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Research Article

Effect of Light Exposure on Serum Melatonin Levels of ICU Patients: A Preliminary Observational Study

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Abstracts

Aim: To examine whether the serum melatonin levels in ICU patients are affected by light exposure in the "light" and "dark" parts of the ICU.

Method: We measured serum melatonin levels of 10 ICU patients having their bed positioned in the "light part" (artificial and natural light) and "dark part" (only artificial light) of the ICU at two different time points, 8:00 ("morning") and 20:00 ("evening") during a 24–96-h period.

Results: Serum melatonin levels did not differ between "morning" (112 ± 15 pg/ml) and "evening" (87 ± 13 pg/ml) in ICU patients. Overall, higher melatonin levels were detected in female patients compared to male patients. Significantly higher light intensity was detected in the "light part" compared to the "dark part" of the ICU, not only in the "morning" but also in the "evening". However, by dividing patients according to their bed positioning ("light part" versus "dark part") in the ICU, no difference was detected in the serum melatonin levels. Similarly, the ratio ("morning" versus "evening") of light intensity and melatonin levels did not differ between the light and dark parts of the ICU.

Conclusion: Studies reporting melatonin patterns in ICU patients are heterogeneous and contradictory, which renders this topic highly challenging. Larger studies regarding the effect of light exposure on melatonin levels in ICU patients are required to reveal the true impact and indicate potential nursing interventions.

Keywords: Serum melatonin levels; ICU patients; Light exposure

Introduction

Melatonin is a hormone synthesised mainly by the pineal gland, and its secretion levels are low during daylight and peak during the dark phase [1,2]. Melatonin is released at night beginning around 21:00 with peak release between 2:00 and 4:00, and it is inhibited typically between 7:00 and 9:00 [3]. Peak plasma levels, which are highly variable, are approximately 100 pg/ml [2]. As an amphiphilic hormone, melatonin acts as a scavenger of free radicals. Moreover, the effects of melatonin are mediated through specific membrane receptors. Melatonin has several pleiotropic actions beginning from controlling the day/night cycle and hypothalamic/pituitary axes to, for example, immunomodulation and modulation of endocrine functions [4]. Melatonin is also considered a hormonal marker of the circadian system's functioning [5].

The circadian system generates circadian approximately 24-h rhythms that are significant in healthy people. Age and diseases significantly reduce the variability of 24-h rhythms of many physiological parameters and biomarkers, including melatonin [6,7]. Melatonin variability is characterised by interindividual differences. Alterations to melatonin levels are observed in critically ill patients at the intensive care unit (ICU) [8]. Plenty of

factors, such as light, noise and interventions pertinent to the ICU environment, have been demonstrated to worsen variability to the 24-h rhythms of many body functions [9]. The 24-h variability of physiological parameters such as heart rate, mean arterial pressure and body temperature are affected [9-11]. Furthermore, the critical illness per se and sepsis, which is a clinical state during the stay in the ICU, can lead to circadian dysrhythmia and melatonin variability disturbance, as many studies have demonstrated [12].

Intense night lights, something prevalent in the ICU environment, can lead, among others, to worse 24-h variability of melatonin secretion. Bed positioning regarding light exposure is one factor that could affect 24-h variability of melatonin. Therefore, in the present study, we examined whether bed positioning regarding light exposure in two parts of the ICU ("light part" and "dark part") influences the serum melatonin levels at two different time points, 8:00 ("morning") and 20:00 ("evening") during a 24–96-h period, in ICU patients.

Materials and Methods

Ethical and research approvals

The study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002), followed by biological rhythm research protocols [13] and independently reviewed and approved by the ethical committee of the hospital. All patients signed informed consent forms, or when patients were unable to sign, consent was obtained from their legal representatives.

ICU design

This descriptive observational study was conducted in a general mixed 9-bed single-ward University Intensive Care Unit at a Greek general hospital in Athens. Total admissions at this ICU are low because the study site is a training hospital without a high dependency unit. High dependency unit patients are treated in the ICU, resulting in a longer mean length of stay. The windows offered access to natural lighting. In addition, artificial lighting consisting of overhead panels containing bright white fluorescent lights illuminated the ICU. The ICU arrangement distinguished between an array of three fully-equipped beds close to the windows in a "light part" and six otherwise identical beds bounded by a corridor in a "dark part" in the same room. Patients were assigned to a bed on either part of the ICU [14], depending on bed availability at the time of admission. The same nursing staff attended both sets of patients. Notably, this study did not manipulate light exposure but took advantage of natural light variability within the existing ICU design. "Morning" was set from 8:00 to 20:00, and "evening" was set from 20:00 to 8:00. Patients in total, 86 subjects were admitted to the ICU during the study period. According to the eligibility criteria, 35 eligible ICU patients were divided into "light part" and "dark part" groups. Because of missing data relating to light exposure, we removed 13 patients from the study post-hoc. From the remaining 22 patients, we obtained qualitatively and quantitatively adequate blood samples from 11 patients for the measurement of serum melatonin. Melatonin concentrations were out of the physiological range in one patient, so we excluded the patient from the data set.

Eligibility criteria

The inclusion criteria in this study were: critically ill patients with respiratory and/or cardiovascular disease, and surgical patients over 18 years old. At least 24 hours before study entry and throughout the whole 24–72-h study period the patients should be afebrile (body temperature < 38.3 °c) without analogue-sedation and mechanical ventilation.

The exclusion criteria were: participation in another clinical study in the past 30 days, use of glucocorticoid medication during the last 14 days, use of vasopressors or β-blockers, less than one week before study entry, delirium, sleep disorders, clinical depression, craniocerebral injury, thyroid disorders, liver cirrhosis, renal failure, haemodialysis, coronary heart disease, sepsis, multi-organ failure or severe coagulopathy. All patients were evaluated within 24 hours of admission, calculating the APACHE II score, a severity-of-disease classification system, and the SOFA score to predict hospital mortality based on six organ dysfunction factors [15]. None of the female participants had a history of menstrual irregularities. Measurement of melatonin levels.

The patients had a central venous catheter routinely inserted at admission to the ICU. Blood samples were drawn from this catheter every 12 hours in a 24–96-h period to measure serum melatonin. In total, ten patients were analysed. Blood was drawn at two time points (8:00 and 20:00), and serum was isolated. Melatonin levels were measured by competitive Enzyme-linked immunosorbent assay (ELISA) using an ELISA kit (Elabscience, E-EL-H2016, Houston, TX, USA). The sensitivity was 9.38 pg/ml, and the detection range was 15.63–1000 pg/ml. The results were expressed in pg/ml, and the mean level was calculated for each time-point for each patient.

Light levels

Light exposure (lux levels) was monitored for 24–96 consecutive hours and analysed separately for "morning" and "evening" using the MotionWatch 8© actigraphy system (MW8, CamNtech, Cambridge, UK). Light data were recorded with a one-minute epoch and tracked with MotionWare 1.1.20 software.

Data analysis and statistical evaluation

We investigate the dependence between multiple variables by a correlation matrix, Pearson correlation test (Figure 1). The Shapiro-Wilk test of normality was applied, and when proven not significant ($p > 0.05$), we used the dependent 2-group t-test (Figure 2 and 4 and Table 1 and 2). If the data did not have a normal distribution, an independent 2-group Mann-Whitney U Test was used (Table 2). Data were analysed also using a two-way repeated measures ANOVA (Fig. 3: time vs gender; time vs ICU part) followed by Tukey's post hoc tests. Differences with $p<0.05$ were considered statistically significant. Data in the text and figures are expressed as the arithmetic mean ± standard error of the mean (SEM). All data analyses and their visualisation were done in R version 3.6.3, packages: ggplot2, ggpubr, Hmisc, corrplot and magrittr [16,17].

Table 1: Characteristics of ICU patients.

	All patients (mean ± SEM) [min – max]	Male (mean ± SEM) [min – max]	Female (mean ± SEM) [min – max]	p-value (male vs female)
n	10	6	4	
n, light part	4	3	1	
n, dark part	6	3	3	
Age (years)	70.1 ± 6.0 [29 – 87]	75.8 ± 4.9 [54 – 85]	61.5 ± 13.0 [29 – 87]	0.362
Length of ICU stay (days)	17.4 ± 6.1 [2 – 58]	23.0 ± 9.7 [2 – 58]	9.0 ± 2.3 [3–13]	0.214
APACHE-II score	24.7 ± 1.9 [11 – 35]	24.5 ± 3.3 [11 – 35]	25.0 ± 0.7 [23–26]	0.889
SOFA	9.5 ± 0.8 [3 – 13]	9.2 ± 1.4 [3 – 13]	10.0 ± 0.8 [8 – 12]	0.613

Table 2: Comparison of the light intensity between the dark and light part of the ICU.

	Light part, lux (mean ± SEM) [min – max]	Dark part, lux (mean ± SEM) [min – max]	p-value
Morning (08:00 – 20:00)	220 ± 41 [147 – 289]	76 ± 22 [32 – 148]	0.048
Evening (20:00 – 08:00)	55 ± 8 [39 – 64]	18 ± 4 [7 – 29]	0.024

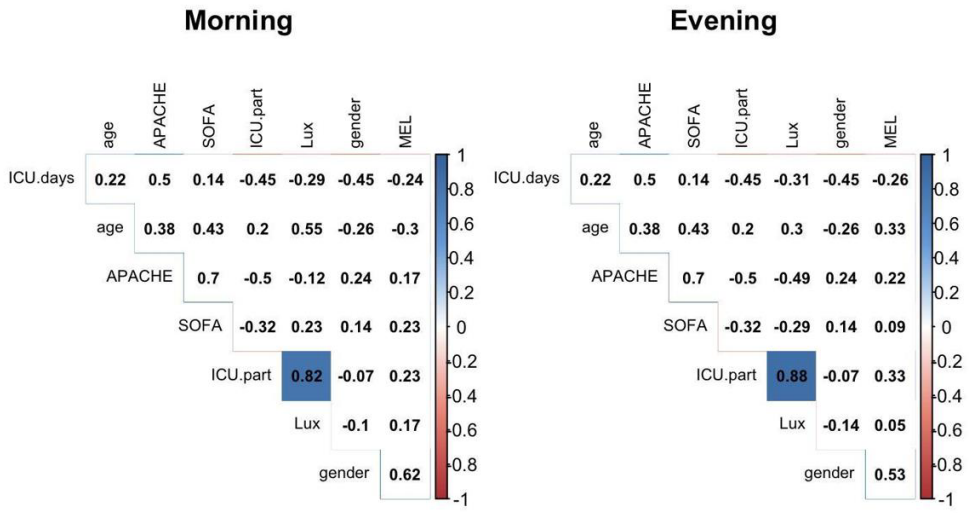

Figure 1: Graphical display of a correlation coefficient matrix of selected parameters separately in the "morning" and "evening". The correlation matrix contains the correlation coefficients. The coloured correlation coefficients represent a significant ($p < 0.05$) correlation. Male = 1, Female = 2, Light ICU part = 1, Dark ICU part = 0.

Results

The mean age of 10 enrolled ICU patients (6 males, 4 females) was 70.1 ± 6.0 years. 4 patients (3 males, 1 female) were positioned in the "light part" of the ICU and 6 patients (3 males, 3 females) were positioned in the "dark part". The mean length of stay in the ICU was 17.4 ± 6.1 days, and the mean APACHE II and SOFA score were 24.7 ± 1.9 and 9.5 ± 0.8, respectively (Tab.1). These parameters were similar between the male and female patients. Similarly, no significant differences were noted between SOFA and APACHE II score, as well as length of stay, when "light part" and "dark part" patients were compared (data not shown).

Significantly higher light intensity was detected in the light part compared to the dark part of the ICU, not only in the "morning" (light part: 220 ± 41 lux, dark part: 76 ± 22 lux, t-test, p=0.048) but also in the "evening" (light part: 55 ± 8 lux, dark part: 18 ± 4 lux, t-test, p=0.024). Accordingly, light intensity in the ICU positively correlated with the ICU part both in the "morning" (r = 0.82, p = 0.013) and in the "evening" (r = 0.88, p = 0.004; Figure 1).

Then, we measured serum melatonin levels in all ICU patients in the "morning" and the "evening", and surprisingly no significant difference was detected between the two time-points (112 ± 15 pg/ml vs 87 ± 13 pg/ml, t-test, p= 0.104; Figure 2).

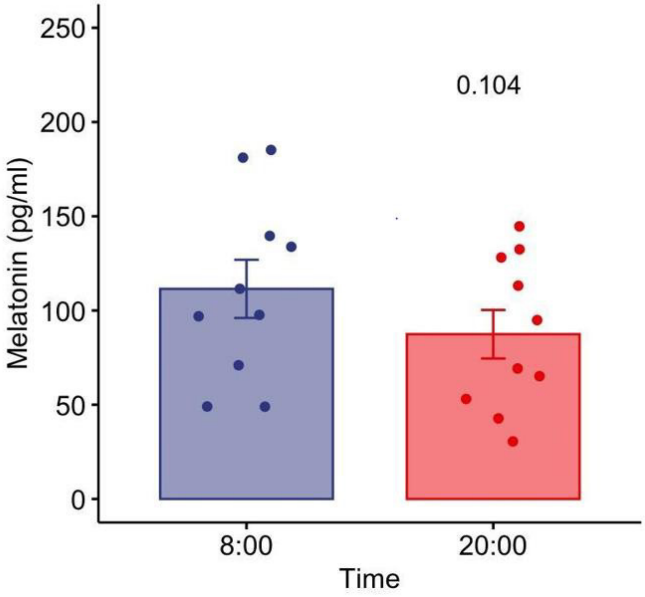

Figure 2: Comparison of serum melatonin measured in the "morning" (8:00; n=10) and in the "evening" (20:00; n=10).

To examine whether the serum melatonin levels were affected by light exposure in the light and dark ICU part, we analysed melatonin levels of the ICU patients according to their bed positioning in the ICU. We found that serum melatonin levels did not differ between ICU patients in the light and dark part of the ICU in the "morning" nor in the "evening" (two-way repeated ANOVA, factor: ICU.part, p = 0.621; Figure 3A). However, analysis of melatonin levels by gender revealed an overall significant effect (two-way repeated ANOVA, factor: Gender, p = 0.042; Figure 3B). Figure 3B). This finding was consistent with the marginally significant, positive correlations between serum melatonin content and gender, both in the "morning" (r = 0.62, p = 0.084) and in the "evening" (r = 0.53, p = 0.078; Figure 1).

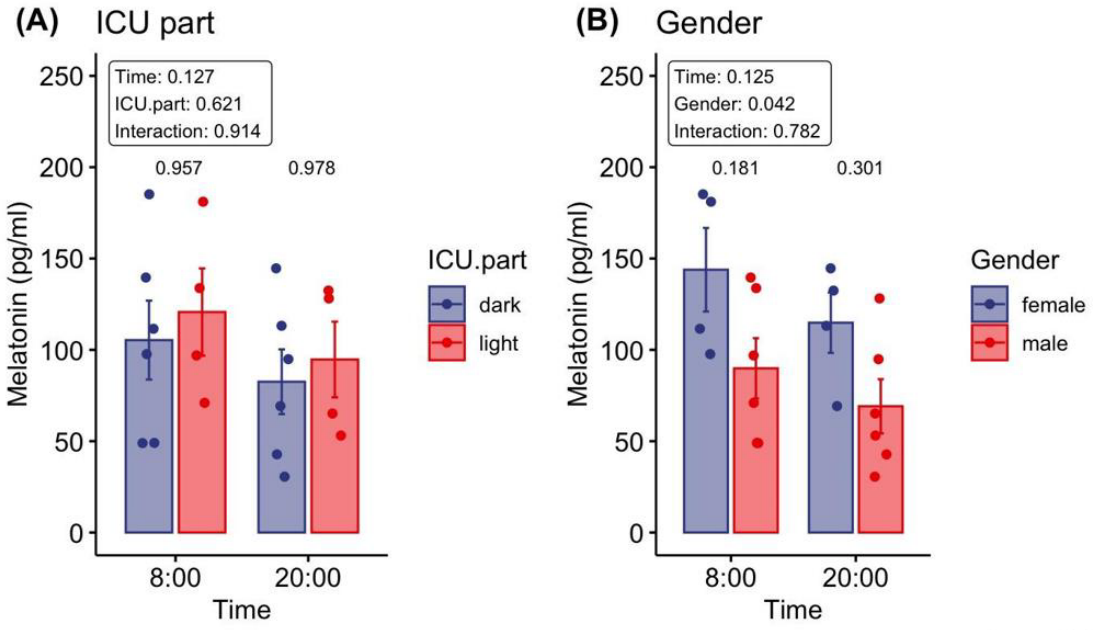

Figure 3: Effects of ICU part (A) and gender (B) and on serum melatonin levels measured in the "morning" (8:00; n=10) and in the "evening" (20:00; n=10).

Absolute (Fig. 3A) and relative (Fig. 4A) plasma melatonin levels did not differ between patients in the dark part and light part of the ICU, although the light intensity was lower than in the light part of the ICU (Tab. 2). On the other hand, the relative light intensity ratio ("morning" vs "evening") did not differ between the light and dark part of the ICU Figure 4B).

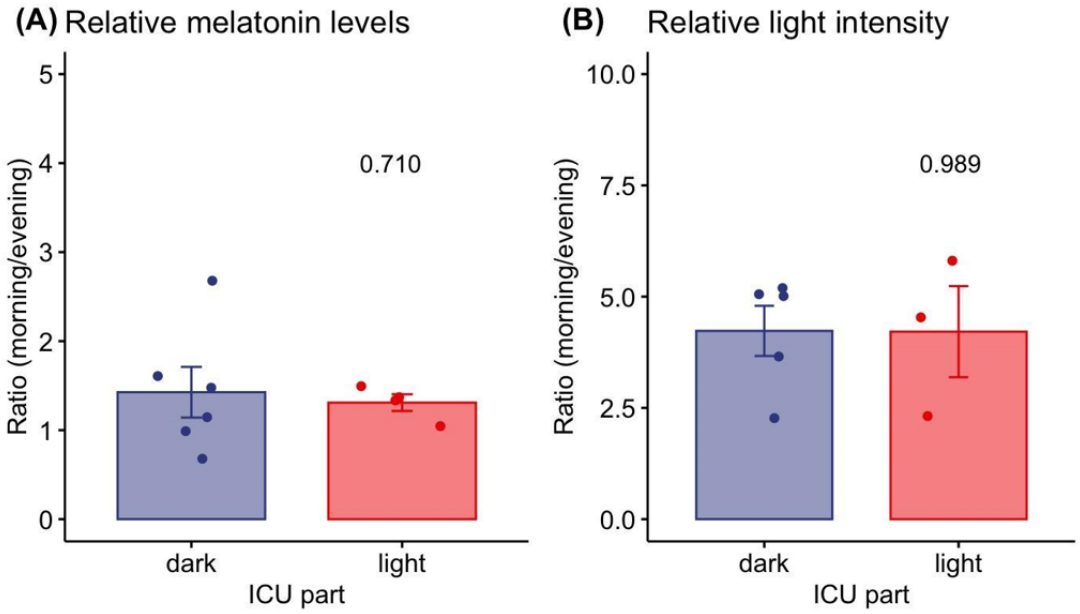

Figure 4: Ratio ("morning" / "evening") of serum melatonin levels (A) and light intensity (B) expressed for ICU patients separately in the light and dark part of the ICU.

Discussion

The current study examined whether the bed positioning regarding light exposure could correlate with altered serum melatonin levels. ICU patients were exposed to environmental situations, like abnormal light, nutritional intake and arousal stimuli (increased and mistimed). Regarding 24-h variability of melatonin, melatonin levels were measured in the patients' serum because this approach is methodologically superior to measuring urine melatonin levels to estimate variability to critically ill patients [2,18]. It was of our knowledge that the two selected time-points, 20:00 ("evening") and 8:00 ("morning"), for the measurement of melatonin are not the typical ones for its release and inhibition respectively, providing light exposure follows a standard cycle of light/darkness. Since, there is a lack of a common pattern to melatonin's release in ICU patients [11,19], we aimed to examine whether bed positioning regarding light exposure in two parts of the ICU ("light part" and "dark part") influences the serum melatonin levels at two different time points during a 24–96-h period, in ICU patients.

Towards this purpose, we measured the serum melatonin levels in patients in the dark and light part of the ICU in the "morning" (8:00) and the "evening" (20:00). At both time-points, no difference was detected regarding bed positioning, demonstrating probably disturbed 24-h variability, which is consistent with data from both healthy and ICU patients [19,20]. Our study demonstrated that serum melatonin levels were slightly higher in the ICU patients relative to those reported in the literature for healthy individuals [2]. This observation possibly depicts the ICU environment, since higher levels of melatonin are associated with inflammation and with people in the ICU [21,22]. The absence of a typical environmental synchronising agent, abnormal lighting, arousals from nursing care, noise pollution can cause dysregulation of melatonin secretion during the ICU patients' stay until their discharge. In addition, ICU patients may have also been experienced with episodes of sepsis during their stay in the ICU; sepsis per se, recovery from which could take some days [23] could alter circadian output and diminish sensitivity to light entrainment since elevated melatonin levels can be a physiological response to critical illness [11]. Moreover, as it is released by β-adrenergic stimulation, melatonin variability is altered regarding the vasopressors that may have been administered to septic patients [18].

Also, feeding and conversely significant food restriction stimulates melatonin production by the enterochromaffin cells of gastrointestinal origin [24]. Thus, it is conceivable that the pattern of inadequate feeding followed by continuous enteral/parenteral feeding in critically ill patients may contribute to the raised serum melatonin levels and, importantly, the lack of 24h variability [2].

Analysis of melatonin data by gender showed higher serum melatonin levels in female than male patients. Our data are in contrast with published data considering the age of our sample. Obayashi et al. found that urinary 6-sulfatoxymelatonin excretion was significantly lower in older females than in males [25]. A

study from Gunn et al. [26] found that younger females, however, exhibited significantly greater levels of plasma melatonin than males. Also, differences with previous studies may be explained, at least partly, due to different laboratory settings, other methods of melatonin measurement regarding the biological fluid (saliva, urine, plasma), and different time-points measurement.

This study focused on evaluating the effect of bed positioning in the ICU on serum melatonin levels. We assumed that the bed positioning in the darker part of the ICU would be associated with higher serum melatonin levels in ICU patients. However, at both time-points 8:00 and 20:00, such an effect was not detected [11]. A previous study showed that plasma melatonin levels were not affected by high lux levels [27].

The absence of an effect of light exposure on the melatonin levels can be explained in two ways: 1) Light intensity ratio ("morning" / "evening") did not differ between the light and dark parts of the ICU. For further studies, it would be good to compare light regimes with a different light intensity ratio ("morning" / "evening"), for example, the same "morning" (day) light intensity but different "evening" (night) light intensity, consider the light history of patients [28,29]. 2) We could not evaluate properties of the 24-h curve, such as acrophase shift or reduction of amplitude [18,22], which are typical for critically ill patients [30], due to two-point measurement. Another limitation of the current study is the lack of difference between melatonin levels at 8:00 and 20:00, indicating that in future studies of melatonin levels in ICU patients, at least six measurements within a 24-h cycle should be performed [10].

Conclusion

Regular control of lighting, following the sleep/wake cycle, meaning more light in the "morning" hours and more darkness during the night, can improve the 24-h variability of physiological parameters, including melatonin, which has pleiotropic effects and enhances recovery. The current study showed that melatonin levels at the beginning and end of the day's light phase are not affected by the bed positioning of the ICU patients neither in the "morning" nor in the "evening". The absence of such an effect can be partially attributed to the same ratio of light intensity in the light and dark part of the ICU or to the study of melatonin levels at only two time-points leading to the inability to assess changes in 24-h melatonin variability. Studies reporting melatonin patterns in ICU patients are highly heterogeneous and contradictory, especially in ICU patients, rendering this topic highly challenging. Our finding indicates that the synthesis and release of melatonin were not impeded at the period we measured before ICU patients' discharge.

Given the circadian rhythm disturbance in our ICU patients regarding melatonin, and the potential consequences of circadian rhythm disruption, several interventions by the ICU nursing personnel might trigger the restoration of circadian rhythmicity.

Potential therapies include modifying the external environment, like bed position oriented to light during the hours of the day with light, interventions to improve 24-h rest-activity circadian rhythm, and medication administration.

Limitations

The results of this study need to be considered in the context of several limitations. First, the sample size was small despite the large group of admitted patients at the beginning. We wanted to exclude various pharmacological and non-pharmacological effects that could affect the results, and thus we excluded a significant part of patients according to the eligibility criteria. Second, differences in the light intensity of the "light part "and "dark part" of ICU during a day, are not warrantied for the significant changes in melatonin levels since melatonin levels are physiologically controlled by several factors and small, incidental changes cannot significantly affect its levels. Finally, we measured melatonin at 8:00 and 20:00. However, melatonin is a hormone predominantly present in plasma during the night, and further studies should take this into account and measure melatonin ideally in the middle of the night. To better understand the relationship between circadian regulation affected by light and melatonin secretion, it is advisable to measure melatonin at least every four hours within a 24-hour cycle.

Relevance to Clinical Practice

Significant circadian variability is a sign of good health. The activity of the circadian system is significantly dependent on the alternation of light and dark. We, therefore, assumed that changing the position of the beds at the ICU could improve the circadian variability of melatonin. A good marker of the circadian state is melatonin, the synthesis of which also depends on the intensity of light at night. By moving the beds in the ICU to the darker part, we did not observe a change in the plasma melatonin concentration compared to the patients in the light part of the ICU. We, therefore, recommend considering the light history; the light intensity during the day in the darker part of the ICU should be like the light part of the ICU.

Disclosure of interest

The authors declare that there is no conflict of interest.

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