META-ANALYSIS

Preventive Effects of Melatonin on Delirium in Intensive Care Unit Patients: A Meta-Analysis of Randomized Controlled Trials

Lianwei Zhao, MM; Zhipeng Feng, MM; Quanzhen Wang, MD; Zhiming Jiang, MD; Xianming Qiu, MM

ABSTRACT

Aims • To investigate the preventive efficacy of melatonin on the incidence of delirium and other clinical outcomes of subjects in the intensive care unit (ICU).

Methods • Randomized controlled trials concerning the effects of melatonin on delirium published from inception to July 2022 were identified from PubMed, Embase, and the Cochrane Library. The primary outcome was delirium incidence. The secondary outcome was the length of ICU stay, the duration of mechanical ventilation, and the mortality in ICU. A meta-analysis was performed. Estimates were presented as risk ratio (RR) or standard mean difference (SMD) with 95% confidence interval (CI).

Results • Eleven RCTs with 2002 patients were included. The forest plots showed that the delirium incidence did not significantly decrease after melatonin administration (RR 0.85; 95% CI, 0.61~1.18, P = .32, I^2=60%, P for heterogeneity = .01). The subgroup analyses confirmed that melatonin significantly reduced the incidence of delirium (RR 0.70; 95% CI, 0.56~0.89, P = .003, I^2 = 32%, P for heterogeneity = .22) for the special ICU patients. Also, for ICU patients, the length of ICU stays, duration of mechanical ventilation, and mortality were not significantly decreased after melatonin treatment (all P > .05).

Conclusion • Melatonin may decrease the incidence of delirium for special ICU patients.

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INTRODUCTION

Delirium is a symptom of brain dysfunction, characterized by disturbance in consciousness, attention, global cognition, and sleep-wake cycle.[1,2] Approximately 50% to 80% of critically ill patients with mechanical ventilation experienced delirium during an intensive care unit (ICU) or hospital stay.[3-5] Delirium poses a risk for extended periods of mechanical ventilation and ICU stay, increased mortality, heightened changes of cognitive complications, and greater healthcare costs.[6-8] The mechanisms underlying delirium remain unclear. Critical illness affects various functional pathways that disrupt normal cognition. Management of delirium in ICU patients has historically been challenging.

Melatonin is a neurohormone mainly secreted by the pineal gland in the brain. The secretion of melatonin is parallel to the light–dark cycle, with a peak level of secretion in darkness. Melatonin has a variety of physiological functions, such as circadian rhythm, immune regulation, prooxidant and antioxidant activity, and neuroprotection.[9] Studies have shown conflicting results about melatonin secretion in critically ill patients.[10-12] Exogenous melatonin is being evaluated as a potential agent to prevent and/or treat delirium in hospitalized patients, especially for elderly patients.[13] Moreover, Sultan et al. demonstrated that melatonin was associated with a significant reduction in the incidence of post-operation delirium.[14] In recent years, clinical trials have reported that melatonin can potentially reduce delirium and improve survival rates of patients. Previous studies reported a conflicting array of findings about preventing delirium through melatonin administration. This study provides a systemic review and meta-analysis to assess the pooled results from studies about the efficacy of melatonin on delirium among critically ill patients.

METHODS

Study Registration

The checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the conduction of this investigation.[15] This meta-analysis was registered on PROSPERO. The registration number was CRD42022354874.

Search Strategy and Selection Criteria

The researchers searched three electronic databases (PubMed, EMBASE, and Cochrane Library) without language restriction to identify RCTs published from database inception to July 2022. Multiple keywords, including "melatonin," "delirium," and "intensive care unit" (or "ICU"), were used for the search strategy. We included RCTs, which compared melatonin with placebo. No limitations were set for the dosage of melatonin and the length of treatment.

Two reviewers performed the study selection. They excluded irrelevant literature by reading titles and abstracts. Then, the reviewers read the full texts of each potentially relevant article to determine which studies were suitable. The same two reviewers independently extracted the data from each eligible study, including characteristics of patients, interventions, comparisons, endpoints, and other related items essential for quality evaluation. Disagreements were resolved by discussion or consultation with the third reviewer.

Inclusion and Exclusion Criteria

Studies meeting the following criteria were included: (1) randomized controlled clinical trials; (2) patients admitted to the intensive care unit with any diagnosis; (3) melatonin was used; and (4) quantitative analysis of delirium and other clinical variables were provided as endpoints. Studies meeting the following criteria were excluded: (1) publications available only in an abstract or as meeting reports and (2) studies with incomplete data.

Data Extraction

The following information was collected from the included articles: first author's family name, year of publication, the dosage of melatonin, the number of participants in the treatment group and the control group, endpoint parameters of interest (e.g., delirium incidence, duration of mechanical ventilation and ICU stay, ICU mortality). Continuous variables were presented as mean and standard deviations (SD). If mean and SD were unavailable, the reviewers approximated them using sample sizes, medians, ranges, and interquartile ranges based on the quantile estimation method described by Wan and Luo.[16-17] Meanwhile, binary variables were expressed through the number of events and frequency in percentage.

Risk of Bias Assessment

The quality of the included literature was evaluated based on the following criteria:[18] sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. Each criterion was classified as low risk, unclear risk, or high risk. The results of the methodological quality assessment were summarized in a standardized figure.

Statistical Analysis

All statistical analyses were performed using SPSS 19.0 software and RevMan 5.3. The risk ratio (RR) was used to analyze dichotomous data, and the standard mean difference (SMD) was used to analyze continuous data. The heterogeneity between studies was assessed using the I^2 test and the chi-square test. $P < .05$ and $I^2 \geq 50\%$ indicated significant heterogeneity, and thus, the random effects model was used. Otherwise, the fixed effects model was used. Subgroup analyses were performed to find the origins of heterogeneity.

RESULTS

Study Selection

The reviewers initially examined 227 relevant articles using the search strategy. Figure 1 illustrates the process of study selection. After analyzing the titles and abstracts, the reviewers retained 89 articles for further study; 78 articles were excluded. Ultimately, 11 eligible RCTs[19-29] were evaluated in depth. Table 1 presents the characteristics of the included articles. Figure 2 presents the risk-of-bias items for each study.

Figure 1. Flow Diagram Of Literature Search and Study Selection

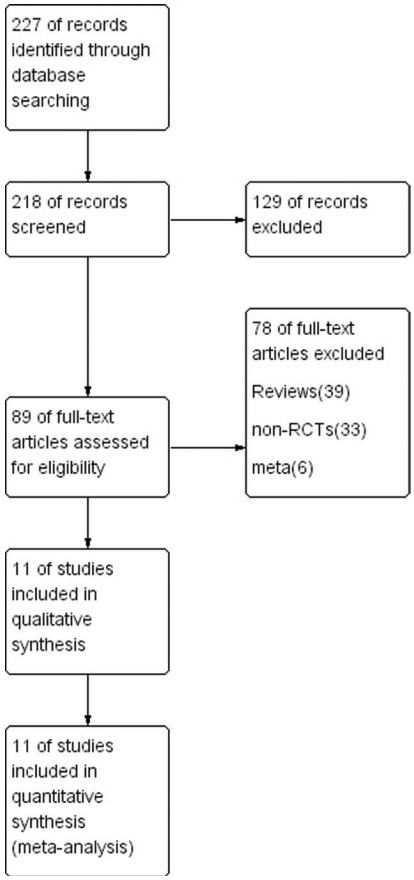
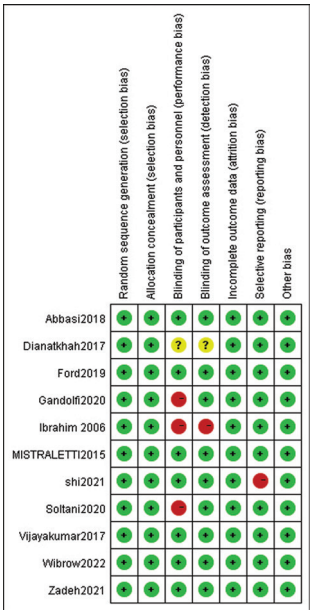


Figure 2. Summary of Authors' Judgements About the Risk of Bias for Each Included Study



Note: Red = High Risk; Yellow = Unclear Risk; Green = Low Risk

Figure 3. Meta-analysis of Melatonin on Incidence of Delirium in ICU Patients

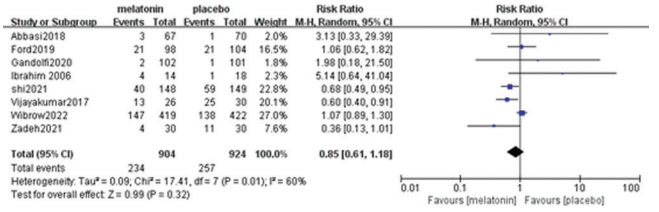
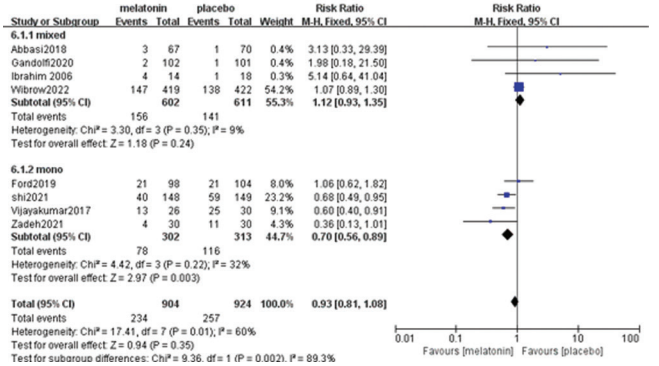


Figure 4. Meta-analysis of Melatonin on Subgroup Delirium Incidence



Quantitative Analysis

Incidence of Delirium. Eight related studies[19,21,23,24,26-29] encompassing 1828 patients served as the basis for calculating the prevalence of delirium in the melatonin and placebo groups. The pooled results (RR 0.85; 95% CI, 0.61~1.18, P = .32, I^2 = 60%, P for heterogeneity = .01) did not show a significant difference in delirium incidence between the melatonin group and placebo group of ICU patients (Figure 3). No significant publication bias was detected by observation of the symmetry of the funnel plot (Supplementary Figure 1). Given the moderate heterogeneity of these studies, subgroup analysis conducted between patients with mixed diseases and those with mono-disease defined general ICU patients and special ICU patients. The subgroup analysis (Figure 4) showed that melatonin administration (RR 0.70; 95% CI, 0.56~0.89, P = .003, I^2=32%, P for heterogeneity = .22) can significantly decrease the occurrence of delirium for special ICU patients. No significant differences in the incidence of delirium were observed for the general ICU patients (RR 1.12; 95% CI, 0.93~1.35, P = 0.24, I^2 = 9%, p for heterogeneity = 0.35).

Duration of Mechanical Ventilation. Six studies investigated the effect of melatonin on the length of mechanical ventilation in ICU patients. The pooled results (pooled SMD = − 0.26; 95% CI, − 0.66~0.14, P = .2) showed that exogenous administration of melatonin was associated with a trend towards decreased duration of mechanical ventilation. However, this difference was not statistically significant (Figure 5).

Duration of ICU Stay. Eight studies explored the effects of melatonin on the duration of an ICU stay in patients. The pooled results (pooled SMD = -0.07; 95% CI, -0.34~0.19, P = .58) showed that exogenous melatonin administration could not decrease the duration of ICU stay (Figure 6).

Figure 5. Meta-Analysis of Melatonin on the Duration of Mechanical Ventilation

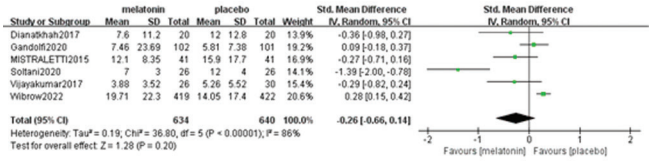


Figure 6. Meta-Analysis of Melatonin on Duration of ICU Stay

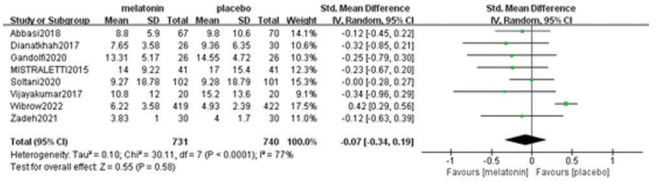
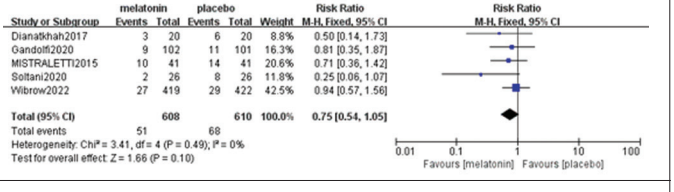


Figure 7. Meta-Analysis of Melatonin on Mortality in ICU



Mortality in ICU. Five studies involving 1218 patients recorded mortality in the ICU. The pooled results (pooled RR = 0.75; 95% CI, 0.54~1.05, P = .10; I^2 = 0%, P for heterogeneity = .49) showed that administration of melatonin was associated with a trend towards decreased mortality during ICU, but this difference was not statistically significant (Figure 7).

DISCUSSION

Delirium is a devastating condition for ICU patients, which has a wide range of impacts for months to years after

Table 1. Characteristics of studies included in the meta-analysis.

Study	Participants	Sample size (M/C)	Measures	intervention	Delirium incidence (M/C, %)
Ibrahim et al (2006)	Tracheostomised patients	14/18	RSAS	3mg melatonin at 22:00	31/7
Mistraletti et al (2015)	ICU patients	41/41	NR	3mg melatonin at 20:00 and mid-night	NR
Vijayakumar et al(2017)	Organophosphorus compound poisoning patients	26/30	CAM-ICU	3mg melatonin at 21:00	50.85/84.81
Dianatkhah et al (2017)	Intubated patients with hemorrhagic stroke	20/20	NR	30mg melatonin every night	NR
Abbasi et al (2018)	ICU patients	67/70	CAM-ICU	3mg melatonin at 21:00	4.5/1.4
Ford et al (2019)	CABG and/or valve replacement patients	98/104	CAM	3mg melatonin	21.4/20.2
Soltani et al (2020)	traumatic intracranial hemorrhage patients	26/26	NR	3mg melatonin at 21:00	NR
Gandolfi et al (2020)	ICU patients	102/101	ICDSC	10mg melatonin at 20:00	2.3/1.7
Shi(2021)	More than 60 years old who underwent PCI in the ICU	148/149	CAM-ICU	3mg melatonin	27/39.6
Zadeh et al (2021)	Elective on-pump CABG	30/30	CAM-ICU	3mg melatonin	10/46.6
Wibrow et al (2022)	ICU patients	419/422	CAM-ICU	4mg melatonin at 21:00	35.1/32.7

Abbreviations: NR, not reported; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for ICU; ICDSC, the Intensive Care Delirium Screening Checklist; M, melatonin; C, placebo; ICU, Intensive Care Unit; RSAS, Riker Sedation–Agitation Scale; CABG, Coronary Artery Bypass Grafting.

critical illness. Clinical practice guidelines regarding preventing and managing pain, agitation, and delirium recommend an optimized environment, decreased stimuli, and a low noise level for adult ICU patients.[30] Currently, no effective pharmacologic therapies prevent or treat delirium. Olofsson et al. found that dyssynchronization of the melatonin secretion rhythm was common in critically ill, especially for mechanically ventilated patients.[31] Patients with delirium showed a significant reduction of plasma melatonin concentration compared with those without delirium.[32] Therefore, clinical researchers hope to explore what role exogenous melatonin can play in preventing delirium.

These researchers' meta-analysis showed that the reported incidence of delirium ranged from 2.3% to 50.85% in the treatment group and from 1.7% to 84.81% in the control group among the reviewed studies. The pooled results (RR = 0.79) suggested that melatonin did not significantly reduce the incidence of delirium. With the subgroup analysis, this study showed that melatonin could reduce the incidence of delirium for special ICU patients. However, such results were not evident for general ICU patients.

The researchers believe this study to be the first meta-analysis appraising the effect of melatonin on general and special ICU patients. However, owing to the high heterogeneity among the patients, the results must be interpreted with caution. Han et al. found that melatonin decreased the risk of delirium in adults who underwent cardiac surgery,[33] which may be due to the specific nature of delirium, the clinical phenotype of which can be classified as hypoxic, septicemic, sedative-related, or metabolic (renal or liver dysfunction) delirium.[34]

Sleep disturbances impair cognition, resulting in apathy and confusion. Improvement in sleep and readjustment of circadian rhythmicity may be therapeutic targets for the prevention and treatment of delirium in the ICU.[35] The researchers also examined the effect of melatonin on other clinical outcomes of ICU patients. It was extrapolated that applying melatonin could improve sleep and, therefore, shorten the duration of mechanical ventilation. However, due to the heterogeneous units and dimensions in this study, no difference in the course of mechanical ventilation, the length of ICU stay, or mortality were identified between the treatment and the control groups.

There were also limitations of this study. First, investigators did not distinguish different types of delirium. Second, due to the small number of studies in the analysis, some parameters and sensitivity analysis might not be available. Third, some pooled authors presented means and SDs for continuous data, and therefore, estimated means and SDs were employed in the analysis.

CONCLUSION

This study concluded that melatonin considerably decreased the incidence of delirium in special ICU patients. Moreover, the duration of mechanical ventilation, the length of ICU stay, and in-ICU mortality were not significantly affected by melatonin. Future studies are needed to confirm the effect of melatonin on these special ICU patients.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

Lianwei Zhao and Zhipeng Feng contributed equally to this paper.

REFERENCES

1. de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *Int J Geriatr Psychiatry*. 2010;25(12):1201-1208. doi:10.1002/gps.2454
2. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older Persons: advances in diagnosis and treatment. *JAMA*. 2017;318(12):1161-1174. doi:10.1001/jama.2017.12067
3. Girard TD, Exline MC, Carson SS, et al; MIND-USA Investigators. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506-2516. doi:10.1056/NEJMoa1808217
4. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009;180(11):1092-1097. doi:10.1164/rccm.200904-0537OC
5. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med*. 2010;38(12):2311-2318. doi:10.1097/CCM.0b013e3181f85759
6. Dessap AM, Roche-Campo F, Launay JM, et al. Delirium and circadian rhythm of melatonin during weaning From mechanical ventilation: an ancillary study of a weaning trial. *Chest*. 2015;148(5):1231-1241. doi:10.1378/chest.15-0525
7. Mehta S, Cook D, Devlin JW, et al; SLEAP Investigators; Canadian Critical Care Trials Group. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med*. 2015;43(3):557-566. doi:10.1097/CCM.0000000000000727
8. Harrison Y, Horne JA, Rothwell A. Prefrontal neuropsychological effects of sleep deprivation in young adults--a model for healthy aging? *Sleep*. 2000;23(8):1067-1073. doi:10.1093/sleep/23.8.1f
9. Marra A, McGrane TJ, Henson CP, Pandharipande PP. Melatonin in critical care. *Crit Care Clin*. 2019;35(2):329-340. doi:10.1016/j.ccc.2018.11.008
10. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30(3):536-540. doi:10.1097/00003246-200203000-00007
11. Verceles AC, Silhan L, Terrin M, Netzer G, Shanholtz C, Scharf SM. Circadian rhythm disruption in severe sepsis: the effect of ambient light on urinary 6-sulfatoxymelatonin secretion. *Intensive Care Med*. 2012;38(5):804-810. doi:10.1007/s00134-012-2494-3
12. Gehlbach BK, Chapotot F, Leproult R, et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *Sleep*. 2012;35(8):1105-1114. doi:10.5665/sleep.1998
13. Oldham MA, Lee HB, Desan PH. Circadian rhythm disruption in the critically ill: an opportunity for improving outcomes. *Crit Care Med*. 2016;44(1):207-217. doi:10.1097/CCM.0000000000001282
14. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth*. 2010;4(3):169-173. doi:10.4103/1658-354X.71132

15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339(jul21 1):b2700. doi:10.1136/bmj.b2700
16. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805. doi:10.1177/0962280216669183
17. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135. doi:10.1186/1471-2288-14-135
18. Higgins JPT, Green SR, eds. *Cochrane Handbook for Systematic Review of Interventions*, Version 5.1.0 [updated March 2011]. Available at: www.handbook.cochraine.org.
19. Ibrahim MG, Bellomo R, Hart GK, et al. A double-blind placebo-controlled randomised pilot study of nocturnal melatonin in tracheostomised patients. *Crit Care Resusc*. 2006;8(3):187-191. doi:10.1016/S1441-2772(23)02086-0
20. Mistraletti G, Umbrello M, Sabbatini G, et al. Melatonin reduces the need for sedation in ICU patients: a randomized controlled trial. *Minerva Anestesiol*. 2015;81(12):1298-1310.
21. Vijayakumar HN, Ramya K, Duggappa DR, et al. Effect of melatonin on duration of delirium in organophosphorus compound poisoning patients: A double-blind randomised placebo controlled trial. *Indian J Anaesth*. 2016;60(11):814-820. doi:10.4103/0019-5049.193664
22. Dianatkhah M, Najafi A, Sharifzadeh M, et al. Melatonin supplementation may improve the outcome of patients with hemorrhagic stroke in the intensive care unit. *J Res Pharm Pract*. 2017;6(3):173-177. doi:10.4103/jrpp.JRPP_17_49
23. Abbasi S, Farsaei S, Ghasemi D, Mansourian M. Potential role of exogenous melatonin supplement in delirium prevention in critically ill patients: a double-blind randomized pilot study. *Iran J Pharm Res*. 2018;17(4):1571-1580.
24. Ford AH, Flicker L, Kelly R, et al. The healthy heart-mind trial: randomized controlled trial of melatonin for prevention of delirium. *J Am Geriatr Soc*. 2020;68(1):112-119. doi:10.1111/jgs.16162
25. Soltani F, Salari A, Javaherforooshzadeh F, Nassajjian N, Kalantari F. The effect of melatonin on reduction in the need for sedative agents and duration of mechanical ventilation in traumatic intracranial hemorrhage patients: a randomized controlled trial. *Eur J Trauma Emerg Surg*. 2022;48(1):545-551. doi:10.1007/s00068-020-01449-3
26. Gandolfi JV, Di Bernardo APA, Chanes DAV, et al. The effects of melatonin supplementation on sleep quality and assessment of the serum melatonin in ICU patients: a randomized controlled trial. *Crit Care Med*. 2020;48(12):e1286-e1293. doi:10.1097/CCM.0000000000004690
27. Shi Y. Effects of melatonin on postoperative delirium after PCI in elderly patients: a randomized, single-center, double-blind, placebo-controlled trial. *Heart Surg Forum*. 2021;24(5):E893-E897. doi:10.1532/hsf.4049
28. Javaherforoosh Zadeh F, Janatmakan F, Shafaeebejestan E, Jorairahmadi S. Effect of melatonin on delirium after on-pump coronary artery bypass graft surgery: a randomized clinical trial. *Iran J Med Sci*. 2021;46(2):120-127.
29. Wibrow B, Martinez FE, Myers E, et al. Prophylactic melatonin for delirium in intensive care (Pro-MEDIC): a randomized controlled trial. *Intensive Care Med*. 2022;48(4):414-425. doi:10.1007/s00134-022-06638-9
30. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299
31. Olofsson K, Alling C, Lundberg D, Malmros C. Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiol Scand*. 2004;48(6):679-684. doi:10.1111/j.0001-5172.2004.00401.x
32. Yoshitaka S, Egi M, Morimatsu H, Kanazawa T, Toda Y, Morita K. Perioperative plasma melatonin concentration in postoperative critically ill patients: its association with delirium. *J Crit Care*. 2013;28(3):236-242. doi:10.1016/j.jcrc.2012.11.004
33. Han Y, Tian Y, Wu J, et al. Melatonin and its analogs for prevention of post-cardiac surgery delirium: a systematic review and meta-analysis. *Front Cardiovasc Med*. 2022;9:888211. doi:10.3389/fcvm.2022.888211
34. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134. doi:10.1016/S0140-6736(08)60105-1
35. Sun T, Sun Y, Huang X, et al. Sleep and circadian rhythm disturbances in intensive care unit (ICU)-acquired delirium: a case-control study. *J Int Med Res*. 2021;49(3):300060521990502. doi:10.1177/0300060521990502