REVIEW ARTICLE

Prophylactic Melatonin for Delirium in Intensive Care Unit: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Introduction: Delirium, being a common disorder among critically ill patients, has a reported incidence ranging 45–83% in the intensive care unit (ICU) population. The prophylactic use of melatonin and melatonergics has been shown to have a positive effect in reducing the incidence of delirium in many clinical trials. Our study was thus proposed to find out the role of melatonin on the incidence and severity of ICU delirium, ICU and hospital length of stay (LOS), requirement, duration of mechanical ventilation, and ICU mortality.

Methodology: A systematic search of various databases was performed to find out the trials which compare melatonin with a placebo or standard therapy for delirium prevention with the results conveyed as mean differences (MDs) or risk ratios. The statistical software, Review Manager (RevMan, version 5.4), was used for data synthesis.

Results: Twelve studies were included in the meta-analysis. Prophylactic administration of melatonin or ramelteon was not associated with a statistically significant reduction in the incidence of delirium (odds ratio [OR] 0.63; confidence interval [CI]: 0.60, 1.32; $p = 0.22$), the severity of delirium (MD: 0.22; 95% CI: From −1.36 to 1.81; $p = 0.78$), ICU LOS (MD: 0.05; 95% CI: From −0.65 to 0.75; $p = 0.89$), hospital LOS (MD: −1.46; 95% CI: From −4.50 to −1.59; $p = 0.35$), need for mechanical ventilation (OR: 0.74, 95% CI: 0.38–1.44; $p = 0.37$), and ICU mortality (MD: 0.78; 95% CI: 0.56; 1.11; $p = 0.62$). However, a significant reduction in the duration of mechanical ventilation (MD: −0.85; 95% CI: From −1.64 to −0.06; $p = 0.03$) was found.

Conclusion: Our meta-analysis suggests that melatonin when given prophylactically has no significant role in reducing the incidence and severity of delirium, ICU and hospital LOS, need for mechanical ventilation, duration of mechanical ventilation, and ICU mortality. Further studies are warranted.

Keywords: Intensive care delirium, Melatonergics, Melatonin, Prophylactic therapy.

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Background

Delirium can be defined as an acute onset fluctuating disorder of the brain with disturbances of cognition and attention and often it is the result or sign of an underlying acute condition.[1] It is common in critically ill patients admitted to intensive care units (ICUs), with an estimated prevalence in the range 45–83%.[2,3] The incidence of delirium in critically ill patients is associated with worse outcomes such as increased morbidity and mortality, longer ICU length of stay (LOS) and hospital LOS, higher hospital costs, more time on a ventilator, increased use of physical restraints, increased requirement for tracheostomy, poorer functional status, and cognitive impairment that persists long after hospital discharge.[4–6]

Sleep deprivation is a common occurrence in the critically ill and is considered a major risk factor for the development of delirium. In healthy states, the Sleep–wake cycle and circadian rhythm are regulated *via* the Melatonin hormone, secreted by the pineal gland. When given exogenously, it increases sleep efficiency and total sleep duration and also decreases sleep onset latency. Thus, exogenous melatonin has the potential to reduce the occurrence of delirium. Recent studies do suggest the potential benefits of melatonin as prophylaxis for ICU delirium.[7–11]

Apart from dysregulation of melatonin secretion, the use of sedatives and analgesia also alters the levels of neurotransmitters which in turn exerts direct insults to the brain[12] leading to increased delirium incidence. The previous meta-analysis[13] about the role of prophylactic melatonin in delirium include both non-critical and critically ill patients, however, the magnitude of the effect of melatonin could differ vastly between the two population leading to increased uncertainty about their conclusions. This systematic review and meta-analysis assessed the role of melatonin in critically ill patients on the following outcomes: incidence of ICU delirium,

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duration of delirium, ICU LOS, hospital LOS, requirement and duration of mechanical ventilation, need for antipsychotics and overall mortality in the ICU.

Methodology

Protocol Preparation and Registration

The protocol has been registered in Prospero (Registration No.: CRD42021253683).

Inclusion and Exclusion Criteria

It was planned to include only randomized control trials (RCTs) which compared melatonin/melatonergics and placebo/standard therapy in the adult critically patients admitted to ICU. Other studies comparing melatonin/melatonergics to other medications in the control arm were excluded.

Data Sources

Independent systematic search was performed by the two reviewers (RM and KDS) in the databases of MEDLINE, Cochrane Central Registry of Controlled Trials (CENTRAL), PubMed, Web of Science, and SCOPUS from inception to March 2022 to include all clinical trials that investigated melatonergics and ICU delirium in humans. Only English language trials were considered. The following search terms were included: critically ill, intensive care, melatonin, mechanical ventilation, ramelteon, and melatonergics. A hand search of bibliographies of clinical trials and meta-analyses were also carried out.

Study Selection

Independent screening of studies was performed by the two reviewers (RM and KDS) for inclusion. The RCTs investigating melatonin or ramelteon use for the prophylaxis of delirium in critically ill patients admitted to ICUs were included in the meta-analysis. The RCTs investigating melatonin or ramelteon in the pediatric population or comparing multiple doses of the drug or other drugs were not selected for the review as per exclusion criteria.

Data Extraction

To determine eligibility, both authors (RM and KDS) performed screening and evaluation of titles and available abstracts. Potentially eligible abstracts were further selected for full-text evaluation and eligibility criteria were applied. The disagreement between the reviewers was mediated by the third senior author (AT) and conflicts were resolved.

Data Items

A standardized data abstraction form was formulated based on the Cochrane Data Collection template. The data were extracted independently by both the reviewers in duplicate after assessing the eligibility of the study. The following information was obtained: Demography, methodology, intervention details, and the outcome data. The incidence of ICU delirium was the primary outcome while Secondary outcomes included the duration of delirium, severity of delirium, ICU LOS or hospital stay, requirement and duration of mechanical ventilation, need for antipsychotics, and ICU mortality rate as reported in the study.

Risk of Bias Assessment

For the risk of bias assessment, the quality assessment scale recommended by the Cochrane Collaboration was used. This tool consists of "low," "high," or "unclear" risk of bias as the response options and evaluates the reviewer's bias, random sequence generation; blinding of participants/healthcare professionals/data collectors/outcome assessors/data analysts; allocation concealment and incomplete outcome data as major domains. Reviewers (RM and KDS) further resolved disagreements by discussion and the arbitration of the senior author (AT) for any unresolved disagreements.

Summary Measures

For the incidence of delirium, ICU mortality, and the need for mechanical ventilation, odds ratio (OR) were estimated while for delirium severity, duration of mechanical ventilation, ICU LOS, and hospital stay differences in means were estimated.

Strategy for Data Synthesis

Random effect models were selected for studies associated with increased heterogeneity whereas fixed effect models were selected for studies with low heterogeneity. Random effect models incorporated both within and between study differences while fixed effect models include only between-study differences. Assessment of heterogeneity of treatment effect was done using I^2 statistics and Cochrane's Q statistics. Subgroup effect or sensitivity analyses were further performed to assess excess heterogeneity. Relative risk ratio (RR) ratio or OR were reported for dichotomous outcomes while standard deviation (SD) and weighted mean difference (MD) were used for reporting continuous endpoints. Individual weightage to the studies was estimated using the inverse of variance approach.

Sensitivity Analysis

In a few studies reporting ICU LOS, the duration of mechanical ventilation and hospital stay has been reported as median interquartile range (IQR) values. For these, estimated mean ± SD values were obtained after conversion using standard methods (formula has been described in result segment) for inclusion in the meta-analysis. Sensitivity analysis was performed by removing these studies to find out the effect of change on the incidence of delirium.

Results

Study Identification and Selection

A total of 698 articles were identified on the initial systematic search of the databases using keywords. A hand search of the published meta-analyses references added 15 records. Titles and abstracts of 565 publications were further searched after removing duplicates. Of these, 497 records were excluded as they failed to meet our criteria for inclusion being not an RCT (n = 101), not assessing delirium (n = 367) full articles not available (n = 7), not related to melatonin (n = 18), not in adults (n = 2), and not done in ICU (n = 2). The rationales for exclusions are mentioned in Figure 1. For the remaining 68 articles, full texts were obtained and assessed. Out of these,12 articles were selected for quantitative synthesis. The other 56 articles were not included as 19 of these were not RCTs; 13 were review articles, full-text articles were not available for 14 of them, 3 were ongoing trials, 2 were observational studies and 2 were retrospective analyses, and 3 of them, placebo or standard therapy was not used in the control group.

Characteristics of the Included Studies

Table 1 presents the characteristics of all the 12 included studies in the meta-analysis. The table describes major domains of

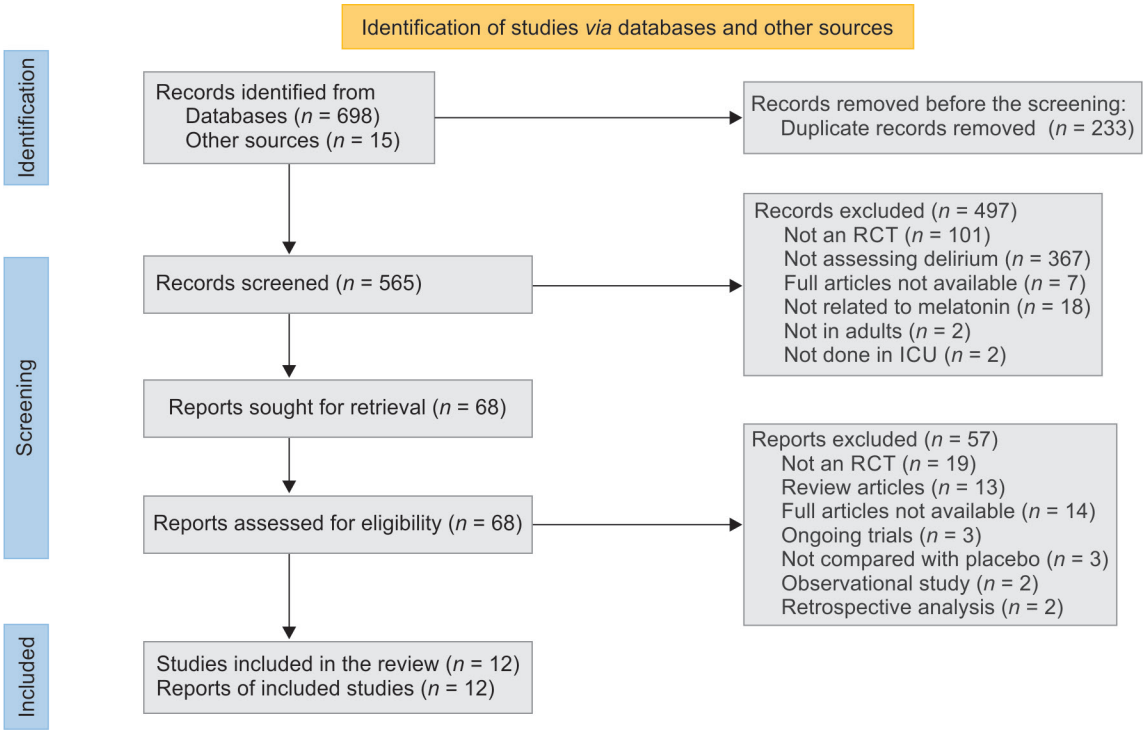

Fig. 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart

included studies such as study design, patient population, their characteristics, intervention done, the method used to assess delirium, the choice of the control group, outcomes reported, and the follow-up. The mean sample size was 252 (ranging from 24 to 419). And most were conducted in the past 10 years. Out of 12 studies, 7 studies reported incidence of delirium in the included patients; 2 studies reported severity of delirium; 10 studies described ICU LOS stay; 2 studies described the need for mechanical ventilation and 6 studies described the duration of mechanical ventilation; only 3 studies described the hospital LOS and 8 studies described ICU mortality. The Cochrane Q statistics were used for the assessment of the heterogeneity.

The intervention in the studies included either melatonin or ramelteon, which is a melatonin receptor agonist. The dose of melatonin or ramelteon used, varied in the studies, ranging from 3 mg to 30 mg and the duration varied from a single dose to 7 days or till ICU discharge. The table also provides the nature of the illnesses of the patients included.

There was variability in the method used for assessing delirium in the studies. Six studies used the confusion assessment method for the intensive care unit (CAM-ICU) questionnaire for assessing delirium, two studies diagnosed delirium according to Diagnostic and Statistical Manual IV (DSM IV) criteria and one study followed Intensive Care Delirium Screening Checklist (ISDSC).

Risk of Bias Assessment

For the domains of RCTs, namely, random sequence generation, allocation concealment, selection bias, and selective reporting, nine studies were judged to be a low risk while two studies[14,15] had an unclear risk of bias for random sequence generation, allocation concealment and blinding. A high risk of attrition bias and detection bias (that could alter the estimation of effect size) was present in one study[14] as they did not report blinding. All studies were judged to have a low risk of selection and reporting bias.

The risk of bias in the included studies is shown in Figure 2.

Primary Outcome: Incidence of Delirium

Only 7 out of 12 RCTs[2,7,9,11,14,16,17] reported delirium incidence with cumulative 1,330 total patients (661 in the melatonin group and 669 in the control group). The analysis showed that the incidence of delirium in the melatonin group was not significantly lower than the incidence in the control group (OR: 0.63, confidence interval [CI] 0.60, 1.32; $p = 0.22$; $I^2 = 71\%$). The estimated heterogeneity was high for the primary outcome (Fig. 3).

Secondary Outcomes

The severity of delirium, need for mechanical ventilation, duration of mechanical ventilation, ICU LOS, hospital LOS, and ICU mortality were secondary outcomes assessed. In a few studies, the duration of mechanical ventilation, ICU LOS, and LOS stay were reported in median (IQR) instead of mean ± SD. Hence for uniformity of comparison, all the results were converted to mean ± SD using the following formula:

$$\text{Mean} = (a + b + 2m)/4$$

where a is the low range, b is the high range, and m is the median

$$\text{Variance } (S^2) = 1/12 \times [(a - 2m + b)^2/4] + (b - a)^2$$

Severity of Delirium

The length of the delirium episodes was considered as a measure of severity of delirium. Only 2 of the 12 studies[7,9] reported the severity of delirium in 225 patients (112 in the experimental arm and 113 in the placebo arm). No significant association was found between the use of melatonin/melatonergics and the severity of delirium.

Table 1: Characteristics of the studies

S.No.	*Study*	*Design/duration*	*Participants*	*Intervention*	*Outcome*	*Method of assessing delirium*
1.	Abbasi et al.[7] 2018	Double-blind/within 24 hours of ICU admission till 8 days after starting melatonin	Adults in ICU/*n* = 172 APACHE II score was 8.1 ± 4.3 in the melatonin group and 7.3 ± 4.6 in the placebo group SOFA score was 3.1 ± 2.0 in the melatonin group and 3.2 ± 2.3 in the placebo group	Melatonin 3 mg for 5 days, starting within 24 hours of ICU admission and followed up till 8 days	Primary endpoint: Incidence of delirium Secondary endpoints: Duration of delirium, cumulative dose of prescribed haloperidol, ICU LOS and hospital LOS, and mortality rate	Persian version of standard CAM-ICU
2.	Bourne and Mills[14] 2008	Double-blind/four nights after initiating melatonin	The ICU patients who had undergone tracheostomy for weaning/*n* = 24 Mean age was 58.7 ± 12.5 in the placebo and 69.9 ± 12 in the melatonin group APACHE II score was 16.8 ± 3.4 in the placebo and 17.3 ± 3.8 in the melatonin group	Oral melatonin 10 mg for 4 nights	Primary outcome: Nocturnal sleep was monitored using BIS index and was expressed in terms of SEI and AUC Secondary outcome: The SEI was measured using actigraphy and nurse and patient assessments	
3.	Bellapart et al.[8] 2020	Double-blind/sleep study done twice – Baseline PSG and postintervention PSG	Adults in recovery phase/ weaning; *n* = 33; the median age was 55 in the melatonin group and 57.5 in controls/ APACHE II was 22 (12–30) in the melatonin group and 24 (14–28) in the control	3-mg melatonin at 21 hours followed by 0.5 mg melatonin hourly till 3 a.m.	Primary outcome: Prevalence of ICU-related delirium Secondary outcome: Polysomnogram analysis of patients' sleep	RASS and CAM
4.	Gandolfi et al.[18] 2020	Double-blind/7 days after initiating melatonin	The ICU patients were administered analgesics and/ or sedatives; *n* = 203; mean age – 60 (melatonin group) 57 (control) SAPS III on ICU admission – 43 ± 13.4 in the melatonin group and 41 ± 11.7 in the control group	A 10-mg melatonin at 8 p.m., 2 hours after dinner for 7 days	Primary outcome: Sleep quality and length of sleeping time Secondary outcomes: Serum melatonin concentration, need for analgo–sedation, and prevalence of delirium or anxiety	ICDSC
5.	Hatta et al.[16] 2014	Rater blinded	About 65–89-years-old ICU or acute ward patients/*n* = 67 Charlson comorbidity index was 2.6 in placebo and 3.2 in ramelteon group/APACHE II score: 14.6 in placebo and 13.5 in ramelteon group	An 8 mg/day ramelteon for 7 days	Primary outcome: Incidence of delirium Secondary outcomes: Sleep parameters, sleep duration, awakenings per night	DSM IV

6.	Mistraletti et al.[19] 2015	Double-blind/from third ICU day till ICU discharge	Critically ill adults with mechanical ventilation >48 hours and SAPS II >32 points; *n* = 82 SAPS II: 44.1 ± 15.3 (placebo) and 45.7 ± 18.2 (melatonin) SOFA score was 5 (3–7) in the placebo group and 4 (3–7) in the melatonin group	A 3-mg melatonin at 8 p.m. and midnight from third ICU day till ICU discharge	Primary outcome: A cumulative amount of sedation required Secondary outcomes: The overall amount of other neuroactive drugs administered, other neurological parameters like target and observed RASS levels, anxiety, pain, use of restraints, duration of agitation, sleep hours, adequacy of sedative therapy, the prevalence of PTSD, ICU LOS, ICU, and hospital mortalities.	DSM IV
7.	Nishikimi et al.[9] 2018	Triple blinded/ from initiation of ramelteon till ICU discharge	The ICU patients taking orally or through an NG tube in the first 48 hrs of admission/ *n* = 88 APACHE II score was 23.98 ± 7.30 in the ramelteon group and 23.95 ± 8.61 in the control group	8 mg ramelteon at 20.00 hours every night till ICU discharge	Primary endpoint: Duration of ICU stay Secondary endpoints: Occurrence rates and duration of delirium, clinical status at discharge	CAM-ICU every 4 hours
8.	Vijayakumar et al.[2] 2016	Double-blind/from the day of ICU admission throughout ICU stay.	The OPC poisoning patients in ICU/*n* = 56 APACHE II: 8.56 ± 4.1 in the control group and 10.2 ± 3.7 in the melatonin group	A 3-mg melatonin at 9 p.m. daily throughout the ICU stay	Primary outcome: Overall incidence of delirium during the ICU stay Secondary outcomes: Duration of mechanical ventilation, sedation and atropine requirement, duration of ICU stay, patients developing VAP, and sepsis	CAM-ICU thrice a day
9.	Dianatkhah et al.[15] 2017	Double-blind/from the day of ICU admission till discharge from ICU	Adult patients with hemorrhagic stroke/*n* = 40 APACHE score was 17.60 ± 4.22 for the melatonin group and 16.9 ± 4.73 for the control group	A 30-mg melatonin *via* NG tube every night throughout the ICU stay	Duration of mechanical ventilation, ICU LOS, and mortality in intubated patients	
10.	Soltani et al.[10] 2020	Double-blind/from 24 hours of ICU admission throughout the ICU stay	Adult ICU patients with traumatic ICH/ *n* = 40 APACHE II was 7.45 ± 4.24 in the melatonin group and 8.14 ± 3.63 in the control group	A 3-mg melatonin at 9 p.m. throughout the ICU stay	Primary outcome: Amount of sedative drugs required Secondary outcomes: Mechanical ventilation time, ICU LOS, GCS, and hemodynamic parameters	

(Contd...)

Table 1: *(Contd...)*

S.No.	Study	Design/duration	Participants	Intervention	Outcome	Method of assessing delirium
11.	Jaiswal et al.[11] 2019	Double-blind/from the night before surgery to a maximum of 6 nights in the ICU	Adults undergoing elective pulmonary thromboendarterectomy/ *n* = 120	An 8-mg ramelteon starting from the night before surgery till a maximum of 6 nights in the ICU	Primary outcome: Delirium incidence Secondary outcomes: Delirium and coma duration, delirium, and coma-free duration	CAM-ICU twice daily
12.	Wibrow et al.[17] 2022	Double-blind/from ICU admission throughout ICU stay followed up till 90 days	Adult ICU patients whose expected LOS >72 hours/ *n* = 419	A 4-mg melatonin at 21.00 hours for 14 consecutive nights or till ICU discharge, whichever occurs earliest	Primary outcome: Incidence of delirium Secondary outcomes: Sleep quality and quantity, hospital LOS and ICU LOS, Hospital and 90-day mortalities	CAM-ICU twice daily

APACHE II, acute physiology and chronic health evaluation II; AUC, area under the curve; CAM, confusion assessment method; BIS, bispectral index; GCS, Glasgow coma scale; ICDSC, intensive care delirium screening checklist; NG, nasogastric tube; PSG, polysomnography; PTSD, posttraumatic stress disorder; RASS, Richmond agitation and sedation scale; SAPS III, simplified acute physiology score III; SEI, sleep efficiency index; SOFA, sequential organ failure assessment

High heterogeneity (MD: 0.22; 95% CI: From –1.36 to 1.81; $p = 0.78$; $I^2 = 89\%$) was seen between the studies (Fig. 4).

Length of Intensive Care Unit Stay

Ten of the twelve studies[2,7–11,15,17,18] with cumulative 1638 patients (820 in the experimental and 818 in the placebo arm) were analyzed for the ICU LOS. A low to medium heterogeneity (MD: 0.05; 95% CI: From −0.65 to 0.75; $p = 0.89$; $I^2 = 36\%$) was observed. The results were not statistically significant. The ICU LOS stay was expressed in the median (IQR) in six of these studies, hence they were converted to mean ± SD as described above. The MD remained statistically non-significant (0.37 [from –1.82 to 1.07; $p = 0.61$]) during sensitivity analysis (removal of these 6 studies from the analysis as an assumption was used for conversion of median to mean) (Fig. 5).

Hospital Length of Stay

The 4 of the 12 studies[7,11,17,18] with cumulative 1,234 patients (641 in the experimental and 593 in the placebo arm) contributed to the hospital LOS (Fig. 4). The heterogeneity was high (MD: –1.46; 95% CI: From −4.50 to −1.59; $p = 0.35$; $I^2 = 84\%$). However, no statistically significant reduction in the ICU LOS was observed in the experimental group (Fig. 6).

Need for Mechanical Ventilation

Only 2 of the 12 studies[2,9] reported the need for mechanical ventilation in 144 patients (71 in the experimental arm and 73 in the placebo arm) as seen in the figure. No significant difference in the need for mechanical ventilation was observed between the two arms. The heterogeneity was absent for this particular outcome assessment (OR: 0.74; 95% CI: 0.38–1.44; $p = 0.37$; $I^2 = 0\%$) (Fig. 7).

Duration of Mechanical Ventilation

Six of the studies[10,11,15,17,18] reported the duration of mechanical ventilation in 1,335 patients (667 in the melatonin arm and 668 in the placebo arm) as seen in Figure 8. The high heterogeneity (MD: −0.85; 95% CI: From –1.64 to –0.06; $p = 0.03$; $I^2 = 83\%$) and statistically significant results was observed (Fig. 8). One among these five studies had the duration of mechanical ventilation expressed in mean ± SD while other studies had reported outcomes in median (IQR) that was transformed to mean ± SD for consistency using the same methodology as described earlier.

Intensive Care Unit Mortality

Eight of the twelve studies[7,9–11,15,17,18] with a cumulative 1,549 patients (773 in the experimental and 776 in the placebo arm) were assessed for ICU mortality. A low heterogeneity (MD: 0.78; 95% CI: 0.56–1.11; $p = 0.62$; $I^2 = 0\%$) was found between the studies. No significant reduction was observed in the ICU mortality in the experimental group (Fig. 9).

Publication Bias

To detect publication bias for the primary outcome-the incidence of delirium a funnel plot was created. The symmetrical plot signifies no apparent publication bias (Fig. 10).

Discussion

The objective of this systematic review and meta-analysis was to ascertain the effect of melatonin/melatonergics in the prevention of ICU delirium. We found that the melatonin did not affect the incidence and severity of delirium, ICU LOS, hospital LOS,

Fig. 2: The risk of bias in the included studies

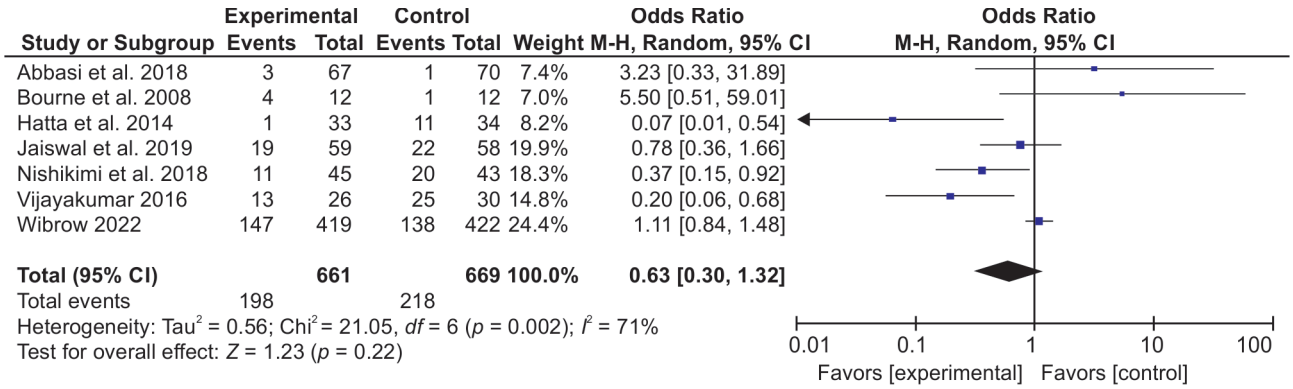

Fig. 3: Primary outcome: Incidence of delirium

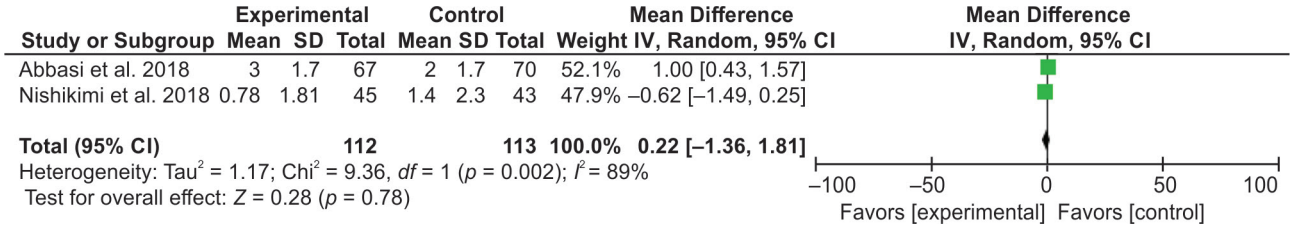

Fig. 4: Severity of delirium

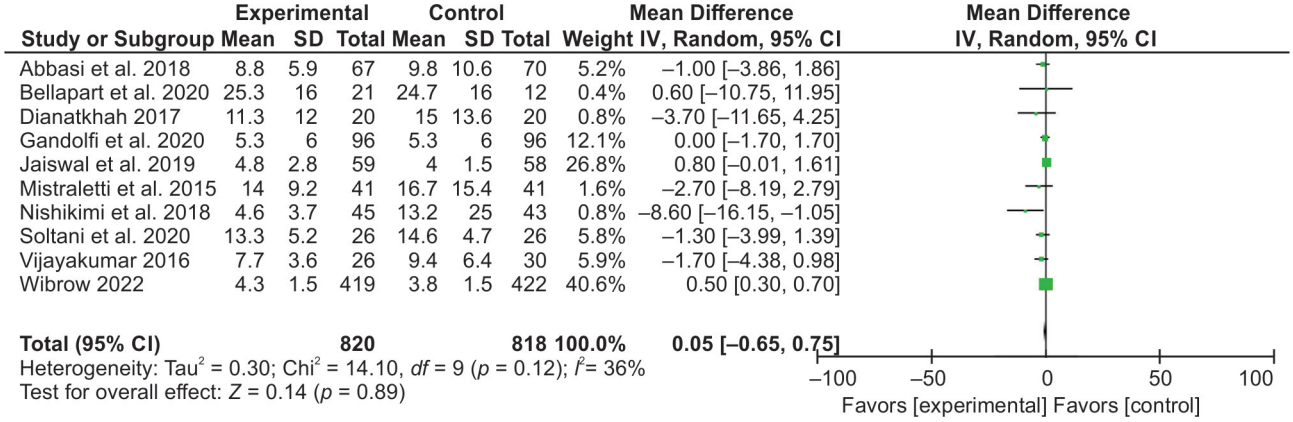

Fig. 5: The ICU LOS

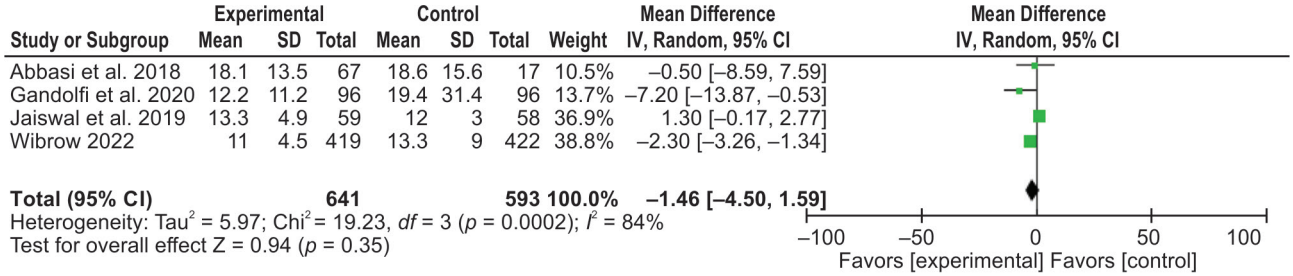

Fig. 6: Hospital LOS

requirement of mechanical ventilation, and ICU mortality. But melatonin had a statistically significant effect in reducing the duration of mechanical ventilation, though the finding was not robust on sensitivity analysis. Also, the lower limit of the CI is 0.06, the difference comes out to be only 1.4 hours, which is not clinically significant. Delirium in critical illness is often related to systemic inflammation present commonly in ICU patients. It occurs due to surgical stress, infection, sepsis, and other acute illnesses. Physiologically, melatonin has been shown to have anti-inflammatory and oxidative effects.[20] These effects have

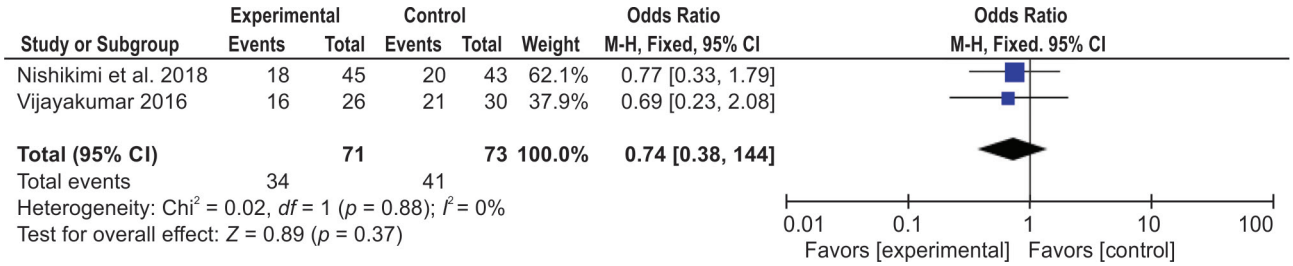

Fig. 7: Need for mechanical ventilation

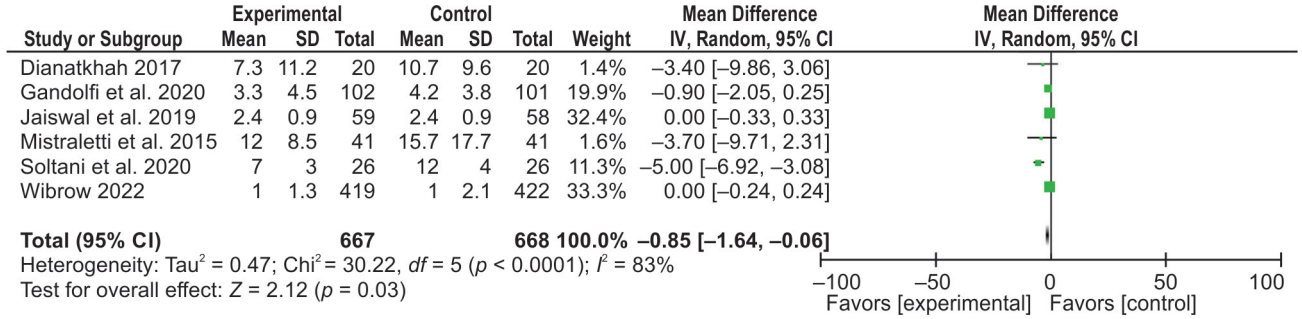

Fig. 8: Duration of mechanical ventilation

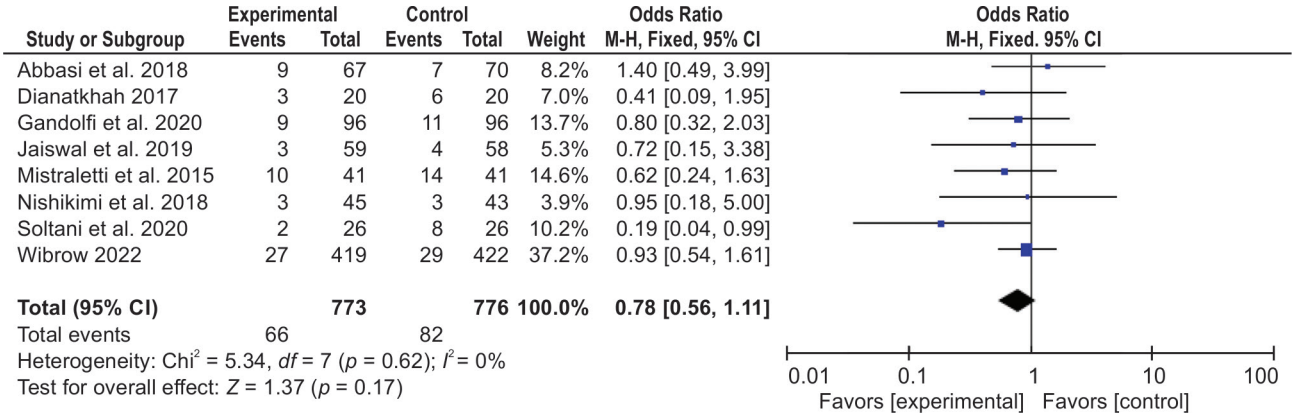

Fig. 9: The ICU mortality

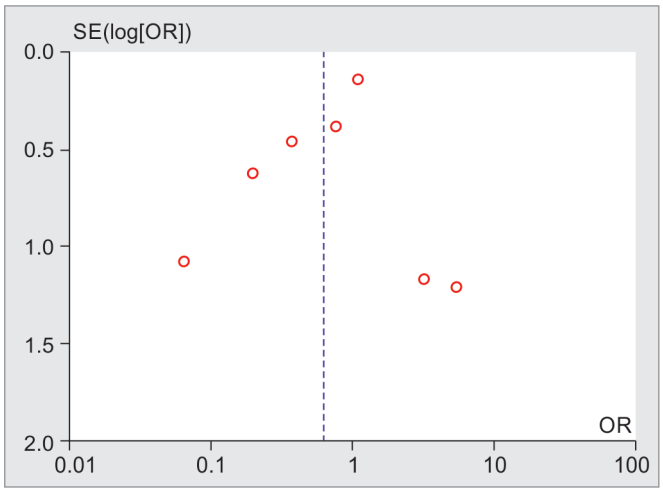

Fig. 10: Publication bias

been postulated to play a pivotal role in reducing delirium risk in the patient cohort by reducing inflammation and minimizing oxidative stress. However, our findings do not show the translation of physiological effects into clinical benefits in terms of patient-centered outcomes. Most outcome endpoints were either non-significant or non-robust on sensitivity analysis, thus failing to show the major effect of melatonin/melatonergics on patient benefits.

During the review, a few assumptions, related to the secondary outcomes had to be made as studies were inconsistent in reporting the characteristics and timelines of endpoints. The median values reported in the studies were converted to mean and SD using empirical formulae. An additional sensitivity analysis planned a priori was performed. In this analysis, all those studies in which reported median was subsequently converted to mean were included. The ICU LOS remained non-significant at 0.37 (from –1.82 to 1.07; $p = 0.61$) while the duration of mechanical ventilation changed from statistically significant to non-significant –0.42 (from

Table 2: The GRADE evidence profile of the studies

Outcome	Total number of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence	Relative effect
	Total	M	C							
Incidence of delirium	1330	661	669	No	Inconsistent	No possible limitations	No possible limitations	None	High	MD = 0.63 (95% CI: 0.60–1.32)
Severity of delirium	225	112	113	No	Inconsistent	No possible limitations	No possible limitations	None	High	MD = 0.22 (95% CI: From −1.36 to −1.81)
ICU LOS	1638	820	818	No	No possible limitations	No possible limitations	Imprecise	None	High	MD = 0.05 (95% CI: From −0.65 to 0.75)
Hospital LOS	1234	641	593	No	Inconsistent	No possible limitations	Imprecise	None	Moderate	MD = −1.46 (95% CI: From −4.50 to −1.59)
Need for MV	144	71	73	No	No possible limitations	No possible limitations	No possible limitations	None	High	MD = 0.74 (95% CI: From 0.38 to −1.44)
Duration of MV	1335	667	668	No	Inconsistent	No possible limitations	Imprecise	None	High	MD = −0.85 (95% CI: From −1.64 to −0.06)
ICU mortality	1549	773	776	No	No possible limitations	No possible limitations	No possible limitations	None	High	MD = 0.78 (95% CI: 0.56–1.11)

MV, mechanical ventilation

−1.29 to 0.45; $p = 0.34$). The previous meta-analyses did not report any similar sensitivity analysis.[4,13]

This meta-analysis included trials performed exclusively on critically ill adults admitted to the ICU. In the previous meta-analysis, Asleson and Chiu[13] concluded the unclear role of melatonin in the prevention of delirium in acute medically ill and peri operative geriatric patients. They attributed the lack of effect on the prevention of delirium to higher heterogeneity, smaller sample sizes, and varied population. The analysis excluded critically ill patients from the ICU. Campbell et al.[4] suggested the possible role of melatonin in the prevention of postoperative delirium in older adults. He reported 37% ($p = 0.006$) lower odds of developing delirium in the melatonin agonists arm compared to the placebo or no treatment arm perioperatively. However, similar results could not be extrapolated to the ICU population due to the variations in baseline health conditions and severity of illnesses. Similarly, Lewandowska et al.[21] concluded that melatonin therapy can significantly reduce the incidence and severity of delirium, by eliminating factors such as sleep deprivation, contributing to their development while Zhu et al.[22] suggested exogenous melatonergics association with decreased incidence of delirium, without significant difference in ICU LOS. This was also per Zhang et al.,[23] who observed a trend suggesting reduced duration of ICU stay in critically ill without any decrease in the duration of mechanical ventilation and in-ICU mortality with the use of melatonin.

The above findings were in contrast to the present analysis. The reasons could be multi-fold. Most of the systematic reviews mentioned above did not include the critically ill adult population of an ICU exclusively. Either the population was non-critical, perioperative, or mixed, thus conclusions could differ. Second, the ICU is a specialized clinical setting with a higher incidence of sleep dysregulation and delirium. The etiology of ICU delirium thus may also differ considerably compared to other hospital settings. It is proposed that ICU delirium may have a unique pathophysiological pathway. The use of sedatives and analgesia is higher in ICUs compared to other hospital settings and they are independent risk factors for delirium incidence thus contributing additionally within the ICUs.[12] These differences in both the type of population and settings may explain the differing conclusion of this analysis showing no association of melatonin to the incidence of delirium and the previous literature. The therapeutic effects of melatonin may also differ from the underlying mechanism of delirium. Hence, the findings in perioperative or geriatric patients cannot be extrapolated to the ICU population with conviction.

Strength and Limitations

After a thorough systematic search of all trials and reports published till February 2022, a total of 12 RCTs were included in the meta-analysis. The majority of included studies had a low risk of bias. We attempted to explain heterogeneity by using sensitivity analysis, wherever possible, and grading of recommendations assessment, development and evaluation (GRADE) evidence profiling to support the conclusion (Table 2). The conclusions have been compared and contrasted with those of previous analyses with all possible explanations.

However, there might be certain limitations in our study. First, the duration of the intervention (from 1 to 14 days), as well as dosages of melatonin (from 0.5 mg/dose to 50 mg/kg weight), were varied and inconsistent. This precludes robust assessment of the effect and may lead to false negative effects. Additionally, the formulations of melatonin which differ considerably (prolonged release or immediate release) and can have different effects were not presented in the included studies. This prevents the assessment of optimum dosage and formulation of melatonin. The prevalent heterogeneity in the included patients, setting, and the outcome measurement further reduces the power to assess the effect of melatonin within the ICU population. A total of 14 studies have been excluded for the lack of complete data, which could have affected the results of this meta-analysis. The CAM or CAM-ICU, the commonest tool used in most RCTs to assess delirium outcomes has reported sensitivity and specificity of 94% and 89%, respectively.[24] However the validity of the outcome measured may be compromised as it is not the gold standards for delirium diagnosis.

Conclusion

Thus, this meta-analysis and systematic review suggest that there is no clear evidence available to suggest a definitive benefit in prophylactic melatonin therapy for delirium in critically ill adults in ICUs. Also, the role of melatonin in the reduction of the need for

mechanical ventilation, ICU LOS, and overall mortality are unclear. Further, large-scale multicentric blinded RCTs involving critically ill ICU patients need to be planned to answer the uncertainties including risk factors, predisposing of conditions, precipitating factors, and method used for diagnosis of delirium in the ICU.

Take-home Message

The conclusion obtained in our meta-analysis appears to contradict many of the recently published studies, which had suggested the probable role of prophylactic melatonin in ICU delirium. The reasons for this contradiction have been discussed and suggestions for planning further trials have been made.

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