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Effect of Administration of Ramelteon, a Melatonin Receptor Agonist, on the Duration of Stay in the ICU: A Single-Center Randomized Placebo-Controlled Trial*

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Objectives: Occurrence of delirium in the ICU is associated with a longer stay in the ICU. To examine whether the use of ramelteon, a melatonin agonist, can prevent delirium and shorten the duration of ICU stay of critically ill patients.

Design: A single-center, triple-blinded, randomized placebo-controlled trial.

Setting: ICU of an academic hospital.

Patients: Eligible patients were ICU patients who could take medicines orally or through a nasogastric tube during the first 48 hours of admission.

Interventions: The intervention group received ramelteon (8 mg/d), and the control group received placebo (1 g/d of lactose powder) at 20:00 hours every day until discharge from the ICU.

Measurements and Main Results: A total of 88 subjects were randomized to the ramelteon group (45 subjects) or the placebo group (43 subjects). As the primary endpoint, there was a trend toward decrease in the duration of ICU stay (4.56 d) in the ramelteon group compared with the placebo group (5.86 d) ($p = 0.082$ and $p = 0.028$ before and after adjustments). As the secondary endpoints, statistically significant decreases in the occurrence rate (24.4% vs 46.5%; $p = 0.044$) and duration (0.78 vs 1.40 d; $p = 0.048$) of delirium were observed in the ramelteon group. The nonintubated patients of the ramelteon group showed statistically significantly fewer awakenings per night and a higher proportion of nights without awakenings.

Conclusions: Ramelteon tended to decrease the duration of ICU stay as well as decreased the occurrence rate and duration of delirium statistically significantly. (*Crit Care Med* 2018; 46:1099–1105)

Key Words: critical care; delirium; duration of intensive care unit stay; melatonin agonist; ramelteon; randomized controlled trial

Melatonin, a substance synthesized in the pineal gland, exhibits pleiotropic physiologic actions (1), and several recent studies have demonstrated a variety of effects of melatonin in vivo, including antioxidant and anti-inflammatory effects, as well as an effect on regulation of the circadian rhythm. Although the melatonin secretion rhythm has been shown to be severely depressed in patients admitted to the ICU because of various environmental factors as well as factors related to the patients' life-threatening conditions themselves and the drugs used (2–4), few studies have been conducted yet to determine whether exogenous melatonin administration in the ICU can improve the outcomes in critically ill patients (5, 6).

One of the most well-known functions of melatonin is to prevent delirium in critically ill patients (7, 8). Delirium is an undesirable, but frequently encountered manifestation in ICU patients (9), and is known to be associated with worse outcomes (9, 10), including longer ICU stay (11), higher mortality rate (12), longer time on the ventilator (13), and higher ICU and hospital costs (14). Considering that recent randomized controlled clinical trials have indicated that melatonin can prevent delirium (15–17),

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we considered that prophylactic administration of melatonin or melatonin agonists may shorten the duration of ICU stay and improve the outcomes in critically ill patients.

Therefore, we performed this single-center, triple-blinded, randomized placebo-controlled trial to examine whether prophylactic administration of ramelteon, a selective melatonin receptor agonist, is effective for shortening the duration of ICU stay in critically ill patients. As secondary endpoints, we measured the mortality rate and the occurrence rate and duration of delirium in ICU patients. To the best of our knowledge, this is the first randomized controlled clinical trial conducted exclusively in ICU patients to determine whether prophylactic administration of ramelteon can shorten the duration of ICU stay and decrease the occurrence rate of delirium in ICU patients.

MATERIALS AND METHODS

Setting and Participants

We conducted this single-center, triple-blinded (the testers, subjects, and statisticians were blinded), randomized placebo-controlled trial with the approval of the Research Ethics Board of Nagoya University Hospital (2015-0005). Nagoya University Hospital is an academic and educational hospital with 1,035 beds, including 10 emergency and medical ICU (EMICU) beds and 16 surgical ICU beds. This trial was performed in the EMICU, and the subjects were patients admitted via the emergency department (emergency ICU) or medical patients admitted via the general ward (medical ICU) who needed critical care treatment. The trial is registered in the University Hospital Medical Information Network Clinical Trials Registry as the Melatonin Evaluation of Lowered Inflammation in ICU Trial (UMIN000016541). We did not have any money from or speak on behalf of the manufacturer of the product used in our study.

The eligible subjects were adults (age ≥ 20 yr old) admitted to our EMICU between May 2015 and April 2017, who could receive their medications orally or through a nasogastric tube during the first 48 hours of admission to the ICU. Patients who were already receiving ramelteon or fluvoxamine maleate prior to their admission to the ICU were excluded from the study because of potential drug interactions. Patients with known allergy to ramelteon were also excluded, as also patients who refused to provide consent for participation in the study.

Randomization and Intervention

This study was performed as a triple-blinded, placebo-controlled randomized trial. Eligible participants were randomly assigned at a 1:1 ratio to the ramelteon group (ramelteon: 8 mg/d) or the placebo group (placebo; 1 g/d of lactose powder) at the end of the baseline assessment. The randomization was performed using stratified block randomization with a block size of four. The randomization list was made by an outsider before the start of enrollment, based on stratification according to the age (≥ 60/< 60 yr) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (≥ 30/< 30 points) and according to whether the patients were intubated or not. Both ramelteon and placebo were pulverized in advance to make them indistinguishable from each other.

Depending on the group assignment, the patients received ramelteon or placebo in a blinded manner at 20:00 hours each day, until they were discharged from our ICU. All of the nurses in the ICU were also blinded to any information about the patients relevant to the study and provided equal care to all patients, including daily preventive care, avoidance of unnecessary immobilization, and regular verbal communication. Visits by the patients' families were limited to twice a day: between 11 AM and 12 noon and between 3 PM and 4 PM; after 10 PM, the lighting and noise in all the ICU rooms were reduced to the minimum. At the baseline, we recorded the demographic data, medical history, and medication history of the patients. Evaluation of the patients by the Richmond Agitation-Sedation Scale (RASS) was performed every 4 hours by trained ICU nurses (the assessment was skipped if the patients were sleeping).

Outcomes and Data collection

The primary endpoint of the study was the duration of ICU stay. The indications for admission and suitability for discharge of the patients were determined at a multidisciplinary conference of ICU doctors and the patients' attending physicians, held twice every day. In both patient groups, the suitability for discharge from the ICU was determined based on the following: no or minimal need for sedative drugs, the oxygen saturation as measured by pulse oxymetry greater than 90% at an F_{IO_2} of less than 0.5 in the absence of mechanical ventilatory support, no or minimal need for inotropes or vasopressor agents, and urine output more than 0.5 mL/kg/hr. Patients who were intubated and not yet tracheotomized and patients who needed continuous hemodiafiltration were not discharged. Patients were considered suitable for discharge when they could be disconnected from all the ICU monitors.

The secondary endpoints of the study were the occurrence rate and duration of delirium in the patients during their ICU stay and the clinical status at discharge. Delirium was assessed every 4 hours using the Confusion Assessment Method for the ICU (18), by trained ICU nurses (the assessment was skipped if the patients were sleeping) and by the ICU doctors as needed.

In regard to analysis of the sleep variables, the number of awakenings per night, the proportion of nights without awakenings relative to the total number of nights in the ICU, and the mean hours of sleep of the nonintubated patients were determined by retrospectively reviewing the electronic charts in both groups. We reviewed the nursing observations and records and the rater observations to collate the data.

Treatment for Delirium

Delirium occurring in the ICU was primarily managed by nonpharmacologic approaches, including early mobilization and creation of an environment conducive to comfortable sleep, together with the removal of any potential cause of delirium, such as pain, discomfort, dyspnea, and anxiety. In cases judged as requiring pharmacologic treatment for the control of delirium, risperidone (1 mg, oral) or continuous infusion of dexmedetomidine at progressively increasing doses as necessary (maximum dose: 0.7 μg/kg/hr) was used initially, according to the clinical

preference of the attending physician. In the event of emergency, in patients who were judged by the treating physician as needing more immediate control of delirium than that afforded by oral treatment, we used haloperidol (5 mg, IV). Additional administration of risperidone, haloperidol, or other medications was considered depending on the severity of the delirium.

Sample Size

For the primary efficacy measure (duration of ICU stay), we assumed a mean of the log-transformed value of the duration of ICU stay of 4.17 (65.28 hr), with a SD of 1.09 in the placebo group, based on the past sample data of patients admitted to our ICU (December 1–31, 2014). It was estimated that a sample size of 91 per group would be needed for detecting a reduction of the duration of ICU stay by 1 day (24 hr) in the ramelteon group, which we assumed as a clinically significant effect size, with at least 80% statistical power at a two-sided significance level of 5% by Student two-sample *t* test. During the sampling period (December 1–31, 2014), 50 patients were admitted to our ICU, and the number of eligible patients was 26. We assumed that about 1 year would be needed for collecting 182 patients and set the study period at May 2015 to May 2016. Because much fewer patients than expected actually met the eligible criteria during the set study period, we did not achieve the target sample size by May 2016 and extended the registration period for the study to April 2017. The target sample size was, however, not met even by the end of the additional registration period.

Statistical Analysis

The statistical analysis was performed on an intention-to-treat basis, and the data of subjects who received ramelteon or placebo at least once during their ICU stay were included. We performed Student *t* test to evaluate the significance of differences in the log-transformed values of the duration of ICU stay. To incorporate possible imbalances in the patients' baseline characteristics between the ramelteon and placebo groups, a multivariate linear regression analysis was conducted to identify factors that were independently associated with the log-transformed value of the duration of ICU stay. The baseline characteristics that were adjusted for in the analysis were those that were considered as potentially influencing the duration of ICU stay: age, APACHE II score, intubation status (intubated/not intubated), presence/absence of dementia before admission, and the mean RASS score during the ICU stay. For analysis of the secondary endpoints, Fisher exact test was used for the categorical variables (occurrence of delirium and mortality at discharge) and Student *t* test for the continuous variables (duration of delirium and sleep variables). All reported *p* values were two sided, and *p* value of less than 0.05 was regarded as denoting a statistically significant difference. All analyses were conducted using the SAS software, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 98 subjects were screened to determine if they met the eligibility criteria for this study; six of these patients who refused to provide consent for participation in this study were excluded. There were no patients who were already receiving ramelteon or fluvoxamine maleate before their admission to the ICU or were known to have allergy to ramelteon. The 92 eligible patients were then randomized to the ramelteon or the placebo group. Of these, four patients (two from the ramelteon and two from the placebo group) were discharged from the ICU even before the start of the intervention (three patients [two from the ramelteon group and one from the placebo group] were transferred to the general ward because of stabilization of the general condition, and one patient [placebo group] died). The remaining 88 patients were included in the intent-to-treat analysis (**Fig. 1**).

The baseline characteristics of the enrolled patients in the ramelteon group and placebo group are summarized in **Table 1**. The distribution of the patient characteristics was generally similar between the two groups, especially in respect of the three allocation factors for the randomization (age, APACHE II score, and intubation status), indicating that the randomization was carried out appropriately. However, we observed slightly greater proportions of subjects with the following characteristics in the ramelteon group: male subjects and subjects with dementia, sepsis, history of habitual heavy use of alcohol, and history of medication.

In the primary endpoint analysis, the median (range) duration of ICU stay was 4.56 days (2.10–7.07 d) days in the ramelteon group and 5.86 days (2.97–14.16 d) in the placebo group, with no statistically significant difference between the two groups, as assessed by the Student *t* test comparing the log-transformed values of the duration of ICU stay ($p = 0.082$) (**Fig. 2**). In the multivariate analysis conducted with adjustments for the five prespecified baseline characteristics, prophylactic administration of ramelteon was identified as being significantly and independently associated with a decrease in the duration of ICU stay ($p = 0.028$) (**Table 2**). In addition, we also performed sensitivity analyses using all the variables shown in Table 1 for adjustment, which also revealed a statistically significant association between prophylactic ramelteon administration and decrease in the duration of ICU stay (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D470).

The results for the secondary endpoints are shown in **Table 3**. The occurrence rate of delirium was 24.4% (11/45) in the ramelteon group and 46.5% (20/43) in the placebo group, the difference between the two groups being statistically significant ($p = 0.044$; odds ratio, 2.69 [1.09–6.65]). Furthermore, the duration of delirium was also statistically significantly shorter in the ramelteon group as compared to that in the placebo group (0.78 vs 1.40 d; $p = 0.048$). The mortality rate at discharge from the ICU was 6.7% (3/45) in the ramelteon group and 7.5% (3/43) in the placebo group, with no significant difference between the two groups ($p > 0.999$).

We also compared the following sleep variables in the nonintubated patients between the ramelteon and placebo groups: the number of awakenings per night, the proportion of nights without awakenings relative to the total number of nights in the ICU, and the mean hours of sleep. In the univariate

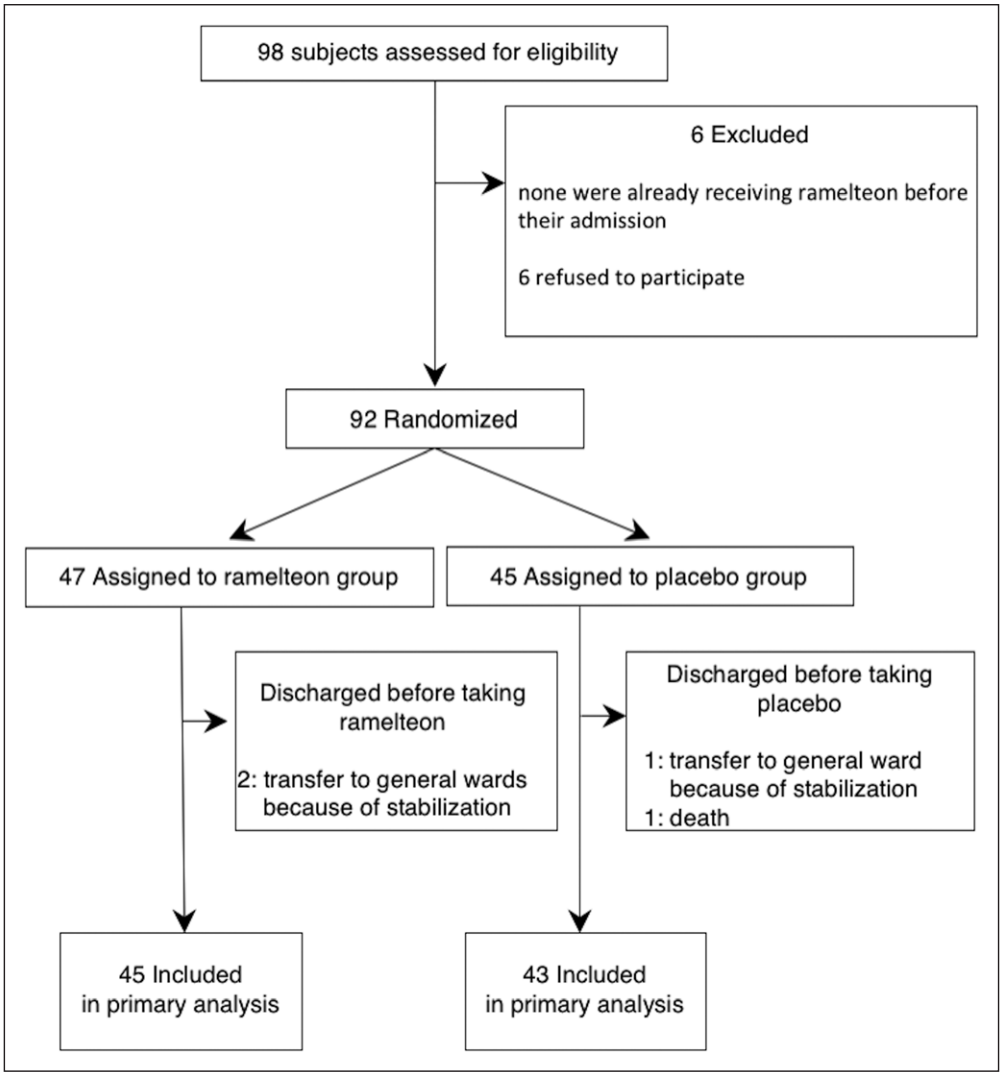

Figure 1. Flow of the participants in this study.

analyses, the ramelteon group showed statistically significantly fewer awakenings per night (0.80 times per night vs 1.31 times per night; $p = 0.045$) and a statistically significantly higher proportion of nights without awakenings (51% vs 30%; $p = 0.048$) as compared to the placebo group, while there was no significant difference in the mean hours of sleep between the two groups (7.29 vs 6.78 hr; $p = 0.252$). Even after adjustments for the baseline characteristics in the multivariate analysis, similar results were obtained ($p = 0.036$, $p = 0.019$, and $p = 0.123$, respectively) (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D471).

DISCUSSION

In this study, prophylactic administration of ramelteon, a selective melatonin receptor agonist, was associated with both a reduced occurrence rate and shortened duration of delirium in the ICU. Although no statistically significant difference in the duration of ICU stay was observed between the two groups, multivariate analysis performed with adjustments for the baseline patient characteristics revealed that prophylactic administration of ramelteon was significantly and independently associated with a shortened duration of ICU stay. To the best of our knowledge, this is the first report to demonstrate a beneficial effect of ramelteon on the duration of ICU stay in critically ill patients.

Ramelteon was demonstrated in an in vitro study as having six-fold and three-fold higher affinities for melatonin receptor 1 and melatonin receptor 2, respectively, compared with melatonin (19). Hatta et al (16) reported a statistically significant decrease in the occurrence rate of delirium associated with the use of ramelteon in elderly patients. However, there are no reported studies on the effect of ramelteon conducted exclusively in ICU patients, although two large randomized clinical trials are ongoing (20, 21). Considering that the occurrence rate of delirium in the ICU is much higher than that in general wards (22), it may not be unreasonable to carefully extrapolate the results of the two aforementioned previous studies to ICU patients. The current study is the first to suggest that prophylactic administration of ramelteon also prevents the occurrence of delirium in ICU patients, as in general ward patients.

Interestingly, our results showed that the ramelteon group had statistically significantly fewer awakenings per night and a higher proportion of nights without awakenings as compared to the placebo group, although unexpectedly, there was no statistically significant difference in the mean hours of sleep between the two groups. This result may provide a clue to explain the biological mechanism underlying the prevention of delirium by ramelteon observed in this study. That is, ramelteon probably reduces delirium by increasing the duration of restful sleep, although further study will be needed.

This study was a small single-center study, which may limit the generalizability of the results. We calculated the power a priori with the goal of obtaining preliminary data for a larger randomized controlled study. We think that a large multicenter randomized clinical trial is needed in the future. Although we had estimated in advance that a total of 200 subjects would be

TABLE 1. Participant Characteristics

Characteristics	Ramelteon Group ($n = 45$)	Control Group ($n = 43$)
Age, median (interquartile range), yr	68 (57–75)	68 (52–78)
Male, *n* (%)	33 (73.3)	24 (55.8)
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	23.98 (7.30)	23.95 (8.61)
Sequential Organ Failure Assessment score, mean (SD)	8.04 (4.16)	8.49 (3.89)
Mechanical ventilation, *n* (%)	18 (40.0)	20 (46.5)
Dementia, *n* (%)	6 (13.3)	1 (2.3)
Habitual heavy use of alcohol, *n* (%)	3 (6.7)	1 (2.3)
Habitual use of a sleeping drug, *n* (%)	7 (15.6)	5 (11.6)
Habitual use of a psychiatric medication, *n* (%)	2 (4.4)	1 (2.3)
Mean of Richmond Agitation-Sedation Scale during the ICU stay, mean (SD)	−1.15 (1.19)	−1.12 (1.15)
Admission diagnosis, *n* (%)		
Heart failure/myocardial infarction	9 (20.0)	11 (25.6)
Respiratory failure	8 (17.8)	10 (23.3)
Sepsis	12 (26.7)	9 (20.9)
Others	16 (35.6)	13 (30.2)

Acute Physiology and Chronic Health Evaluation II score and Sequential Organ Failure Assessment score were calculated with the worst values within 24 hr after patient's admission.

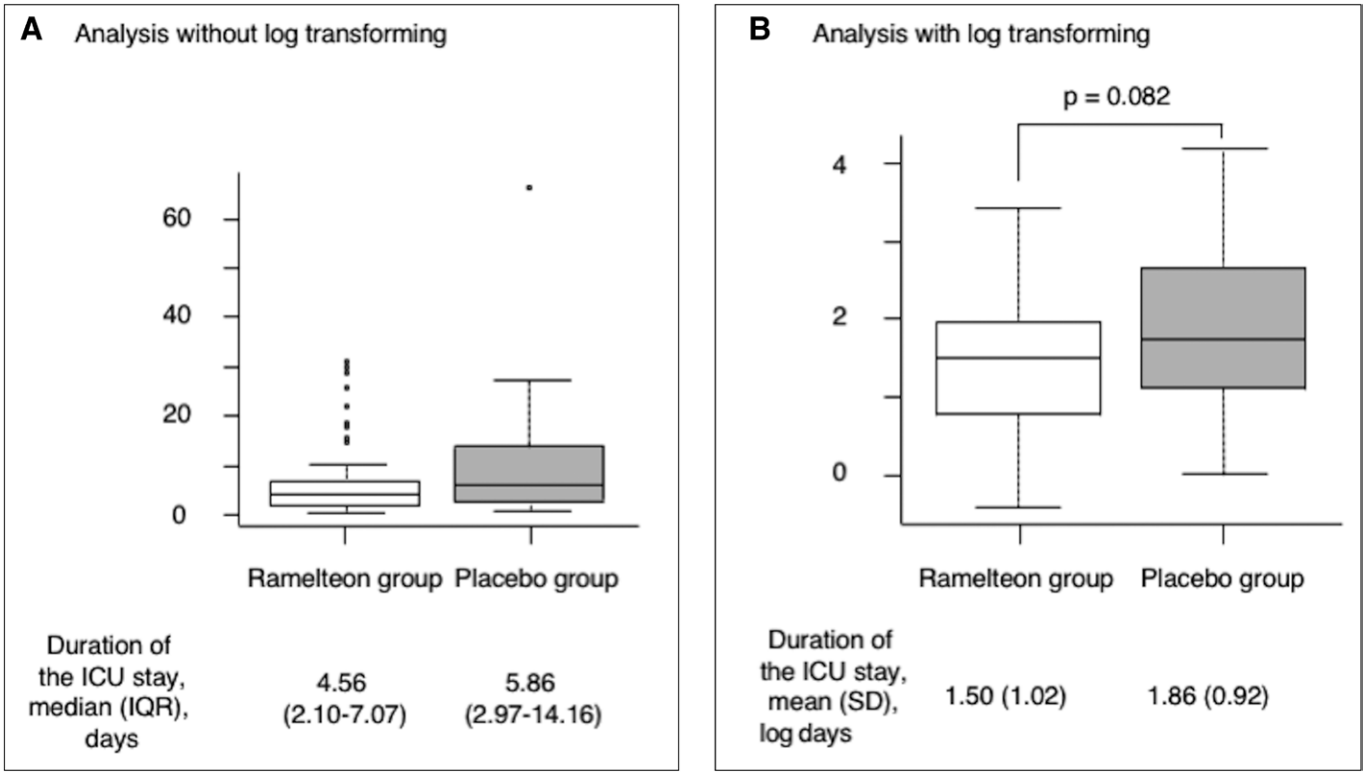

Figure 2. Duration of ICU stay in the ramelteon and control groups. **A**, Analysis without log transformation of the duration of the ICU stay. **B**, Analysis with log transformation of the duration of ICU stay. We used Student *t* test to compare the duration of ICU stay between the two groups. IQR = interquartile range.

TABLE 2. Mulitivariate Analysis to Compare a Primary Endpoint

Variables	β Coefficient (SE)	*t* Statistic	*p*
Ramelteon or placebo	−0.379 (0.169)	−2.24	0.028
Age ≥ 60 (vs < 60)	−0.110 (0.189)	−0.59	0.560
Acute Physiology and Chronic Health Evaluation II score < 30 (vs ≥ 30)	−0.184 (0.204)	−0.90	0.371
Mechanical ventilation	0.720 (0.246)	2.93	0.004
Dementia	0.442 (0.324)	1.27	0.176
Mean of Richmond Agitation-Sedation Scale during the ICU stay	−0.248 (0.103)	−2.42	0.018

The multivariate analysis was used for variables. Versus (vs) in the table means the reference value.

TABLE 3. Analysis of Secondary Endpoints

Variables	Ramelteon Group (*n* = 45)	Control Group (*n* = 43)	OR (95% CI)	*p*
The occurrence of delirium, *n* (%)	11 (24.4)	20 (46.5)	2.69 (1.09–6.65)	0.044
The length of delirium, mean (SD), d	0.78 (1.81)	1.40 (2.30)		0.048
Mortality at their discharge, *n* (%)	3 (6.7)	3 (7.5)		> 0.999

OR = odds ratio.
The Fisher exact test was used for category variables and the Student *t* test for continuous variables.

required, only 88 subjects could be enrolled within the set registration period because fewer patients than we expected actually met the eligibility criteria during the study period. Therefore, the study may have been underpowered. During the study period, visits by the patients' families were limited to twice a day, even though an open-door visiting policy is promoted in ICUs nowadays for reducing the occurrence of delirium. In this study, we did not assess the type of delirium, hyperactive, hypoactive, or mixed type delirium. Finally, this dose of haloperidol (5 mg) may be much higher than the usual dose used around the world as rescue treatment for delirium patients.

It is interesting that the estimated effect size of ramelteon was 1.30 days in the unadjusted comparison, which was greater than the effect size of 1.00 day that we had calculated in advance, during the sample size calculation, as a clinically significant effect size. Although there was no statistical significance in the unadjusted comparison analysis, this large estimate of the effect size could be one of the main reasons for obtaining *p* value equals to 0.082, which is close to the value of α equals to 0.05, and also a statistically significant result ($p = 0.028$) in the adjusted analysis, in spite of the smaller than expected sample size. It is noteworthy that in our study also, we observed no adverse events associated with ramelteon administration, which is consistent with the results of previous studies (23, 24). Prophylactic administration of ramelteon may have a potential advantage in terms of the safety and efficacy among ICU patients, and it would be great interest to investigate the cost-effectiveness of prophylactic administration of ramelteon in the ICU.

CONCLUSIONS

Ramelteon administration was associated with a tendency toward a decreased duration of ICU stay, as well as significant decreases in the occurrence rate and duration of delirium in patients admitted to the ICU.

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