Assessment of Melatonergics in Prevention of Delirium: A Systematic Review and Meta-Analysis

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**Background:** Delirium is a commonly found comorbidity in hospitalized patients and is associated with adverse outcomes. Melatonin is an endogenous hormone that exerts multiple biological effects, mainly in regulating diurnal rhythms and in inflammatory process and immune responses. We aimed to assess the efficacy of exogenous melatonergics in the prevention of delirium.

**Methods:** We conducted a search to identify relevant randomized controlled studies (RCTs) in PubMed, Cochrane Library, and EMBASE databases that had been published up to December 2019. Hospitalized adult patients administered melatonergics were included. The primary outcome measure was the incidence of delirium. The secondary outcome measure was the length of stay in intensive care unit (ICU-LOS). The pooled effects were analyzed as the risk ratio (RR) for delirium incidence, weighted mean difference (WMD) for ICU-LOS, and 95% confidence intervals (CIs).

**Results:** Nine RCTs with 1,210 patients were included. The forest plots showed that melatonergics were associated with a decreasing incidence of delirium (RR, 0.51; 95% CI, 0.30–0.85; I² = 70%; p = 0.01). There was no significant difference in ICU-LOS (WMD, −0.08; 95% CI, −0.19–0.03; I² = 0; p = 0.17).

**Conclusion:** Administration of exogenous melatonergics to hospitalized patients seems to be associated with a decreasing incidence of delirium.

**PROSPERO registration number:** CRD42019138863.

Keywords: melatonin, delirium, prevention, critical care medicine, systematic review
BACKGROUND

Delirium is a complex neuropsychiatric syndrome characterized by cognitive impairment and attentional deficits (1). Delirium in the intensive care unit (ICU) has a high incidence (30–60%) (2–4) and is strongly associated with adverse outcomes, such as increased mortality, prolonged length of stay in ICU (ICU-LOS), increased costs, and long-term cognitive sequelae (5). As increasingly recognized, delirium has become one of the most concerning problems for intensive care physicians. Although delirium appears to have a high incidence and is associated with adverse outcomes, clinical strategies have been very limited (6).

Melatonin is a neurohormone that exerts multiple biological effects, mainly in regulating diurnal rhythms and in modulating inflammatory as well as immune responses (7, 8). Abundant evidence has indicated that decreasing melatonin levels are linked with delirium (9). Melatonergics include melatonin and other melatonin agonists such as ramelteon. Whether supplementation with exogenous melatonin and melatonin agonists could reduce the risk of delirium remains uncertain. Several randomized controlled studies (RCTs) have been conducted related to this issue. Taking Sultan and colleagues’ study (10) as an example, 300 elderly patients undergoing hip arthroplasty were randomly assigned to one of four groups; these groups were administered with melatonin, midazolam, clonidine, or no medication, respectively. The results of this study showed that melatonin was associated with a significant reduction in the incidence of delirium compared with the control group, as well as the other two parallel groups. However, a meta-analysis including four RCTs indicated no significant difference (11). Since then, several well-designed RCTs have been conducted (12–16). A recent meta-analysis evaluated delirium as a subset but included only three RCTs for this result (17). With the updated results (12–16), we aimed to conduct a meta-analysis in attention to reevaluate the efficacy of melatonergics in the prevention of delirium.

METHODS

Study Registration

The protocol has been registered on the PROSPERO (registration no. CRD42019138863) based on the Preferred Reporting Items for Systematic review and Meta-analysis Protocols guidelines (18).

Search Strategy and Selection Criteria

Three electronic databases (PubMed, Cochrane Library, and EMBASE) were searched without language restriction to identify RCTs published from 1960 to December 2019. Multiple keywords including “melatonin,” “melatonergic,” or “ramelteon” combined with “delirium” were developed for the search strategy. The reference lists were searched manually for potentially relevant articles.

Abbreviations: AMT, Abbreviated Mental Test; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CIs, confidence intervals; ICU, intensive care unit; ICU-LOS, length of stay in intensive care units; OR, odds ratio; RCTs, randomized controlled studies; RR, risk ratio; WMD, weighted mean difference.

Data Extraction and Quality Assessment

Two reviewers (J.Z.M. and Z.Y.B.) independently extracted data to fill in a predesigned form including the characteristics of the studies, year of publication, demographics and baseline of subjects, intervention, and outcomes. Two reviewers (Z.Y.B. and W.Y.) independently rated the quality of the RCTs and extracted the items for the risk-of-bias assessment (19). Disagreements between reviewers were resolved by two experts (X.X.M. and Y.Y.M.).

Outcome and Statistical Analysis

The primary outcome measure was the incidence of delirium. The pooled effects were analyzed as risk ratio (RR) using the Mantel–Haenszel technique and 95% confidence intervals (CIs). Sensitivity analyses of the primary outcome were conducted. Subgroup analyses of the primary outcome included (a) differed melatonergics, including melatonin and ramelteon; (b) different age groups, including elderly subjects (mean age, >60 years), middle-aged subjects (mean age, 40–60 years), and younger subjects (mean age, <40 years); (c) different ICU types, including surgical ICU, medical ICU, and mixed ICU; and (d) different delirium assessment methods including the Confusion Assessment Method for the ICU (CAM-ICU), the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Abbreviated Mental Test (AMT), the Confusion Assessment Method (CAM), the nurse observation, and the methods not reported. The secondary outcome measure was ICU-LOS. The pooled ICU-LOS was measured in days and analyzed using the weighted mean difference (WMD) and 95% CI. If high clinical or statistical heterogeneity was observed, a random-effects model was chosen. Otherwise, a fixed-effects model was used. The I² statistic was used to estimate statistical heterogeneity (I² < 30% as low heterogeneity, I² of 30–70% as medium heterogeneity, and I² > 70% as high heterogeneity). P < 0.05 was considered to be statistically significant.

RESULTS

Study Selection

A total of 257 potentially relevant articles were identified according to the search strategy. The full text of 31 articles was obtained after screening the titles/abstracts. Twenty-two studies failed to meet the inclusion criteria; therefore, nine studies were included in this meta-analysis. Figure 1 presents the process of study selection.
Study Characteristics and Quality

Melatonin was administered in seven RCTs (10, 12–14, 16, 20, 21) with different doses. Ramelteon was administered in the other two (15, 22). The subjects of six RCTs (10, 13, 15, 20–22) were elderly (mean age, >60 years), whereas they were apparently younger (mean age, <40 years) in the other (12). Table 1 presents the characteristics of the included studies. The nine RCTs were of high quality. Figure 2 presents the risk-of-bias items for each study.

Outcomes

Nine RCTs with 1,210 patients were involved to analyze the incidence of delirium. Forest plots showed that melatonergics were associated with a decreasing incidence of delirium (RR, 0.51; 95% CI, 0.30–0.85; $I^2 = 70%$; $p = 0.01$; Figure 3). The statistical heterogeneity of the data was high. In the sensitivity analyses, the difference between the melatonergics and the control groups remained significant when we excluded any single RCT (Table 2). In the subgroup analyses, melatonergics showed an association with lower delirium incidence in the subgroup of elderly patients, younger patients, medical ICU patients, delirium screening methods of CAM-ICU, AMT, and CAM. In the melatonin, ramelteon, middle-aged, surgical and mixed ICU, delirium screening methods of DSM-IV, nurse observation, and methods not reported subgroups, there was no significant difference (Table 3).

For the secondary outcome, the ICU-LOS in the melatonergics group was numerically shorter than that in the control group, with no significant difference (WMD, $-0.08$; 95% CI, $-0.19$–$0.03$; $I^2 = 0%$; $p = 0.17$; Figure 4).

DISCUSSION

The results of the present meta-analysis indicated that melatonergics were associated with a decreasing incidence of delirium in critically ill patients. Based on the encouraging results of the primary RCTs (10, 12, 20, 22), suggesting that administration of melatonin and melatonin agonists might be a promising medication for the prevention of delirium in at-risk populations, our meta-analysis provided advanced evidence. These encouraging results were considered to be quite reasonable. First, sleep deprivation is a crucial risk.
Thus, supplementation with exogenous melatonin can remedy melatonin levels is associated with the development of delirium. Meanwhile, a reduction in sleep duration in some settings. First, there were only five RCTs with 744 patients included in this outcome measure. The result should be interpreted more cautiously because of the limited sample size. Second, because the context of the ICU is linked to the delirium onset and is bad for delirium recovery, physicians might tend to discharge patients with delirium or a high risk of delirium to general wards more aggressively. This confounder makes the association between delirium and ICU-LOS more obscure and hard to interpret.

**Strengths and Limitations**

There are strengths to our study. First, in comparison to another meta-analysis (11), we excluded previously diagnosed delirium [according to what the authors reported (21)] and analyzed incident delirium to reduce confounding factors and clinical heterogeneity. Second, our sensitivity analyses showed steady and consistent results, which increased the grade of evidence.

There are also limitations to our study. First, clinical heterogeneity was obvious between the RCTs due to varied

**TABLE 1 | Characteristics of included studies.**

| References | Participants | Sample size (M/C) | mean age (M/C) | Mean APACHE II score (M/C) | Interventions | Measures | Delirium incidence (%) | Outcomes |
|------------|--------------|------------------|----------------|---------------------------|---------------|----------|------------------------|----------|
| Sultan (10) | Elderly subjects undergoing hip arthroplasty | 53/49 | 70.4/72.3 | 14.6/13.5 | MT (5 mg) vs. no medication administered preoperative bedtime, 90 min preoperation, and 3 nights postoperation | Delirium assessed by AMT | 11 | MT group with lower delirium rate |
| Nickkhohlg et al. (16) | Middle age subjects undergoing liver surgery | 18/18 | 59/56 | NR | MT (50 mg/kg BW) vs. placebo administered on the day of surgery | NR | 3 | MT group with lower delirium rate |
| Al-Aasma et al. (20) | Elderly subjects on internal medicine service | 61/61 | 84.3/86.4 | NR | MT (0.5 mg) vs. placebo given flexibly between 6 pm and midnight | Delirium assessed by CAM; delirium severity assessed by MDAS | 34 | MT group with lower delirium rate; no difference in delirium severity |
| Hatta et al. (22) | Elderly subjects in the ICU and on internal medicine wards | 33/34 | 78.2/78.3 | 13.5/14.6 | Ramelteon (8 mg) vs. placebo at 9 pm for up to seven nights | Delirium assessed by DSM-IV; delirium severity assessed by DSR-98 | 68 | Ramelteon group with lower odds of delirium; ramelteon group with longer time to delirium |
| de Jonghe et al. (21) | Elderly subjects undergoing hip surgery | 186/192 | 84.1/83.4 | NR | MT (3 mg) vs. placebo in the evening for 5 days | Delirium assessed by DSM-IV | 28 | MT group with higher delirium rate |
| Dianatkhah et al. (13) | Elderly subjects undergoing CAGB surgery | 66/71 | 60.0/62 | NR | MT (3 mg) vs. oxazepam 1 h before sleep time from 3 days before surgery to discharge | Delirium assessed by nurse records | 10 | MT group with lower delirium rate |
| Vijayakumar et al. (12) | Younger subjects with lesser comorbidity | 26/30 | 36.9/38 | 10.2/8.6 | MT (3 mg) vs. placebo at 9 pm throughout the ICU stay | Delirium assessed by CAM-ICU | 28 | MT group with a longer delirium free day; MT group with lower incidence |
| Abbasi et al. (14) | Middle age subjects in mixed ICU | 67/70 | 52.5/49.9 | 8.1/4.3 | MT (3 mg) vs. placebo at 9 pm for 5 days | Delirium assessed by CAM-ICU | 3 | MT group with higher delirium rate |
| Nishkimi et al. (15) | Elderly subjects on internal medicine service | 45/43 | 68/68 | 23.9/23.9 | Ramelteon (8 mg) vs. placebo at 8 pm every day until discharge from ICU | Delirium assessed by CAM-ICU | 35 | Ramelteon group with lower incidence of delirium |

AMT: Abbreviated Mental Test; APACHE II: Acute Physiology and Chronic Health Evaluation II; CAGB: coronary artery bypass graft; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method for the ICU; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSR-98: Delirium Rating Scale—revised-98; ICU, Intensive care unit; M/C: melatonin or melatonin agonist group/control group; MDAS, Memorial Delirium Assessment Scale; MT: melatonin; NR: not reported.
A Each risk of bias item for each included study

B Each risk of bias item presented as percentages across all included studies

FIGURE 2 | Risk of bias. A summary of (A) each risk of bias item for each included study and (B) each risk-of-bias item presented as percentages across all included studies.

FIGURE 3 | Forest plot. Administration of melatonergics was associated with a reduction of the incidence of delirium.
TABLE 2 | Sensitivity analyses on delirium incidence.

| References                  | Patients remaining (M/C) | Events remaining (M/C) | RR (95% CI) | I² (%) | p   |
|-----------------------------|-------------------------|------------------------|--------------|--------|-----|
| Sultan (10)                 | 496/510                 | 89/126                 | 0.58 (0.35–0.97) | 64     | 0.04|
| Nickkhah et al. (16)        | 532/642                 | 94/182                 | 0.51 (0.30–0.87) | 73     | 0.01|
| Hatta et al. (22)           | 517/626                 | 93/172                 | 0.56 (0.34–0.93) | 68     | 0.003|
| de Jonghe et al. (21)       | 364/468                 | 39/134                 | 0.43 (0.27–0.69) | 41     | 0.0006|
| Al-Aama et al. (23)         | 494/608                 | 92/173                 | 0.56 (0.33–0.94) | 69     | 0.03|
| Dianatkhan et al. (13)      | 484/589                 | 90/174                 | 0.51 (0.29–0.89) | 73     | 0.02|
| Vijayakumar et al. (12)     | 524/630                 | 81/158                 | 0.47 (0.23–0.93) | 73     | 0.03|
| Nishiki et al. (15)         | 487/599                 | 83/162                 | 0.50 (0.26–0.94) | 76     | 0.03|
| Abbasi et al. (14)          | 483/590                 | 91/182                 | 0.47 (0.28–0.79) | 72     | 0.005|

CI, confidence interval; C, control group; M, melatonergics group; No., number; RR, risk ratio.

TABLE 3 | Subgroup analyses on delirium incidence.

| Group              | Reference | Patient no. (M/C) | Event (M/C) | RR (95% CI) | I² (%) | p   |
|--------------------|-----------|-------------------|-------------|-------------|--------|-----|
| Melatonergics     | Melatonin | 10, 12, 13, 14, 18, 20, 21 | 472/583 | 82/152 | 0.56 (0.31–1.02) | 71 | 0.06|
|                    | Ramelteon | 15, 22            | 78/77      | 12/31       | 0.28 (0.05–1.61) | 67 | 0.15|
| Age                | Elderly   | 10, 13, 15, 20, 21, 22 | 493/542 | 78/156 | 0.47 (0.23–0.93) | 73 | 0.03|
|                    | Middle    | 14, 18            | 85/88      | 3/2         | 1.35 (0.16–11.35) | 23  | 0.78|
|                    | Younger   | 12                | 26/30      | 13/25       | 0.60 (0.40–0.91) | NA  | 0.02|
| ICU type           | Medical   | 15, 20, 22        | 134/129    | 14/41       | 0.27 (0.09–0.82) | 55  | 0.02|
|                    | Surgical  | 10, 13, 18, 21    | 323/431    | 64/116      | 0.53 (0.19–1.48) | 78  | 0.22|
|                    | Mixed     | 12, 14            | 93/100     | 16/26       | 0.98 (0.20–4.65) | 56  | 0.98|
| Assessment tools   | CAM-ICU   | 12, 14, 15        | 138/143    | 27/46       | 0.60 (0.41–0.90) | 14  | 0.01|
|                    | DSM-IV    | 21, 22            | 219/226    | 56/60       | 0.40 (0.03–5.02) | 85  | 0.47|
|                    | AMT       | 10                | 53/150     | 5/57        | 0.25 (0.11–0.59) | NA  | 0.001|
|                    | CAM       | 20                | 56/42      | 2/10        | 0.19 (0.04–0.81) | NA  | 0.02|
|                    | Nurse     | 13                | 66/71      | 4/9         | 0.48 (0.15–1.48) | NA  | 0.20|
|                    | NR        | 18                | 18/18      | 0/1         | 0.33 (0.01–7.68) | NA  | 0.49|

C, control group; CAM-ICU, Confusion Assessment Method for the ICU; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICU, intensive care unit; M, melatonergics group; NA, not applicable; No., number; RR, risk ratio.

FIGURE 4 | Forest plot. There was no significant difference in the length of stay in ICU.

CONCLUSIONS

Exogenous melatonergics seem to be associated with a decreased incidence of delirium. No significant difference in ICU-LOS was
identified. Additional studies are needed to further evaluate the efficacy and safety of melatonin in preventing delirium.

AUTHOR CONTRIBUTIONS

ZI, YZ, and HH searched the scientific literature and drafted the manuscript, collect the data, and performed statistical analyses. RX, CR, YW, YY, and WenL polished and revised the manuscript. Weil., XX, and BD contributed to conception, design, data interpretation, manuscript revision for critical intellectual content, and supervision of the study. All authors read and approved the manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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