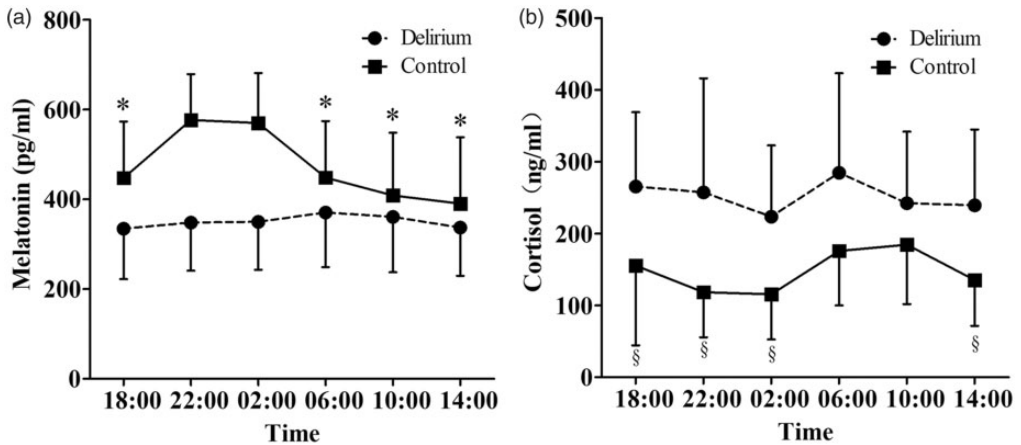


Figure 1. Melatonin (a) and cortisol (b) excretion in patients with or without delirium at different time points within 24 hours. Values are shown as means and error bars indicate standard deviations. * $P < 0.001$, compared with the peak melatonin value at 22:00 hours in the control group (one-way analysis of variance). § $P < 0.001$, compared with the peak cortisol value at 10:00 hours in the control group (one-way analysis of variance)

in Figure 1. In the delirium group, peak values of melatonin and cortisol were observed at 06:00 hours. However, in the control group, peak melatonin and cortisol values were observed at 22:00 and 10:00 hours, respectively. There were significant differences between peak melatonin and

cortisol values and values at other time points (except for 02:00 hours for melatonin and 06:00 hours for cortisol) in the control group (all $P < 0.001$), but these differences were absent in the delirium group.

The peak and mean levels of melatonin were significantly lower in the delirium

group than in the control group (both $P < 0.0010$) (Table 3). In contrast, the peak and mean levels of cortisol were significantly higher in the delirium group than in the control group (both $P < 0.001$). Additionally, the mean melatonin level was significantly lower and the mean cortisol level was significantly higher in the daytime (06:00–14:00 hours) than in the nighttime (18:00–02:00 hours) in the control group ($P < 0.001$ and $P = 0.006$, respectively). However, diurnal and nocturnal differences were absent in the delirium group (Table 3).

Risk factors of delirium

The areas under the curves for REM sleep and mean melatonin and cortisol levels in the delirium group were 0.761 (0.614–0.909), 0.880 (0.780–0.981), and 0.866 (0.760–0.973), respectively (Figure 2). Receiver operating characteristic analysis showed that the optimal cutoff values that predicted ICU-acquired delirium were as follows. For REM sleep, the optimal cutoff was $\leq 1.05\%$, with a sensitivity of 79.2% and a specificity of 75.0%.

Table 3. Serum melatonin and cortisol levels and circadian rhythm.

Variables	Delirium group (n = 24)	Control group (n = 24)	P value
Melatonin			
Peak value (pg/mL)	461.88 ± 85.39	629.01 ± 93.41	<0.001*
Mean value (pg/mL)	349.97 ± 71.91	473.53 ± 90.94	<0.001*
Mean daytime value	356.03 ± 89.23	415.74 ± 118.57 [▲]	0.070
Mean nighttime value	343.91 ± 74.94	531.32 ± 83.96	<0.001*
Cortisol			
Peak value (ng/mL)	371.48 (276.11–425.52)	239.66 (192.23–281.31)	<0.001 [#]
Mean value (ng/mL)	252.14 ± 82.22	144.16 ± 43.05	<0.001*
Mean daytime value	255.46 ± 96.17	165.22 ± 55.40 [▲]	<0.001*
Mean nighttime value	248.82 ± 98.56	122.25 ± 47.79	<0.001*

Values are shown as mean ± standard deviation or median (interquartile range). *t-test; [#]Mann–Whitney U-test;

[▲] $P < 0.01$, compared with the mean nighttime value in the control group.

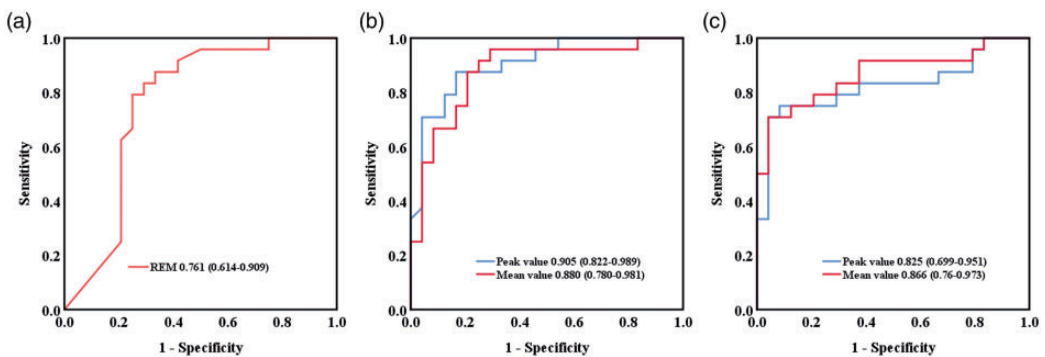


Figure 2. Receiver operating characteristic curves for prediction of delirium. REM sleep (a), melatonin levels (b), and cortisol levels (c). The areas under the receiver operating characteristic curve values (95% CIs) are shown.

REM, rapid eye movement.

For melatonin levels, the optimal cutoff was ≤ 422.09 pg/mL, with a sensitivity of 91.7% and a specificity of 75.0%. For cortisol levels, the optimal cutoff was ≥ 212.14 ng/mL, with a sensitivity of 70.8% and specificity of 95.8%.

After adjustment for age, sex, the APACHE II score, and lactic acid levels, REM sleep (OR = 0.44; 95% CI, 0.21–0.88; $P = 0.021$), the mean melatonin value (OR = 0.972; 95% CI, 0.945–1.00; $P = 0.039$), and the mean cortisol value (OR = 1.05; 95% CI, 1.01–1.09; $P = 0.014$) were independently associated with delirium.

Discussion

Delirium is highly prevalent among critically ill patients and is associated with increased morbidity and mortality rates. The relationships among sleep, circadian rhythm, and delirium in the ICU are complex and likely bidirectional. To the best of our knowledge, this is the first prospective study to examine continuous 24-hour PSG data and the circadian rhythms of melatonin and cortisol secretion among patients in the ICU. We found that REM sleep and melatonin and cortisol levels were associated with delirium.

Research has suggested that memory consolidation is impaired by disruption of the natural slow-wave sleep and REM sleep cycle.²⁰ Notably, REM sleep enhances procedural and emotional memory, and previous studies have shown that sleep disturbances can qualitatively and quantitatively alter memory representations.^{21,22} Loss of sleep on the first night post-surgery may be an early predictor of subsequent delirium.²³ Taken together, these studies highlight the close relationship between sleep and delirium. In accordance with the findings of previous studies,¹⁰ we observed decreased REM sleep in patients with delirium. Therefore, disruption of sleep may play an important role in the

occurrence and development of delirium among patients in the ICU.

In mammals, the melatonin rhythm is generated by an endogenous circadian master clock. Melatonin secretion is normally low during the daytime, increases soon after the onset of darkness, and peaks in the middle of the night.²⁴ The melatonin circadian rhythm is severely disrupted in critically ill patients.^{25,26} Boyko et al.²⁷ found that melatonin secretion in critically ill patients still followed a diurnal curve with the acrophase at 04:30 hours. Our study showed that serum melatonin rhythms were altered in patients with delirium. We observed a loss of the melatonin circadian rhythm with the acrophase at 06:00 hours in patients with delirium. Additionally, fluctuations in melatonin secretion were moderate in patients with delirium. However, circadian variation and a diurnal curve of melatonin secretion were observed in patients in the control group. These findings suggest that the physiological pattern of melatonin secretion is greatly disturbed among patients in the ICU.

In addition to abolished rhythmicity, the peak and mean melatonin values were significantly lower in the delirium group than in the control group. Similar to our observations, some studies have reported that patients with brain injury show reduced melatonin levels and more pronounced rhythm disturbances.²⁸

Cortisol is a glucocorticoid hormone involved in the hypothalamic–pituitary–adrenal axis and it plays an important role in coordinating adaptive responses to stressful events. Cortisol secretion also shows circadian variation. In the present study, altered cortisol rhythms and higher cortisol levels were found in the delirium group compared with the control group. Additionally, there were significant differences between daytime and nighttime levels of cortisol secretion in the control

group, while these diurnal changes were not observed in the delirium group. Other studies have also reported an association between higher cortisol levels and lower cognitive ability.^{29,30} Cortisol levels are increased in patients with severe sepsis and brain dysfunction³¹ and such an increase is associated with postoperative delirium.^{13,32}

Although several studies have investigated the potential risk factors for delirium among patients in the ICU, their findings have been heterogeneous and no definitive conclusions have been achieved.^{33,34} Moreover, changes in sleep-related biomarkers may precede the symptoms of delirium.^{23,32,35} In our study, REM sleep, melatonin levels, and cortisol levels were independently associated with an increased risk of delirium among patients in the ICU, which validated our hypothesis. An REM stage of $\leq 1.05\%$, a mean melatonin value ≤ 422.09 pg/mL, and a mean cortisol value ≥ 212.14 ng/mL showed good sensitivity and specificity for the diagnosis of delirium in the ICU.

Melatonin and melatonin receptor agonists are widely used agents in the therapy of sleep disturbances. Consistent with our findings, there is also some evidence for the efficacy of melatonin for delirium in the ICU. Some studies have reported that oral melatonin treatment improves sleep quality in healthy participants who are exposed to a simulated ICU environment and patients with critical illness.^{36,37} Taken together, these previous studies and our results support the notion that sleep quality is associated with melatonin and cortisol secretion. Recent studies have shown that melatonin treatment decreases postoperative delirium and delirium in older adults who are admitted to acute care facilities.^{38,39} However, two studies reported that treatment with 3 mg of melatonin did not prevent delirium in non-ICU patients.^{40,41} Therapy with melatonin and ramelteon (a melatonin receptor agonist) minimizes the effect of risk factors on

development of delirium. This is a natural form of therapy, which prevents the circadian rhythm being disturbed by the ICU environment.⁴² To a certain extent, these discrepant findings confirm that there are potential differences in the pathogenesis of simple delirium and ICU-related delirium.

This study has several limitations. First, the study was in a single center and comprised a small sample. Larger, multicenter studies are required to verify our preliminary findings. Second, PSG recordings and biological data were collected only for 24 hours. Therefore, we did not perform a before and after comparison, which might be important for determining the incidence of delirium in the ICU.

Conclusion

In the present study, patients with delirium showed markedly less REM sleep compared with patients without delirium. Furthermore, serum melatonin levels were lower, while cortisol levels were higher in patients with delirium than in those without delirium. Decreased REM sleep, lower melatonin levels, and higher cortisol levels were independently associated with an increased risk of delirium. Therefore, improvement in sleep and readjustment of circadian rhythmicity may be therapeutic targets for prevention and treatment of delirium in the ICU. Further research is required to understand the underlying physiological relationships and develop effective prevention and therapeutic strategies.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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