DOCTORAL THESIS

The Efficacy of Ramelteon to Prevent Postoperative Delirium After General Anesthesia in the Elderly: A Double-Blind, Randomized, Placebo-Controlled Trial

全身麻酔後の高齢者におけるせん妄の予防へのラメルテオンの効果についての二重盲検無作為化プラセボ対照比較試験

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The Efficacy of Ramelteon to Prevent Postoperative Delirium After General Anesthesia in the Elderly: A Double-Blind, Randomized, Placebo-Controlled Trial

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ABSTRACT

Objective: *Postoperative delirium is common and serious in elderly patients. Several drugs have been proposed as potential prophylactic agents for postoperative delirium. Studies on melatonin receptor agonists showed heterogeneity in age, cognitive function, anesthesia, surgery, interventions, methodologies for assessing outcomes, and results. Our objective was to examine the effect of ramelteon to prevent postoperative delirium in elderly patients, including those with dementia.* ***Design:*** *A stratified, double-blind, randomized, placebo-controlled trial (UMIN000028436, jRCTs031180054).* ***Setting:*** *Tertiary medical center.* ***Participants:*** *Patients aged older than or equal to 65 years undergoing elective surgery under general anesthesia.* ***Intervention:*** *Ramelteon (8 mg orally) or placebo (lactose) for six nights (the preoperative night and five consecutive nights from postoperative day 1 to 5) at around 9 P.M.* ***Measurements:*** *Patients were screened for postoperative delirium using the Confusion Assessment Method for the Intensive Care Unit twice daily until the sixth postoperative day. Patients with positive results were referred to a consultant psychiatrist to establish the diagnosis of delirium.* ***Results:*** *A total of 108 patients were randomly assigned to receive ramelteon (n = 55) or placebo (n = 53). Most of the*

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patients' characteristics were reasonably well-balanced between the two groups. The stratified log-rank test showed no significant difference in preventing postoperative delirium between ramelteon and placebo ($\chi 2 = 0.30$, degrees of freedom = 1, $p = 0.60$). The Cox proportional hazard ratio for ramelteon compared to placebo was 1.40 (95% confidence interval: 0.40−4.85, $\chi 2$ for likelihood ratio test = 0.29, degrees of freedom = 1, $p = 0.60$). ***Conclusion:*** *There was no significant difference in the incidence of postoperative delirium between ramelteon and placebo after general anesthesia in elderly patients.* (Am J Geriatr Psychiatry 2023; ■■:■■−■■)

Highlights

- **What is the primary question addressed by this study?**

  Does ramelteon prevent postoperative delirium after general anesthesia in elderly patients, including those with dementia?
- **What is the main finding of this study?**

  There was no significant difference in the incidence of postoperative delirium between ramelteon (8 mg orally) and placebo (lactose) after general anesthesia in elderly patients.
- **What is the meaning of the finding?**

  The findings do not support the routine administration of ramelteon to prevent postoperative delirium after general anesthesia in elderly patients.

OBJECTIVE

Delirium is defined as a disturbance in attention and awareness that develops over a short period of time, with changes in baseline attention and awareness, and fluctuates throughout the day, according to the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1] Delirium is a common, serious, and often fatal disorder that impairs autonomy, hinders communication, and increases the risk of complications, leading to longer hospital stays and increased healthcare costs and mortality.[2]

Postoperative delirium is defined as delirium that meets the DSM-5 criteria and occurs in the hospital up to 1 week postprocedure or until discharge.[3] Postoperative delirium affects at least 13%−50% of patients undergoing non-cardiac surgery.[2] Thus, prevention of postoperative delirium is a public health priority. First-line preventive interventions for delirium are nonpharmacological interventions,[4] whereas several drugs, including melatonin receptor agonists, have been proposed as potential prophylactic agents for delirium.

Melatonin is a neurohormone secreted mainly by the pineal gland. It has multiple roles, including circadian rhythm regulation, and has sedative, analgesic, anti-inflammatory, antioxidative, and oncostatic effects.[5] Decreased nocturnal plasma or serum melatonin levels have been reported in healthy elderly individuals,[6] and decreased plasma melatonin levels have been reported in surgical patients.[7,8] Because sleep disturbance is a modifiable risk factor for postoperative delirium, melatonin receptor agonist supplementation may minimize circadian rhythm disruption and reduce the incidence of postoperative delirium. Although melatonin showed conflicting evidence for the prevention of postoperative delirium in previous randomized controlled trials (RCTs), [9,10] its selective receptor agonist, ramelteon, showed protective effects in observational studies of surgical patients,[11,12] and significant protective effects in an RCT of medical patients.[13] Previous studies in surgical patients, with a wide age range, examined various

agonists at different doses, focused on a limited number of procedures and anesthetic techniques, and usually excluded patients with dementia at baseline.[9,14]

Therefore, we tested the hypothesis that perioperative administration of ramelteon reduces the incidence of postoperative delirium in patients aged older than or equal to 65 years, including those with dementia, undergoing elective surgery under general anesthesia.

METHODS

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was first approved by the Institutional Review Board on March 10, 2017, and further approved by the certified review board (3180026) on October 12, 2018 under the Clinical Research Act implemented in Japan in 2018. Written informed consent was obtained from each subject or proxy. The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000028436, Principal Investigator: Makoto Ogura, Date of registration: July 29, 2017) prior to the start of the trial and any patient enrollment undertaken and the Japan Registry of Clinical Trials (jRCTs031180054, Principal Investigator: Makoto Ogura, Date of registration: December 12, 2018). This manuscript adheres to the applicable CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Design

We conducted a stratified, double-blind, randomized, placebo-controlled trial of ramelteon (8 mg orally) or placebo (lactose) for six nights (the preoperative night and five consecutive nights from postoperative Day [POD] 1 to 5) at around 9 P.M. for the prevention of postoperative delirium after general anesthesia at the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology.

Patient Sample

We enrolled patients aged older than or equal to 65 years undergoing major elective surgery (general, urological, vascular, or thoracic surgery) under general anesthesia who had an American Society of Anesthesiologists physical status (ASA-PS)[15] of I, II, or III. The exclusion criteria were: 1) Delirious on registration; 2) currently taking ramelteon; 3) previous adverse reaction to ramelteon; 4) taking medications contraindicated for co-administration with ramelteon; 5) lactose intolerance; 6) non-per os on POD 1; 7) expected discharge on or before POD 6; 8) Mini-Mental State Examination (MMSE)[16] score $\leq$ 10; 9) severe hepatic impairment; and 10) Lewy-body dementia.

Preoperative delirium was ruled out by a consultant psychiatrist, according to the DSM-5 criteria,[1] when attention deficits were observed using the Japanese version of the Montreal Cognitive Assessment.[17] Although we intended to include patients with dementia, to improve the generalizability of the findings, we excluded patients with an MMSE score less than or equal to 10; the lower limit of the MMSE score for screening postoperative delirium using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[18] was set at 11. Patients with Lewy-body dementia were excluded because their cognitive fluctuations could not be distinguished from postoperative delirium. Proxy consent was obtained for patients who could not provide informed consent, as obtained for anesthesia.

Interventions

All patients were admitted to the hospital by the morning of the day before surgery. Patients received pulverized ramelteon (8 mg orally) or placebo (lactose) for six nights (the preoperative night and five consecutive nights from POD 1 to 5) at around 9 P.M. Ramelteon (8 mg orally) is the approved dose for the treatment of insomnia, and the dose investigated in previous studies to prevent delirium as off-label use.[11–13,19–22] In compliance with the postoperative fasting instructions, no drug was administered orally on the night of surgery (POD 0). Bedside nurses monitored the administration of the study drug and recorded the time.

Data Collection

We recorded patient characteristics, preoperative laboratory data, prescribed medications, and adverse events through individual interviews with the patients and reference to medical records. Data on the type of surgery and course of anesthesia were obtained from anesthetic records. Anesthesia was performed at the discretion of the responsible anesthesiologist.

Primary and Secondary Outcomes

The primary outcome was the incidence of postoperative delirium diagnosed by a consultant psychiatrist, according to DSM-5 criteria.[1] Perioperative delirium was screened by trained bedside nurses or clinical research coordinators once in the evening of the preoperative day and twice daily in the morning and evening for 7 days from POD 0 to 6, according to the Japanese version of the CAM-ICU,[18] with a sensitivity of 78% and a specificity of 97%. When the results were positive, a consultant psychiatrist diagnosed delirium within the next 4 days, based on the patient examination, interviews with nurses and family members, and chart review. Secondary outcomes included the onset, duration, and severity of delirium, according to the Japanese version of the Memorial Delirium Assessment Scale (MDAS),[23] adverse events, and adherence. The MDAS score was assessed by the same consultant psychiatrist who diagnosed delirium until POD 6 (on working days).

Sample Size Calculation

The incidence of delirium in this study sample was predicted to be 25%, because 25.8% (n = 8) of patients aged older than or equal to 65 years had positive CAM-ICU results after elective general surgery in our ICU during the second half of 2015. The risk ratio for delirium with melatonin receptor agonists compared to placebo ranged from 0.09 to 1.16 in previous studies at the time of the study design.[9,10,13,24] We referred to a risk ratio of 0.09, provided by the only published RCT on ramelteon.[13] Considering a one-tailed alpha error (type I error) of 0.025, a beta error (type II error) of 0.2, and an incidence of delirium with a placebo of 0.25, the required sample size was calculated to be 86 (n = 43 per group). A dropout rate of 20% was applied, and a total of 108 patients were enrolled.

Randomization

Sequence Generation Patients were randomly assigned to the ramelteon or placebo group using a computer-generated blocked stratified randomization sequence prepared by a clinical statistician. Randomization was stratified into three subsets: age (65−79 years; 80+), the presence of dementia (MMSE 11−23; 24−30), and ASA-PS (I and II; III). Advanced age, dementia, and poor physical status are known risk factors for delirium.[2,25,26] We adopted the most common cutoff MMSE score (23/24) for dementia.[27] The allocation ratio was 1:1.

Allocation Concealment Mechanism and Implementation The investigators approached all potential participants, obtained consent, and confirmed their eligibility. The clinical research coordinators double-checked the eligibility criteria and informed the pharmacist of the participant's stratum. The independent pharmacist dispensed the study drug, using random allocation tables, which were kept in the pharmacy, and were not visible to other study personnel until the end of the study.

Blinding Participants, caregivers, investigators, and outcome evaluators were blinded to the allocation.

Statistical Analysis

The statistical analysis plan was approved by the authors before the analysis began. We analyzed data using the modified intention-to-treat principle. Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean and standard deviation. For the primary outcome, we used a stratified log-rank test to test the null hypothesis that the incidence of postoperative delirium was the same in both groups. We used a one-tailed test and set a p-value of less than 0.025 as statistically significant because the intervention would be clinically acceptable only if the intervention group was significantly superior to the placebo group in efficacy. We had specified as such in the protocol and followed it in the analysis. Confidence intervals (CIs) were set at 95%. We intended to determine

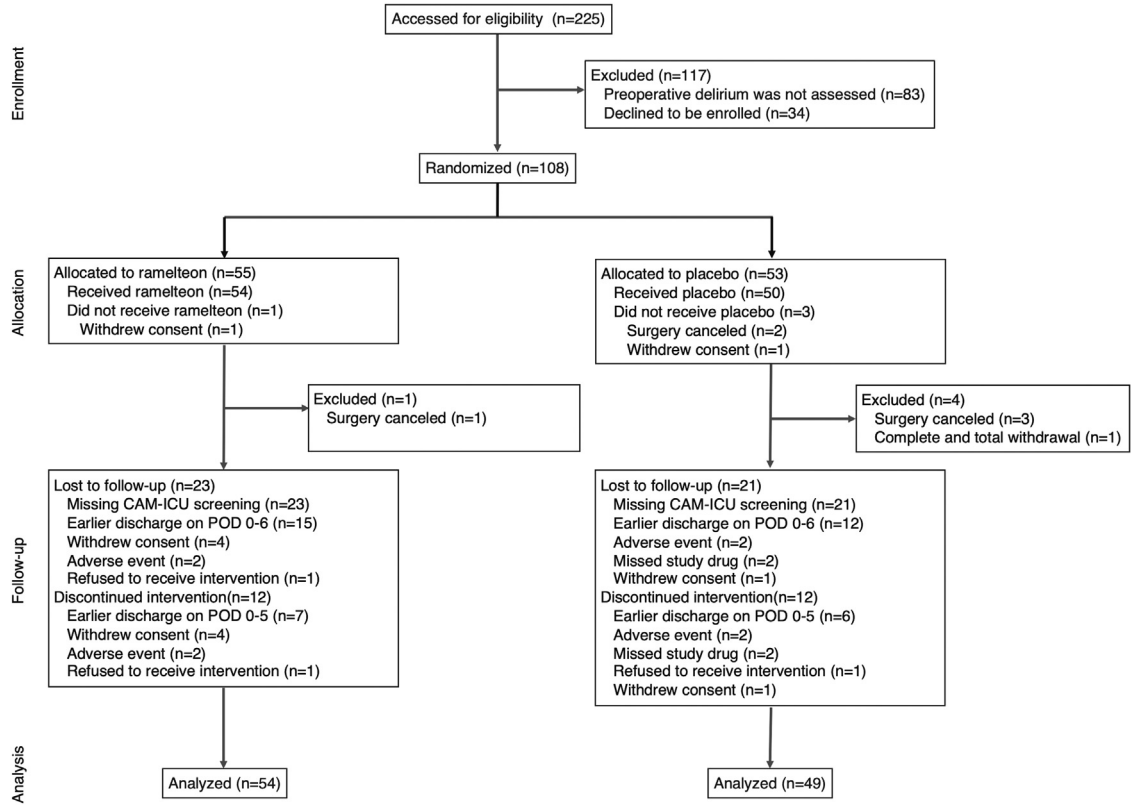
cumulative delirium-free survival, median delirium-free survival, and delirium-free survival on POD 6 using the Kaplan-Meier method, and calculate 95% CIs using Greenwood's formula. Subsequently, we used a stratified Cox proportional hazards model to calculate the hazard ratios (HRs) and 95% CIs for the preventive effect between the groups. For the secondary efficacy outcomes, we compared the onset of delirium, duration of delirium, and worst-evaluated MDAS score based on two-sample *t*-tests. For the secondary safety and adherence outcomes, we compared the proportion of each outcome based on Fisher's exact test. No interim analysis was performed, because of the small sample size. Data were analyzed using JMP Pro 16 (SAS Institute Inc., Cary, NC), R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria), and EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[28]

RESULTS

Participant Flow

Figure 1 shows the flow of enrollment, allocation, follow-up, and analysis. Among 225 patients who met the inclusion and exclusion criteria, 83 patients who did not undergo preoperative delirium assessment were excluded. Of the remaining 142 patients, 108 (76.1%) patients or their proxies provided informed consent and were enrolled in the study. Participants were randomly assigned to receive ramelteon (n = 55) or placebo (n = 53). Twenty-three

FIGURE 1. CONSORT flow diagram of enrollment, allocation, follow-up, and analysis of the study. Some patients were lost to follow-up or discontinued the intervention due to multiple reasons. CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CONSORT, Consolidated Standards of Reporting Trials; POD, postoperative day.



(41.8%) patients in the ramelteon group and 21 (39.6%) patients in the placebo group were lost to follow-up but were included in the survival analysis. Patients lost to follow-up included those who were discharged on POD 6 or earlier, withdrew consent, discontinued the intervention (due to discharge on POD 5 or earlier, withdrawal of consent, adverse events, refusal, or missed doses of the study drug), and missed one or more CAM-ICU assessments. Any deviation was censored upon its occurrence.

Recruitment

We approached potential participants at our clinic, or on the ward, to provide them with the opportunity to participate in the study, from August 1, 2017, to November 20, 2019.

Numbers Analyzed

The primary outcome was not assessed in one participant in the placebo group who withdrew consent and requested the removal of all data, and in four participants (one in the ramelteon group and three in the placebo group) who had their surgery canceled. Subsequently, 103 participants (54 in the ramelteon group and 49 in the placebo group) were analyzed (Fig. 1).

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the participants in each group. Most of the characteristics were reasonably well-balanced between the groups. The presence of dementia and ASA-PS distribution were comparable, demonstrating effective stratification based on MMSE scores and ASA-PS. Several characteristics differed between the groups, such as age (although age was used for stratification), history of delirium, method of anesthesia, and duration of anesthesia. All participants were extubated in the operating room.

TABLE 1. Baseline Characteristics of the Patients

	Ramelteon (n = 54)	Placebo (n = 49)
Sex		
Male, n (%)	28 (51.9)	26 (53.1)
Female, n (%)	26 (48.1)	23 (46.9)
Age (years), mean (SD)	78.1 (6.9)	75.4 (5.6)
Height (cm), mean (SD)	156.8 (9.8)	157.5 (8.3)
Weight (kg), mean (SD)	57.1 (11.6)	59.2 (11.9)
BMI ($kg \cdot m^{-2}$), mean (SD)	23.1 (3.5)	23.8 (4.1)
ASA-PS		
I, n (%)	1 (1.9)	1 (2.0)
II, n (%)	36 (66.7)	33 (67.3)
III, n (%)	17 (31.5)	15 (30.6)
CCI, mean (SD)	2.8 (2.3)	3.3 (2.4)
History		
Delirium, n (%)	4 (7.4)	1 (2.0)
Dementia, n (%)	7 (13.0)	7 (14.3)
MMSE score, mean (SD)	26.4 (3.1)	27.1 (3.6)
Stroke, n (%)	6 (11.1)	12 (24.5)
Parkinson's disease, n (%)	2 (3.7)	1 (2.0)
Hemiplegia, n (%)	1 (1.9)	5 (10.2)
Peripheral artery disease, n (%)	7 (13.0)	14 (28.6)
Habitual alcohol use, n (%)	15 (27.8)	15 (30.6)
Laboratory data		
Hemoglobin (g/dL), mean (SD)	12.5 (1.6)	12.8 (1.5)
Albumin (g/dL), mean (SD)	3.7 (0.5)	3.7 (0.4)
Medications on admission		
Antidepressants, n (%)	0 (0.0)	1 (2.0)
Corticosteroids, n (%)	1 (1.9)	1 (2.0)
Hypnotics and sedatives, n (%)	12 (22.2)	9 (18.4)
Type of surgery		
General, n (%)	23 (42.6)	18 (36.7)
Urological, n (%)	14 (25.9)	11 (22.4)
Vascular, n (%)	5 (9.3)	11 (22.4)
Thoracic, n (%)	12 (22.2)	9 (18.4)
Method of general anesthesia		
Inhalation anesthesia (and blocks), n (%)	38 (70.4)	39 (79.6)
Inhalation anesthesia, n (%)	8 (14.8)	19 (38.8)
Inhalation anesthesia and blocks, n (%)	30 (55.6)	20 (40.8)
TIVA (and blocks), n (%)	16 (29.6)	10 (20.4)
TIVA, n (%)	11 (20.4)	9 (18.4)
TIVA and blocks, n (%)	5 (9.3)	1 (2.0)
Duration of anesthesia (minutes), mean (SD)	223 (64)	263 (107)
Dose of intravenous fentanyl (mcg), mean (SD)	231(115)	239 (111)
Intraoperative blood transfusion, n (%)	8 (14.8)	5 (10.2)

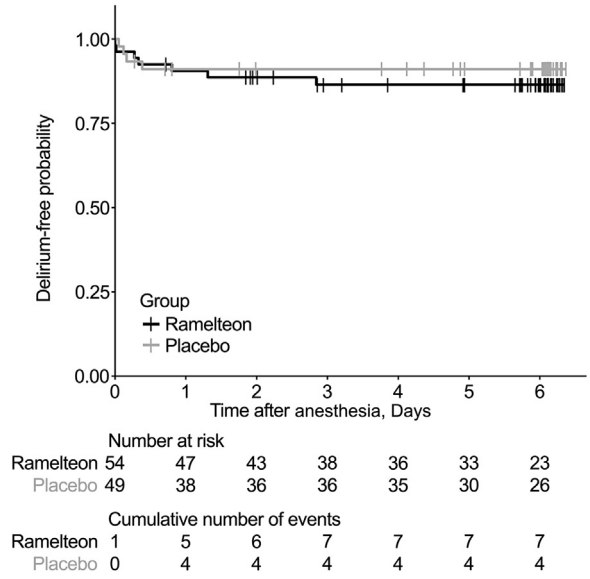
Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CCI, Charlson Comorbidity Index; MMSE, Mini-Mental State Examination; SD, standard deviation; TIVA, total intravenous anesthesia.

Outcomes and Estimation

Figure 2 shows the time to develop postoperative delirium, the number of patients at risk, and the cumulative number of events. The stratified log-rank test showed no significant between-group differences in preventing postoperative delirium (χ^2 = 0.30, degrees of freedom [df] = 1, p = 0.60).

Table 2 presents the seven-day prevalence of postoperative delirium and event analysis. Eleven patients (seven [10.7%] in the ramelteon group and four [8.2%] in the placebo group) had screened positive and all of them were diagnosed with delirium.

FIGURE 2. Delirium-free probabilities in the ramelteon (black) and placebo (grey) groups plotted against time after anesthesia, with the number of participants at risk and cumulative number of postoperative delirium events presented below. The vertical tick marks indicate participants who were censored at that time point. The stratified log-rank test showed no significant difference in preventing postoperative delirium between ramelteon and placebo (χ^2 = 0.30, degrees of freedom = 1, p = 0.60).



Delirium-free survival on POD 6 was 0.87 (95% CI: 0.78−0.96) in the ramelteon group and 0.91 (95% CI: 0.83−1.00) in the placebo group. The Cox proportional HR for ramelteon compared to placebo was 1.40 (95% CI: 0.40−4.85, χ^2 for Likelihood ratio test = 0.29, df = 1, p = 0.60).

Table 3 presents the secondary outcomes. The secondary efficacy outcomes were analyzed in the event cases as a subgroup analysis with a small sample size (n = 7 in the ramelteon group and n = 4 in the placebo group). The onset of delirium and worst (i.e., highest) MDAS score did not differ significantly between the groups. The duration of delirium was not available, because psychiatric follow-up was limited to working days.

Ancillary Analysis

Given the small number of events with an uneven number of patients in each stratum, we performed a post hoc log-rank test of the null hypothesis and found no between-group differences (χ^2 = 0.40, df = 1, p = 0.53), similar to the findings obtained using a predetermined stratified log-rank test. A post hoc Cox proportional hazards regression model (df = 8) was performed to estimate the HR of postoperative delirium, according to the type of intervention, risk stratification, history of delirium, and method of anesthesia (Table 4). The Cox proportional HR was significantly higher in the presence of dementia, a history of delirium, and older age.

Adverse Events

Adverse events are summarized as secondary safety outcomes in Table 3. The denominator was all patients who received at least one dose of the study drug. No intervention-related deaths occurred during the observation period. A total of 701 adverse events were reported by 83 (80.6%) patients. Most cases involved postoperative sequelae and transient events. Five patients experienced seven severe adverse events, none of which were causally related to study participation. Secondary safety outcomes did not differ significantly between the groups.

TABLE 2. Seven-Day Prevalence of Postoperative Delirium and Event Analysis

	Ramelteon (n = 54)	Placebo (n = 49)	p-value
Seven-day prevalence of postoperative delirium, *n* (% [95% CI]) [a]	7 (13.0 [5.0−25.0])	4 (8.2 [2.3−20.0])	0.53
Risk difference of seven-day prevalence of postoperative delirium for ramelteon compared to placebo, % [95% CI]	4.8 [−7 to 17.0]	–	
Delirium-free survival on POD 6 [95% CI] [b]	0.87 [0.78−0.96]	0.91 [0.83−1.00]	
Cox proportional HR for ramelteon compared to placebo [95% CI] [c]	1.40 [0.40−4.85]	–	0.60

[a] Seven-day prevalence of postoperative delirium was compared based on Fisher's Exact Test.
[b] Delirium-free survival on POD 6 was calculated using the Kaplan-Meier method and Greenwood's formula.
[c] Cox proportional HR for ramelteon compared to placebo was calculated using a stratified Cox proportional hazards model and tested by likelihood ratio test (χ^2 for likelihood ratio test = 0.29, degrees of freedom = 1).
Abbreviations: CI, confidence interval; HR, hazard ratio; POD, postoperative day.

TABLE 3. Secondary Outcomes

	Ramelteon	Placebo	p-value
Secondary efficacy outcomes	**(*n* = 7)**	**(*n* = 4)**	
Onset of delirium (days), mean (SD)	0.8 (1.0)	0.2 (0.1)	0.53[a]
Worst-evaluated MDAS score, mean (SD)	10.9 (4.7)	11.8 (4.8)	0.71[a]
Secondary safety outcomes[b]	**(*n* = 54)**	**(*n* = 49)**	
Adverse events	43 (79.6) 390	40 (81.6) 311	0.52[c]
Non-serious adverse events	43 (79.6) 387	39 (79.6) 307	0.48[c]
Serious adverse events	2 (3.7) 3	3 (6.1) 4	0.58[c]
Seizure	0 (0.0) 0	1 (2.0) 1	0.48[d]
Respiratory arrest	0 (0.0) 0	1 (2.0) 1	0.48[d]
Cerebral infarction	0 (0.0) 0	1 (2.0) 1	0.48[d]
Pulmonary leakage requiring reoperation	0 (0.0) 0	1 (2.0) 1	0.48[d]
Thromboembolism	1 (1.9) 2	0 (0.0) 0	0.58[c]
Ileus	1 (1.9) 1	0 (0.0) 0	1.00[d]
Secondary adherence outcomes[e]	**(*n* = 54)**	**(*n* = 49)**	
Adherence	42 (77.8)	37 (75.5)	0.82[e]
Non-adherence	12 (22.2)	12 (24.5)	0.82[e]
Discharge on POD 5 or earlier	7 (13.0)	6 (12.2)	1.00[e]
on POD 0 or 1	0 (0.0)	0 (0.0)	NA
on POD 2	1 (1.9)	1 (2.0)	1.00[e]
on POD 3	1 (1.9)	0 (0.0)	1.00[e]
on POD 4	1 (1.9)	1 (2.0)	1.00[e]
on POD 5	4 (7.4)	4 (8.2)	1.00[e]
Withdrawal of consent	4 (7.4)	1 (2.0)	0.37[e]
Adverse events leading to discontinuation of the intervention	2 (3.7)	2 (4.1)	1.00[e]
Refusal of intervention	1 (1.9)	1 (2.0)	1.00[e]
Missed doses of the study drug	0 (0.0)	2 (4.1)	0.22[e]

[a] Secondary efficacy outcomes were analyzed in the event cases using Mann-Whitney test.
[b] Secondary safety outcomes are presented as number of patients who experienced each adverse event (% in all the patients who received at least one dose of the study drug) count of each adverse event.
[c] Secondary safety outcomes of occurrence were analyzed, using Fisher's exact test.
[d] Secondary safety outcomes of count were analyzed, using Mann-Whitney test.
[e] Secondary adherence outcomes are presented as number of patients (% in the same sample as that of the primary outcome) and were analyzed, using Fisher's exact test.
Abbreviations: CI: confidence interval; df: degrees of freedom; Inf: infinity; MDAS: Memorial Delirium Assessment Scale (Japanese version); NA: not available; POD: postoperative day; SD: standard deviation.

TABLE 4. Cox Proportional Hazards Regression Analysis

	HR [95% CI]	p-value [a]
Intervention (ramelteon versus placebo)	1.41 [0.27−7.23]	0.68
Age (80+ versus 65−79 y)	4.50 [1.06−19.17]	0.04
MMSE (11−23 versus 24−30)	8.30 [2.34−29.44]	< 0.01
ASA-PS (III versus I/II)	1.72 [0.44−6.79]	0.44
History of delirium (present versus absent)	7.83 [1.20−51.26]	0.03
Method of anesthesia (compared to TIVA+block)		
Inhalation	0.84 [0.06−11.92]	0.90
Inhalation+block	0.54 [0.05−5.93]	0.61
TIVA	0.80 [0.06−10.30]	0.86

A post hoc Cox proportional hazards regression model was performed to estimate the HR of postoperative delirium, according to the type of intervention, risk stratification, a history of delirium, and method of anesthesia (df = 8).
[a] Likelihood ratio test (df = 1) was performed.
Abbreviations: ASA-PS: American Society of Anesthesiologists physical status; CI: confidence interval; df: degrees of freedom; HR: hazard ratio; MMSE: Mini-Mental State Examination; TIVA: total intravenous anesthesia.

Adherence

Secondary adherence outcomes are shown in Table 3. The denominator was the same sample as that of the primary outcome. The overall adherence rate was 76.7%. Nonadherence included discharge on POD 5 or earlier, withdrawal of consent, adverse events, refusal of intervention, and missed doses of the study drug. Secondary adherence outcomes did not differ significantly between the groups.

DISCUSSION

In this study, ramelteon did not significantly reduce the incidence, delay the onset, or decrease the severity of postoperative delirium in elderly patients after general anesthesia. Post hoc analysis indicated that

dementia, a history of delirium, and older age were risk factors for postoperative delirium. No severe adverse events were attributed to the study drug.

Recent meta-analyses showed that melatonin receptor agonists significantly reduced the incidence of delirium, comparable to the effects of nonpharmacological interventions (risk ratio, 0.57 [95% CI: 0.46−0.71]; I^2 = 39%).[29] A recent meta-analysis showed that melatonin receptor agonists significantly reduced the incidence of delirium (risk ratio, 0.61 [95% CI: 0.42−0.89]; I^2 = 66%), and their subgroup analysis by drug showed particular benefit of ramelteon, and their subgroup analysis by care setting showed particular benefit in surgical patients.[30] A more recent Asian-specific meta-analysis exclusive to ramelteon showed that ramelteon reduced the incidence of postoperative delirium (risk ratio, 0.27 [95% CI: 0.08−0.84]; I^2 = 0%).[31] The most recent meta-analysis exclusive to ramelteon showed that ramelteon reduced delirium in hospitalized patients (odds ratio, 0.50 [95% CI: 0.29−0.86]; I^2 = 17.48%) but their subgroup analysis of a patient group (surgical versus medical) found no significant difference between ramelteon and placebo.[32] We examined ramelteon in surgical patients and found no significant reduction in postoperative delirium, consistent with the findings of each four previous RCTs.[20−,22,31] Setting clinically meaningful risk ratios and exploring sufficient dosing regimens would be essential. Subgroup analysis of the most recent meta-analysis showed lower odds of delirium occurrence in the multiple (more than three) dosage group (k = 5; odds ratio, 0.34 [95% CI: 0.14−0.82]; I^2 = 44.24%). A small RCT suggested that low-dose (4 mg) ramelteon administered for 2 weeks or longer may be effective in preventing postoperative delirium.[31] Early intervention may result in preventive effects because patients with chronic insomnia tended to require repeated interventions for subjective improvement in sleep duration.[33] Intervention timing also needs to be carefully considered, because dosing at 7 P.M. was found to be more effective than dosing at 9 P.M., in preventing delirium in an observational study.[34]

Studies of genetic predisposition to delirium, although scarce, may provide insight into its pathophysiology.[35] Genetic polymorphisms in the *MTNR1B* gene encoding the melatonin receptor, MT2, were associated with postoperative delirium.[36]

Delayed onset or reduced severity of postoperative delirium has not been reported previously, consistent with our findings for the secondary efficacy outcomes of this study, although we analyzed them exploratively in a subset of patients who developed delirium.

Post hoc analysis confirmed the known risk factors for postoperative delirium: Dementia, a history of delirium, and older age. These are not modifiable but were strongly associated with the development of postoperative delirium in a systematic review of older adults undergoing elective surgery;[37] thus, they are amenable factors for future interventional studies.

Dementia and delirium are associated with several critical symptoms. Sleep and circadian disturbances are more pronounced in patients with Alzheimer's disease, a leading cause of dementia,[38] and nocturnal melatonin levels in the blood are low in these patients.[39] The results of the post hoc analysis were consistent with the findings showing no difference in the incidence of postoperative delirium, according to the method of general anesthesia.[40]

This study has several limitations. First, it was a single-center study with a small sample size. Second, the incidence of postoperative delirium in the placebo group (8.2%) was lower than expected (25%). The following reasons may explain the lower-than-expected incidence of postoperative delirium in the placebo group: 1) The incidence of delirium decreases over time, owing to the detection of delirium and various nonpharmacological interventions on the ward; 2) Twice-daily screening may have missed time-varying events; and 3) Random censors may have underestimated the delirium events. A lower-than-expected incidence of postoperative delirium may have also undermined the statistical power. Third, informative censoring may have occurred, with deviations from intended interventions and missing outcome assessments in 23.3% and 43.7% of cases, respectively. Appropriate follow-up periods are needed. Finally, despite stratification, patients in the ramelteon group were older. However, the Cox proportional HR for ramelteon compared to placebo, adjusted for age and other factors, was similar to a predetermined stratified Cox proportional HR.

This study also has several strengths. It was a stratified, double-blind, randomized, placebo-controlled trial. Allocation concealment was controlled by a pharmacist. The number of patients met the predetermined sample size. For clinical relevance, we

included patients with cognitive impairment whose MMSE scores were between 11 and 23. Consent to participate was obtained from 76.1% of the patients approached, maintaining external validity. The observation period for diagnosis was adequate, the incidence of delirium was screened using a standardized and validated instrument, and positive screening results were referred to a psychiatrist for diagnosis. No protocol violations occurred.

In conclusion, there was no significant difference in the incidence of postoperative delirium between ramelteon (8 mg orally for six nights [the preoperative night and five consecutive nights from POD 1 to 5] at around 9 P.M.) and placebo (lactose) after general anesthesia in elderly patients. Future pharmacological studies to prevent postoperative delirium may focus on high-risk procedures or target vulnerable samples, such as those with cognitive impairment or a history of delirium, along with optimization of duration, timing, and dosing.

AUTHOR CONTRIBUTIONS

MK: This author helped with the conception and design of the study, acquisition of data, drafting the manuscript, and revising the manuscript critically for important intellectual content. TM: This author helped with the conception and design of the study, drafting the manuscript, and revising the manuscript critically for important intellectual content. MT: This author helped with the conception and design of the study, statistical analysis, and revising the manuscript critically for important intellectual content. MO: This author helped with the conception and design of the study, acquisition of data, drafting the manuscript, and revising the manuscript critically for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PREVIOUS PRESENTATION

The data has not been previously presented orally or by poster at scientific meetings.

DATA SHARING STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

DISCLOSURES

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論文目録

Ⅰ 主論文（本人を筆頭とする原著論文）

The Efficacy of Ramelteon to Prevent Postoperative Delirium After General Anesthesia in the Elderly: A Double-Blind, Randomized, Placebo-Controlled Trial

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II 副論文（主論文の内容と関係のある論文，本人筆頭）

なし

III 参考論文（主論文の内容以外の論文）

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