Ramelteon for Delirium Prevention in Hospitalized Patients: A Meta-analysis and Trial Sequential Analysis of Randomized Controlled Trials

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Key point

Question: Is ramelteon a reliable and effective therapeutic option for delirium prevention in hospitalized patients?

Findings: In this systematic review and meta-analysis of 8 trials with 587 hospitalized patients, ramelteon was associated with a lower odds of delirium occurrence compared with placebo (odds ratio: 0.50, 95% confidence interval: 0.29-0.86, I^2= 17.48%), and the trial sequential analysis suggested that such evidence is reliable with a 50% relative risk reduction threshold.

Meaning: The findings suggest reliable evidence for the efficacy of ramelteon on delirium prevention in hospitalized patients.

Abstract

Importance: Few studies have examined the reliability of the efficacy of ramelteon on delirium prevention.

Objective: To conduct an updated meta-analysis and examine the reliability of the existing evidence regarding the effect of ramelteon on delirium prevention among hospitalized patients.

Data sources: The MEDLINE, PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Clinical trials.gov, and World Health Organization (ICTRP) were systematically searched to identify randomized controlled trials (RCTs) examining the efficacy of ramelteon in delirium prevention without language restriction from database inception to October, 31, 2022.

Study selection: Only RCTs that used ramelteon for delirium prevention were included. Observational, cohort, and case-control studies, conference abstracts, reviews, letters, case reports, and case series were excluded.

Data extraction and Synthesis: The systematic literature review was performed per Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Data were independently extracted by 4 authors. Data were pooled using a frequentist restricted maximum likelihood (REML) random-effects model. A trial sequential analysis (TSA) was performed using relative risk reduction (RRR) thresholds of 50%. Analysis was performed from November 1 through November 15, 2022.

Main outcomes and Measures: The primary outcome was an incidence of delirium (reported as odds ratio (OR) with 95% confidence intervals). The secondary outcomes were the days of delirium, all-cause mortality, and all-cause discontinuation.

Results: Of 187 potentially eligible studies identified, eight placebo-controlled RCTs (n = 587) were included. The updated meta-analysis showed that ramelteon was associated with lower odds of delirium occurrence compared with placebo (0.50, 0.29-0.86; I^2= 17.48%). In TSA, the effect of ramelteon across the superiority boundary when using RRR threshold ranging 40% to 60%. In subgroup analyses, ramelteon compared with placebo was associated with lower odds of delirium occurrence in the elderly group (k=5; 0.28, 0.09-0.85; I^2= 27.93%) and the multiple dosage group (k=5; 0.34, 0.14-0.82; I^2= 44.24%), but not in the non-elderly group and the non-multiple dosage group. No significant between-group differences were found in the secondary outcomes.

Conclusions and Relevance: There is reliable evidence that ramelteon compared with placebo reduces the risk of delirium occurrence among hospitalized patients, suggesting ramelteon is a safe and efficacious option for delirium prevention.

Key words: ramelteon; delirium prevention; trial sequential analysis; meta-analysis; hospitalized patients

Introduction

Delirium, an acute brain dysfunction characterized by inattention, cognitive impairment, and sleep/wake cycle disturbances is associated with increased mortality, longer hospital stays, and poorer cognitive function[1,2]. Multiple pathophysiologic mechanisms have been hypothesized, including neurotransmitters dysregulation, neuroinflammatory, neural aging, neuroendocrine, sleep-wake cycle disturbance, and oxidative stress[3]. Regarding neurotransmitters, previous randomized controlled trials (RCTs) mostly focused on cholinergic deficiency and dopamine excess [4]. However, recent attention has been paid to melatonin and melatonergic agents for the prevention of delirium occurrence.

Melatonin is an endogenous hormone from the pineal gland, having several potential effects on delirium prevention, such as regulation of circadian rhythm, anti-oxidation, anti-inflammatory, and regulation immune process[5]. Although preliminary data reported therapeutic effects of melatonin on delirium prevention, a recent meta-analytic study including 14 RCTs suggested that such evidence is still inconsistent and unreliable[6]. Ramelteon, a melatonin agonist, has higher affinity on melatonin receptor MT1 and MT2, higher central penetration ability in the brain, and longer half-life compared to melatonin[7]. These findings may imply ramelteon as a better therapeutic option on delirium prevention than melatonin. The first RCT conducted by Hatta et al. reported a that ramelteon decreased the risk of delirium in elderly patients with medical illnesses (relative risk [RR]: 0.09, 95% confidence interval [CI]: 0.01-0.69)[8]. In addition, several RCTs were conducted examining the efficacy of ramelteon for delirium prevention in various clinical populations. However, recent two meta-analytic studies with slightly different inclusive criteria reported inconsistent findings [Khaing et al. (2021)[9]: k=5; RR, 0.51, 95%CI, 0.27-0.93; Wang et al. (2022)[10] : k=4; RR, 0.89, 95%CI, 0.44-1.78].

Importantly, the results of meta-analyses with few trials or participants have poor credibility with possible type I error (overestimated) and type II error (underestimated)[11]. A trial sequential analysis (TSA) is a statistical method to control for type I and II errors in systematic reviews and meta-analyses, and to estimate the reliability of the existing body of evidence[12]. In addition, the futility analysis of TSA could examine whether the anticipated intervention effect is achievable or not, when the required information size is still not reach[12]. Therefore, TSA can be used to assess whether the body of evidence is sufficiently large and consistent and whether the assumed effect is considered unachievable.

To date, no study has specifically examined the efficacy and safety of ramelteon on delirium prevention using trial sequential analysis. Furthermore, there were three newly published RCTs newly[13-15]. The aim of the current study was to synthesize all the updated data from RCTs that examined the efficacy of ramelteon in preventing delirium emergence in hospitalized patients and assess the reliability of the existing evidence by TSA. Our study findings help inform clinical physicians the application of ramelteon in delirium prevention.

Materials and Methods

The protocol of the current systematic review and meta-analysis was registered a priori in OSF (10.17605/OSF.IO/B7XV3) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement (Appendix 1)[16]. Ethical approval is waived in this meta-analytic study.

Search strategy and selection criteria

The MEDLINE, PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Clinical trials.gov, and World Health Organization (ICTRP) were systematically searched to identify RCTs examining the efficacy of ramelteon for delirium prevention without language restriction from database inception to October, 31 2022. Reference lists of relevant reviews were also searched manually. The full details of the search strategies and the reasons of exclusions are provided in the Supplement (Appendix 2). The PICO (population, intervention, comparison, outcome) settings of the current meta-analysis were: (1) P: hospitalized patients; (2) I: ramelteon; (3) C: placebo or active control; and (4) O: delirium occurrence. Observational studies (e.g., cohort or case-control studies), conference abstracts, reviews, letters, case reports, and case series were excluded. Screening and selection of studies were performed independently by four authors (CLY, AFC, TT, TCT), with each study assessed by a minimum of two authors. Disagreements were resolved by consulting with the corresponding author.

Outcome definition and data extraction

The primary outcome was incidence of delirium. The secondary outcomes were the duration of delirium (day), all-cause mortality, and all-cause discontinuation. At least two authors double-checked the data-transfer accuracy and calculations. We extracted data on study characteristics (e.g., sample size, authors, publication years), patient populations, interventions (dose, frequency), and reported outcomes from included studies or published meta-analyses.

Data analysis

The Cochrane Risk of Bias Assessment Tool[17] was used to assess the quality of the included studies by two independent authors (PTT, CWH). Any discrepancies were be resolved by consensus. A frequentist restricted maximum likelihood random-effects model was performed to calculate the effect size. An intention-to-treat approach was used. The pooled effect size was odds ratio (OR) for the categorical variable and mean difference for the continuous variables. The Cochran's Q test, I^2 statistic, and Galbraith plot were used to evaluate heterogeneity. Publication bias (Egger's test with visual inspection of funnel plots) analyses were conducted. Subgroup meta-analysis was performed when at least three sets of data were available. Meta-regression was performed if ten or more studies were included. A series of sensitivity analyses were performed: (1) excluding high risk of bias (ROB) study, (2) iteratively removing one study, and (3) using generalized linear mixed model if both-arm-zero-event study existed, which helped to explore the sources of heterogeneity and the stability of the summary results. Data management and analysis were carried out using Stata (version 16) and R-Project (V.4.0.3, R Foundation). A p value of <0.05 is considered significant (two-tailed).

We performed TSA using TSA software version 0.9.5.10 Beta (www.ctu.dk/tsa). TSA was set to maintain the overall risk of type I error of 5% and power of 80% and report the information size, an estimate of optimum sample size for statistical inference from a meta-analysis, after considering heterogeneity of included studies. We used a 50% of relative risk reduction (RRR) threshold for the primary outcome. Sensitivity analysis of TSA was performed using RRR thresholds of 40%, 45%, 55%, and 60%.

Results

Study characteristics

After searching the databases and excluding duplicate records, we identified 187 potential articles. Finally, eight blinded RCTs with 587 participants were included (Table 1)[8,13-15,18-21]. The flowchart of our search strategy is presented in Figure 1. The complete search strategies (Appendix 2) and reasons for exclusion (Appendix 3) are shown in the online supplement. The eight RCTs included 297 participants in the ramelteon group (mean age ranged from 5.4 to 78.2 years; 25–58% female) and 290 in the control group (mean age ranged from 5.2 to 78.3 years; 21–68% female).

Methodology quality of the included studies

One of the included studies had high ROB in performance bias because of single blinded study design[8](eFigure 1 and eFigure 2). The percentage of studies with high, unclear, and low ROB for the individual items was: 0%, 12.5%, and 87.5% for randomization, 0%, 25%, and 75% for allocation concealment, 12.5%, 0%, and 87.5% for blinding of participants and personnel, 0%, 0%, and 100% for blinding of outcome assessment, 0%, 12.5%, and 87.5% for incomplete outcome data, 0%, 25%, and 75% for selective reporting, and 0%, 0%, and 100% for other biases.

Primary outcome and trial sequential analysis

Figure 2 presents that ramelteon was associated with a reduction of delirium occurrence in hospitalized patients compared to placebo (k=8; OR: 0.50, 95% confidence interval [CI]: 0.29-0.86) without significant heterogeneity (I^2=17.48%, Q=9.34, p=0.23). Figure 3 shows the result of TSA using a 50% of RRR threshold. The z-curve crosses the superiority boundary after three RCTs, which indicates that available evidence is sufficient to suggest that ramelteon compared with placebo would reduce a 50% of relative risk of delirium in hospitalized patients. Besides, the required sample size was also reached. When using 40%, 45%, 55%, and 60% of RRR thresholds (eFigure 3 to eFigure 6), all the z-curves cross the superiority boundary and reached the required sample sizes, except for a 40% of RRR threshold (crossing the superiority but not reaching the required sample size).

Subgroup analyses for primary outcome

We conducted two subgroup analyses: (1) an elderly group (defined as ≥65 years) vs. a non-elderly group and (2) a multiple dosage group (defined as > two doses) vs. a non-multiple dosage group. The subgroup analyses showed that a lower odds of delirium occurrence was observed in the elderly group (k=5; OR: 0.28, 95% CI: 0.09-0.85; I^2=27.93%, Q=5.13, p=0.27) but not in the non-elderly group (k=3; OR: 0.64, 95% CI: 0.37-1.10; I^2=7.45%, Q=2.16, p=0.34) (eFigure 7). Besides, a lower odds of delirium occurrence was observed in the multiple dosage group (k=5; OR: 0.34, 95% CI: 0.14-0.82; I^2=44.24%, Q=6.33, p=0.18) but not in the non-multiple dosage group (k=3; OR: 0.79, 95% CI: 0.33-1.86; I^2=0%, Q=1.84, p=0.40) (eFigure 8).

Publication bias analysis and sensitivity analyses for primary outcome

In the Galbraith plot (Figure 4), there was no study consider outlier, and the effect sizes of the included studies were within the region of 95% CI. Therefore, there was no significant

heterogeneity of the included studies for the primary outcome. In the funnel plot (eFigure 9), there was no evidence of publication bias (Egger's test, p = 0.14. In the leave-one-out test, ramelteon compared with placebo was still associated with a lower odds of delirium occurrence, except for leaving Nishikimiet al. 2018 out (OR: 0.52, 95%CI: 0.26-1.03, p=0.06)[20](eFigure 10). When excluding the study with high ROB[8], ramelteon was still associated with a reduction of delirium occurrence in hospitalized patients with low heterogeneity (k=7; OR: 0.58, 95% CI: 0.37-0.93; I^2=17.48%, Q=5.42, p=0.49) (eFigure 11).

Secondary outcomes and sensitivity test for secondary outcomes

The forest plots of all-cause mortality, all-cause discontinuation, and delirium duration can be found in the Supplement (eFigure 12 to eFigure 14). Compared with placebo, ramelteon did not differ from placebo in the three secondary outcomes. Because there were both-arm-zero-event studies in the secondary outcomes, we condurcted the generalized linear mixed-effects models, showing no differences between ramelteon and placebo in all-cause mortality (OR: -0.20, 95%CI: -1.32-0.93, p=0.73) and all-cause discontinuation (OR: 0.74, 95%CI: -0.39-1.88, p=0.20) (eTable 1).

Discussion

In the current meta-analytic study, we examined the efficacy and safety of ramelteon in preventing delirium occurrence and used TSA to assess the reliability of such evidence. The main findings of the study were as follows. First, ramelteon compared with placebo was associated with a 50% lower odds of delirium occurrence in hospitalized patients, and the results of TSA support that ramelteon might reduce the relative risk of delirium by 40%-60% than placebo. Second, the subgroup analyses suggested that the efficacy of ramelteon on delirium prevention was only observed in the elderly group but not in the non-elderly group. Third, the subgroup analyses suggested that the efficacy of ramelteon on delirium prevention was only observed in the multiple dosage group but not in the non-multiple dosage group. Four, there was some evidence that ramelteon may be safe and tolerable, based on the lack of apparent differences in mortality or acceptability compared with placebo.

The mechanism underlying the effects of ramelteon on delirium prevention might be related to correction of circadian rhythm disturbance. Evidence suggests a variety of possible predisposing factors of delirium, such as age, medical comorbidities, dementia, medication using, and circadian rhythm disturbance[1]. In the elderly, several mechanisms have been proposed for circadian rhythm desynchronization in the elderly, such as changed architecture of sleep including decreased slow-wave sleep, fragmented sleep, and early waking[22]. Importantly, neural aging, including declined function of suprachiasmatic nucleus and declined melatonin secretion would also influence the circadian rhythm[23]. Ramelteon is a high-affinity MT1 and MT2 melatonin receptor agonist, which could activate the MT1 melatonin receptor within the suprachiasmatic nucleus, and further overt the circadian rhythm[24]. The correction of the predisposing factor of circadian rhythm disturbance by ramelteon might be one of the explanations for better efficacy of ramelteon on delirium preventing in elderly group. However, circadian rhythm disturbance might not be a major predisposing factor for delirium occurrence in non-elderly patients. Therefore, the role played by ramelteon may not be major in delirium prevention in these populations.

In our analysis, single or twice doses of ramelteon administration was not significantly associated with a lower odds of delirium occurrence. Notably, participants in the three RCTs [13,14,18] in the non-multiple doses group were all surgical patients. The precipitating factors of delirium for surgical patients might continue for a long period of time, such as postoperative pain, withdrawal from anesthetics, inflammation, anemia due to blood loss, or hypoactivity might not resolved [25]. Peak concentration of ramelteon is reached approximately 45 minutes, and the elimination half-life is about 2.6 hours[26]. Thus, once or twice administration of ramelteon might not adequately cover the high-risk period of postoperative delirium. Well-designed clinical trials with different doses of ramelteon were warranted in surgical patients.

In recent years, growing evidence supports the efficacy of dexmedetomidine (an alpha-2 agonist) in delirium prevention [27]. A previous large network meta-analytic study including 84 RCTs reported that dexmedetomidine was the most effective drug in reducing the incidence of delirium occurrence compared to placebo (OR: 0.46, 95% CI: 0.32-0.66, high strength of evidence) [27].

However, dexmedetomidine caused higher drop-out rate compared with placebo [27], with common adverse effect of bradycardia and hypotension[27]. In our study, ramelteon was associated with a similar effect but not with a higher mortality or a lower acceptability compared with placebo [28]. Therefore, ramelteon might be a safer option than dexmedetomidine when choosing a therapeutic option for delirium prevention.

Limitation

Several limitations should be considered when interpreting our findings. Although our primary outcome did not show significant heterogeneity, clinician heterogeneity needs to be considered. The demographics of the included participants varied. There were also various screen tools of delirium and various administration of ramelteon (dose, duration, and timing). Second, the results of TSA support the reliability of the efficacy of ramelteon in preventing delirium occurrence in hospitalized patients; however, future large-scale RCTs are still warranted. Our subgroup analyses showed that such efficacy was observed in the elderly and the multiple dosage groups but not in the non-elderly and the non-multiple dosage groups. It remains unknown the candidate group and the most effective dosing protocol using ramelteon on delirium prevention. Third, although our study is the largest meta-analytic study addressing ramelteon on delirium prevention, data on other delirium-related outcomes are limited, including delirium severity, sleep quality, or length of ICU/hospital stay. Likewise, only three RCTs[14,19,20] among the included studies reported delirium duration which might limit the statistic power.

Conclusion

Delirium is a frequent phenomenon among older hospitalized patients and has been associated with increased costs and complication rates, including long hospital stay, poor functional status and need for institutional care, long-term cognitive decline, and even mortality.[29,30] Importantly, the etiology of delirium is complex, and thus clinical contexts and multifactorial programs needs to be considered in the prevention and treatment of delirium. Based on our meta-analysis with TSA involving eight RCTs, we suggest that ramelteon is an effective intervention for delirium prevention among hospitalized patients and no evidence was found that ramelteon cannot be tolerated or increases mortality. Further large-sale RCTs are encouraged to address the dosing schedule and candidate population.

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