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Ramelteon for Prevention of Postoperative Delirium: A Randomized Controlled Trial in Patients Undergoing Elective Pulmonary Thromboendarterectomy*

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Objectives: To assess the efficacy of ramelteon in preventing delirium, an acute neuropsychiatric condition associated with increased morbidity and mortality, in the perioperative, ICU setting.

Design: Parallel-arm, randomized, double-blinded, placebo-controlled trial.

Setting: Academic medical center in La Jolla, California.

Patients: Patients greater than or equal to 18 years undergoing elective pulmonary thromboendarterectomy.

Interventions: Ramelteon 8 mg or matching placebo starting the night prior to surgery and for a maximum of six nights while in the ICU.

Measurements and Main Results: Incident delirium was measured twice daily using the Confusion Assessment Method-ICU. The safety outcome was coma-free days assessed by the Richmond Agitation-Sedation Scale. One-hundred twenty participants were enrolled and analysis completed in 117. Delirium occurred in 22 of 58 patients allocated to placebo versus 19 of 59 allocated to ramelteon (relative risk, 0.8; 95% CI, 0.5–1.4; $p = 0.516$). Delirium duration, as assessed by the number of delirium-free days was also similar in both groups (placebo median 2 d [interquartile range, 2–3 d] vs ramelteon 3 d [2–5 d]; $p = 0.181$). Coma-free days was also similar between groups (placebo median 2 d [interquartile range, 1–3 d] vs ramelteon 3 d [2–4 d]; $p = 0.210$). We found no difference in ICU length of stay (median 4 d [interquartile range, 3–5 d] vs 4 d [3–6 d]; $p = 0.349$), or in-hospital mortality (four vs three deaths; relative risk ratio, 0.7; 95% CI, 0.2–3.2; $p = 0.717$), all placebo versus ramelteon, respectively.

Conclusions: Ramelteon 8 mg did not prevent postoperative delirium in patients admitted for elective cardiac surgery. (*Crit Care Med* 2019; 47:1751–1758)

Key Words: delirium; melatonin receptor agonists; ramelteon; sleep

*See also p. 1813.

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Trial Registration: Registered at ClinicalTrials.gov: NCT02691013. Registered on February 24, 2016, by principal investigator, Dr. Owens.

Data Statement: The protocol and de-identified data for this study are available upon reasonable request to the authors via email to rowens@ucsd.edu.

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Delirium is a clinical syndrome of acute brain dysfunction that is associated with multiple negative short- and long-term patient outcomes, including increased mortality and worsened long-term cognition (1–4). Age and illness severity increase the risk for delirium development, which is common in the medical and surgical ICUs (1, 5). Patients undergoing cardiac surgeries, such as coronary artery bypass grafting (CABG) and valve replacements, have particularly high rates of delirium

compared with other operations, possibly due to cardiopulmonary bypass and/or induced hypothermia (1, 6–8). Additionally, these patients most often have postoperative needs (e.g., mechanical ventilation and pressor requirements) that necessitate recovery in the ICU, where the environment and frequent care interruptions may contribute to rates of delirium ranging from 40% to 60% independent of surgical procedures (9). Pulmonary thromboendarterectomy (PTE) surgery is the recommended treatment for symptomatic chronic thromboembolic pulmonary hypertension and is performed using cardiopulmonary bypass, deep hypothermia, and circulatory arrest. Historically, PTE patients of all ages have commonly experienced delirium and/or cognitive dysfunction, although there have been multiple changes in perioperative management since prior reports (10–13).

Sleep deprivation may contribute to delirium (14–16), and the ICU environment, critical illness, and surgery can all disrupt sleep (17–19). Accordingly, others have used melatonin or melatonin-receptor agonists to try and reduce delirium rates by improving sleep and/or regulating the endogenous circadian rhythm. Hatta et al (20) showed that ramelteon reduced delirium in older medical patients in the ICU and general wards, a finding consistent with other studies (21–24). These data have garnered interest in the use of ramelteon and melatonin for preventing ICU delirium, with many physicians prescribing ramelteon to treat/prevent delirium after publication of these studies.

Based on this conceptual framework, we conducted a trial of ramelteon for delirium prevention among patients undergoing elective PTE surgery. These patients have a defined insult and receive protocolized care by a limited number of providers in standardized hospital settings. The purpose of our study was to test the hypothesis that ramelteon would prevent delirium in the postoperative, ICU setting using a relatively homogeneous population.

MATERIALS AND METHODS

This was an investigator-initiated, randomized control trial at a single academic medical center in La Jolla, CA. The study protocol was approved by the University of California, San Diego (UCSD) Human Research Protections Program and was registered at ClinicalTrials.gov (NCT02691013) prior to enrollment. Our primary outcome listed on ClinicalTrials.gov was total sleep duration. However, due to funding and logistical constraints, only a subset of subjects would have been able to undergo the continuous electroencephalography monitoring used for sleep assessment. Thus, we focused on our a priori secondary outcome of incident delirium, a change made before the start of data collection or analysis. Our initial sample size calculation (see below) revealed adequate power to detect a clinically meaningful reduction in postoperative delirium. Only some (rather than all) subjects underwent continuous electroencephalography, otherwise, the study protocol and data collection were not changed.

Participants and Recruitment

Eligible patients were greater than or equal to 18 years and admitted for elective PTE. Patients who did not speak English, were pregnant, had cirrhosis, or used fluvoxamine (selective serotonin reuptake inhibitor that interacts with ramelteon) were excluded. We approached patients the night prior to surgery for recruitment using written, informed consent. Recruitment occurred according to investigator availability from March 16, 2016, to December 12, 2017, when enrollment goals were met. Investigators were required for all study procedures from enrollment until discharge from the study, thus enrollment was not possible when it conflicted with other investigator responsibilities (e.g., clinical rotations lasting 2 or 4 wk).

Surgery

Specifics of the PTE procedure are published elsewhere (25, 26). Briefly, the operation includes a median sternotomy incision, cardiopulmonary bypass, and deep hypothermia to 20°C with periods of circulatory arrest. Patients remain intubated and are transferred to the cardiovascular ICU postoperatively, where they are cared for by health professionals with specialized training in the care of PTE patients. This unit also provides postoperative care for CABGs, valve repair/replacements, heart and lung transplants, as well as care for decompensated heart failure including those needing mechanical circulatory support such as extracorporeal membrane oxygenation. In general, patients are sedated with propofol and IV fentanyl is used for analgesia. On postoperative day (POD) 1, daily spontaneous awakening trials and spontaneous breathing trials are begun per protocol.

Randomization and Intervention

At enrollment, subjects were randomly assigned to either ramelteon (U.S. Food and Drug Administration approved for insomnia, but not delirium prevention) or matching placebo. The ramelteon tablet (only available in 8 mg dosing) was over-encapsulated with an opaque, gelatin capsule and back-filled with lactose; the same gelatin capsule was filled with lactose to create an identical placebo. We used a computer-generated, four-factor blocked randomization schedule known only to the investigational drug pharmacists, who dispensed the medication according to the random allocation sequence. Investigators, subjects, and other clinical care providers remained blinded to drug assignment until trial completion and all data collection and analysis were completed. The study drug was administered nightly at 9 PM by the patient's nurse beginning the night prior the surgery (POD1) for a maximum of seven nights (through POD5) while still in the ICU; patients did not continue to receive the study medication if discharged from the ICU prior to POD5. Patients received the medication orally or crushed via nasogastric tube if intubated.

Delirium and Coma Assessments

Delirium was assessed bid by a physician member of the research team using the Confusion Assessment Method for the ICU (CAM-ICU) (27), with one morning (AM) and one afternoon (PM) assessment done at least 6 hours apart, starting with the PM assessment upon arrival to the ICU postoperatively. Assessments continued until discharge from ICU or through POD8 if the patient remained in the ICU. Patients were considered delirious if they met criteria for being CAM-ICU positive (CAM+). Sedation levels were assessed using the Richmond Agitation-Sedation Scale (RASS); coma was defined as a RASS score of –4 or –5.

Other Measurements

Basic demographics, length of stay (LOS), and Charlson Comorbidity Index data were collected for all participants. A Sequential Organ Failure Assessment score was calculated daily starting on POD0 upon patient arrival to the ICU. Total doses of opiates, benzodiazepines, and antipsychotics that patients received throughout the study were quantified. Opiate and benzodiazepine doses were converted to morphine and lorazepam milligram equivalents, respectively, and included drips, IV pushes, and oral drugs. Other daily clinical data, including mechanical ventilation, sedation medications, and pressor requirements were also recorded.

Outcomes

The main prespecified outcome was incident delirium, as measured by CAM-ICU. Given risk of sedation with ramelteon, coma duration was the primary safety outcome, and we also compared depth of sedation between groups using RASS, which is one of the core features of CAM-ICU (thus, coma is assessed anytime a CAM-ICU is performed). Participants who died during the study were assigned an outcome of delirium. Thus, an intervention that increased death and/or decreased opportunity for patients to be assessed as delirious would not be found superior. Duration of delirium and coma were calculated as delirium /coma-free days and coma-free days as in prior literature (28, 29). Subjects were considered to have a delirium/coma-free or coma-free day when "neither" of the bid CAM and RASS assessments reflected delirium or coma, respectively. Delirium duration was measured as the number of days that a subject had at least one CAM+ assessment. We also recorded the number of hours between the first CAM+ assessment and the first CAM– assessment with no subsequent CAM+ assessments. Coma duration was measured as the number of days that a subject had at least one assessment with a RASS score of –4 or –5.

In order to normalize for variable ICU LOS, delirium, and coma metrics were also measured as a percentage of ICU LOS, with a maximum ICU LOS of 9 days (maximum possible length of the study period postoperatively).

If a CAM assessment by the investigators was missed, the clinically recorded CAM assessment was used, and compared with the pre and post missing assessments.

Power Calculations

Although initially powered based on sleep duration, the primary outcome was changed to incident delirium prior to data collection. Sample size analysis was based on a 20% incidence of delirium. We assumed up to a 20% attrition rate (accounting for drop out, mortality, and persistent coma), and an expected effect size of a 20% relative reduction in delirium with ramelteon. Using alpha of 0.05, we had greater than 90% power to detect this difference with a sample size of 48 subjects in each group.

Data Analysis and Statistics

Study data were managed using Research Electronic Data Capture tools hosted at UCSD (30). Following unblinding, data were exported for analysis in R (Vienna, Austria). After analysis of the prespecified outcomes, we conducted post hoc subgroup analyses for age greater than or equal to 65, as well as for those with more than one CAM+ assessment in order to account for short-term possibly sedation-related episodes of delirium (31). Secondary analyses included in-hospital mortality and newly-initiated antipsychotic use between groups. In a post hoc analysis, we also compared variables relevant to the development of delirium in those who became delirious versus those who did not.

Normally distributed, numerical outcomes are reported as mean ± SD, and were compared using two-tailed, independent, and pooled *t* tests. Nonparametric distributions are reported as median and interquartile range (IQR) and were compared using the Mann-Whitney *U* test for independent samples.

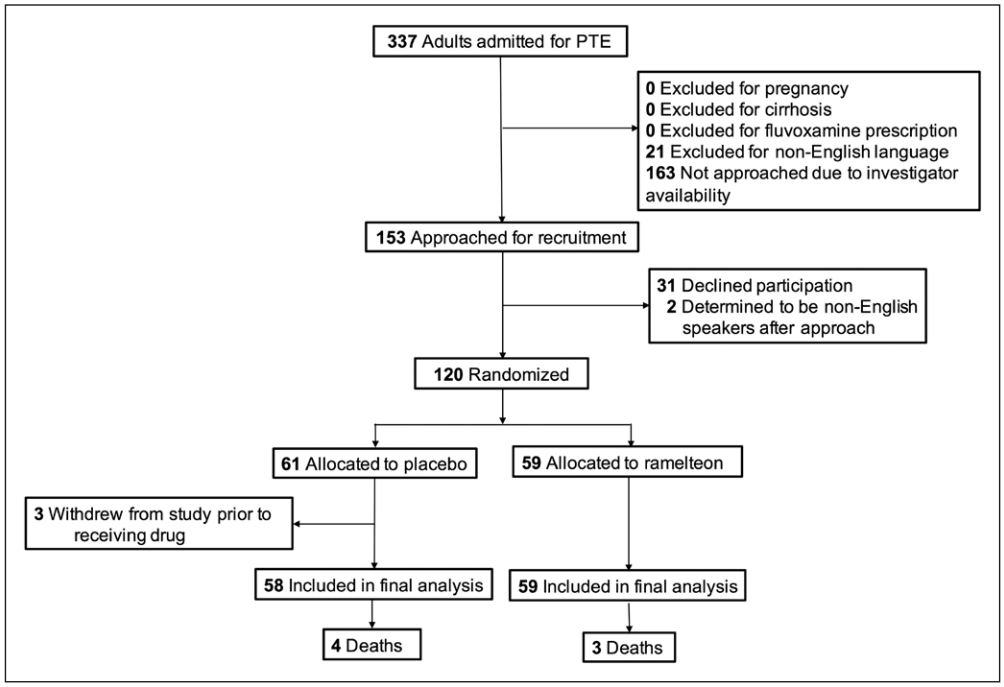

Figure 1. Participant flow. Three-hundred thirty-seven patients were admitted for pulmonary thromboendarterectomy (PTE) surgery from March 2016 to December 2017. No subjects were excluded for pregnancy, cirrhosis, or for being on fluvoxamine. Twenty-one were excluded due to being non-English speakers as identified by the electronic medical record. Recruitment efforts were based on investigator availability to enroll and assess subjects, but otherwise consecutive patients were approached. Thus, of the 337 patients admitted, 153 subjects who met inclusion criteria based on initial screening were approached for enrollment. Of these, 31 declined enrollment and two were found to be non-English speakers. One-hundred twenty subjects were randomized. A total of three subjects dropped out prior to receiving any medication. Of the 117 individuals who completed the protocol, there were seven in-hospital deaths.

Categorical outcome data were compared using a chi-square analysis or Fisher exact test (for cell counts ≤ 5). Relative risk (RR) ratios and associated 95% CIs are reported for categorical outcomes, whereas the absolute mean difference and associated 95% CI is reported for data with numerical outcomes.

RESULTS

Recruitment and Baseline Data

The participant flow diagram is shown in **Figure 1**. Fifty-eight participants who received placebo and 59 who received ramelteon were used for final analysis (per-protocol group). Both groups were equally matched for baseline characteristics (**Table 1**). Less than 10% of participants received benzodiazepines, and total dosages were similar between groups. The median duration of ventilation, including POD0 for the cohort was 2 days (IQR, 2–3 d). Median ICU LOS was 4 (IQR, 3–6) for the cohort and was similar between groups (Table 1).

Study Drug Administration and CAM Assessments

Both groups had good adherence to the study medication (278/292 possible doses [95%] placebo vs 296/309 [96%] ramelteon; $p = 0.728$ by chi-square test), with lack of enteral access the most common reason for missed doses. We completed 1,060 out of 1,076 (98.5%) possible CAM-ICU assessments, with 418 of 1,060 (39.4%) scored as coma for RASS –4 or –5. In only two cases were pre and post missed assessment CAMs discordant.

Efficacy of Ramelteon for Delirium Prevention

When considering all 120 randomized subjects (intention-to-treat), delirium frequency was similar between groups (36.0% placebo vs 32.2% ramelteon; RR, 0.9, 95% CI, 0.5–1.4; p = 0.656).

Delirium frequency was similar between groups (36.0% placebo vs 32.2% ramelteon; RR, 0.9, 95% CI, 0.5–1.4; $p = 0.656$).

Delirium frequency (**Table 2**) was also similar in the per-protocol cohort. In an effort to exclude rapidly reversible, sedation-related delirium (31), we compared delirium occurrence only in patients with greater than one CAM+ assessment, which was not different between groups. Nor was there a difference in delirium when examining individuals age greater than or equal to 65.

Efficacy of Ramelteon on Delirium and Sedation Duration

We found no differences in delirium/coma-free days, coma-free days, delirium duration, or sedation duration between groups (**Fig. 2*A*** and Table 2). These outcomes also did not differ when results were normalized for ICU LOS.

TABLE 1. Baseline Characteristics of Patients Receiving Placebo Versus Ramelteon

Characteristic	Placebo (*n* = 58)	Ramelteon (*n* = 59)	*p*
Age, mean (± SD)	56.1 (15.8)	58.1 (14.1)	0.471
Female sex, *n* (%)	29.0 (50.0)	30.0 (50.8)	0.927
Body mass index, kg/m^2, mean (± SD)	33.0 (8.7)	31.2 (9.8)	0.296
Charlson Comorbidity Index, mean (± SD)	3.2 (2.0)	3.3 (1.6)	0.822
Operating room time, min, median (IQR)	526.0 (480–540)	510.0 (480–540)	0.843
Cardiopulmonary bypass time, min, median (IQR)	256.0 (232–266)	260.0 (237–280)	0.353
Circulatory arrest time, min, median (IQR)	39.0 (31–56)	39.0 (32–46)	0.570
Highest Sequential Organ Failure Assessment score, mean (± SD)	6.7 (2.0)	6.6 (2.1)	0.891
Opiate usage over ICU stay, morphine milligram equivalent, median (IQR)	42.0 (16–74)	31.7 (16–78)	0.827
Subjects receiving benzodiazepines, *n* (%)	6.0 (10.3)	5.0 (8.5)	0.729
Benzodiazepine usage including continuous IV infusions[a], median lorazepam mg equivalents (IQR)	33.9 (2–84)	2.0 (1–2)	0.519
Benzodiazepine usage excluding continuous IV infusions, median lorazepam mg equivalents (IQR)	1.0 (1–2)	1.3 (1–2)	0.854
Duration of ventilation, d, median (IQR)	2 (2–3)	2.0 (2–3)	0.458
ICU length of stay, d, median (IQR)	4.0 (3–5)	4.0 (3–6)	0.349
Hospital length of stay, d, median (IQR)	12.0 (10–14)	12.0 (10–16)	0.720

IQR = interquartile range.

[a]Four out of 11 individuals received continuous infusions of benzodiazepine.

Group means were compared using a two-tailed *t* test, whereas group medians were compared using the Mann-Whitney *U* test. No significant differences were found in baseline characteristics of subjects in the ramelteon versus placebo group. Benzodiazepine usage calculations reflect doses given during the participant's ICU stay and include only the 11 individuals who received medications in this class.

TABLE 2. Delirium and Coma Outcomes

Outcome Variable	Placebo ($n = 58$)	Ramelteon ($n = 59$)	95% CI	p
Delirium occurrence, *n* (%)			Relative Risk	
Per-protocol group	22 (38)	19 (32)	0.8 (0.5–1.4)	0.516
Group with > 1 Confusion Assessment Method for the ICU positive assessment	9 (16)	9 (15)	1.0 (0.4–2.3)	0.969
[a]Group with age ≥ 65 yr	9/19	6/20	0.6 (0.3–1.4)	0.265
Delirium and coma duration, d, median (IQR)			Absolute mean difference	
Delirium/coma-free	2.0 (2–3)	3.0 (2–5)	0.4 (−1.1 to 0.3)	0.181
Coma-free	2.0 (1–3)	3.0 (2–4)	0.3 (−1.0 to 0.3)	0.210
Delirium	0.0 (0–1)	0.0 (0–1)	0.0 (−0.4 to 0.4)	0.576
Coma	2.0 (1–3)	2.0 (1–2)	0.3 (−0.4 to 0.9)	0.288
Duration of delirium, hr, median (IQR)			Absolute mean difference	
All delirious subjects	16.0 (10–29)	24.0 (14–37)	0.3 (−28.8 to 30.5)	0.583
Delirious for > 1 assessment	34.0 (26–41)	37.0 (24–47)	11.8 (−44.0 to 67.5)	0.965
Normalized duration of delirium and coma, median % of ICU length of stay (IQR)			Absolute mean difference	
Delirium/coma-free	75.0 (50–100)	100.0 (54–100)	4.7 (−17.3 to 8.0)	0.331
Coma-free	66.7 (50–75)	71.4 (53–80)	5.3 (−15.5 to 4.9)	0.122
Delirium	0.0 (0–22)	0.0 (0–14)	0.9 (−6.2 to 8.0)	0.517
Coma	78.9 (61–100)	71.4 (50–100)	9.3 (−2.9 to 21.5)	0.173
Other clinical outcomes			Relative Risk	
In-hospital mortality, *n* (%)	4 (6.9)	3 (5.1)	0.7 (0.2–3.2)	0.717
Antipsychotic use (newly initiated), *n* (%)	7 (12.1)	7 (11.9)	0.9 (0.4–2.6)	0.973
			Absolute mean difference	
Ventilator-free days, d, median (IQR)	2.0 (2–3)	2.0 (2–3)	0.3 (−0.4 to 0.9)	0.285

IQR = interquartile range.

[a]The "*n*" for this subgroup within each arm is denoted as the denominator, whereas the numerator represents the fraction of these individuals who became delirious.

Per-protocol group and age ≥ 65 group include patients who died that were assigned an outcome of delirium. Subjects labeled as coma when Richmond Agitation-Sedation Scale −4 or −5.

Figure 2*B* shows the percentage of CAM+ subjects in the placebo and ramelteon groups at each delirium assessment, while **Figure 2*C*** shows a comparison of the mean RASS score for each assessment time. A two-way, unbalanced analysis of variance of this analysis did not reveal any differences in sedation scores between groups ($p = 0.759$).

Description of Mortality

In-hospital mortality rates were similar between groups (Table 2). Four participants died during the study period (two ramelteon vs two placebo). As above, these patients were considered to have incident delirium. However, none of these four could be assessed based on RASS –4/–5 and were thus considered coma at all assessments for purposes of coma duration. Three individuals died after the study period. One was assessible for delirium (CAM+, received placebo), whereas the other two remained comatose for all assessments.

Analysis of Ventilator Days and Treatment With Antipsychotics

Each cohort experienced approximately three ventilator-free days and equivalent numbers received newly-initiated antipsychotics, suggesting that similar numbers of patients received treatment for delirium-related symptoms (e.g., agitation/hallucinations) in both groups (Table 2).

Variables Associated With Postoperative ICU Delirium

As expected, ICU LOS was found to be longer in delirious patients (**Supplemental Table 1**, Supplemental Digital Content

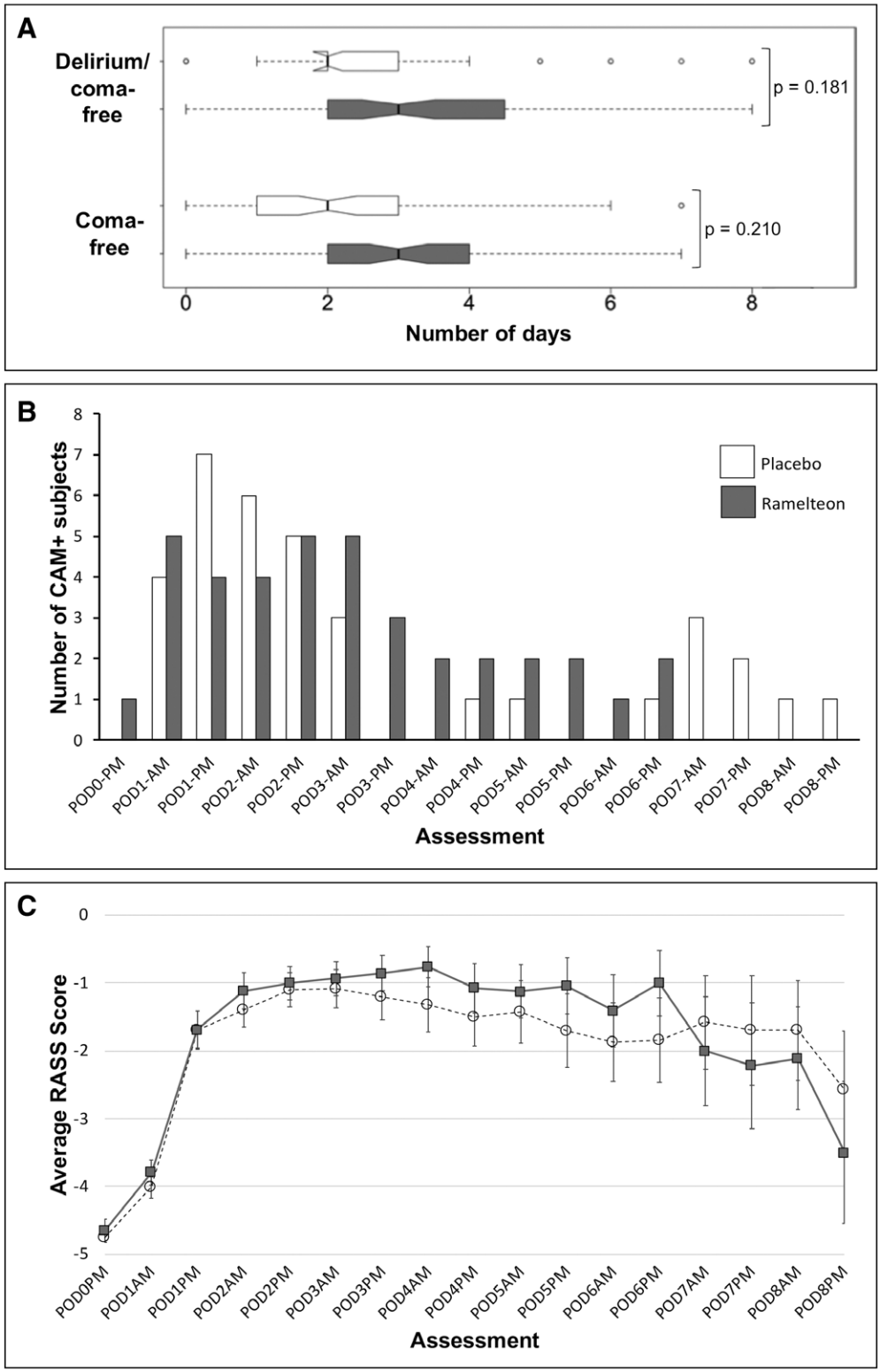

Figure 2. Delirium and sedation during the study. **A**, Delirium/coma-free and coma-free ICU days. *Boxplots* show medians, interquartile ranges, and outliers. *White coloring* indicates placebo group, whereas *gray shading* indicates ramelteon group. **B**, Delirium by assessment. Comparisons of the number of subjects noted to be Confusion Assessment Method for the ICU positive (CAM+) at each postoperative assessment. Placebo group ($n = 58$) shown in *white*, whereas *gray* indicates ramelteon group ($n = 59$). **C**, Sedation level by assessment. Compares mean sedation levels, based on Richmond Agitation-Sedation Scale (RASS) scoring, between each group at each postoperative assessment. Ramelteon did not result in significantly lower sedation levels. POD = postoperative day.

1, http://links.lww.com/CCM/E933), although whether this finding was a cause or effect of the delirium could not be ascertained. Other variables were similar between groups. A similar number of delirious and nondelirious participants received postoperative benzodiazepines (10.8% vs 7.0%; Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/E933), and doses were not different between groups, although we note that the sample size was small.

DISCUSSION

Ramelteon did not reduce incident delirium in patients undergoing cardiopulmonary bypass surgery for thromboendarterectomy, nor did it improve delirium duration. We did not find any harms associated with its use, with no evidence of increased sedation/coma duration.

Our results conflict with those of Hatta et al (20) and a recent publication by Nishikimi et al (24), both of which reported reductions in incident delirium using ramelteon. Hatta et al (20) showed a marked reduction in delirium in a mixed, nonintubated population of older adults (age ≥ 65 yr). Nishikimi et al (24) performed an randomized controlled trial (RCT) in critically ill patients and found that ramelteon use significantly reduced incident delirium and delirium duration, although ICU LOS, their main outcome, was unaffected. In both of these studies, subjects had a variety of diagnoses, but were generally medical, not surgical, patients. Individuals in these studies were older and more often had dementia. This notion might suggest that

while ramelteon could have efficacy in an elderly population, it may not have broader effectiveness in preventing delirium. Importantly, mean delirium duration in those studies was short (< 1.5 d), suggesting that sedation-related delirium was not accounted for, as was done in our study. In the surgical literature, to our knowledge, there have been no prospective randomized studies and only smaller, retrospective studies that have suggested benefit of ramelteon in delirium after surgery (23, 32).

Another possible explanation for the discordant results is the underlying causes of delirium in the various studies. Girard et al (33) have presented data regarding delirium phenotypes (e.g., hypoxemic, medication-induced, sepsis-related), suggesting that there are different pathways to the common endpoint of delirium. Our patients could have had delirium related to circulatory arrest. Thus, it is possible that ramelteon may affect one endotype of delirium but not another. However, preventative measures such as the Awakening and Breathing coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family engagement guidelines (34, 35), appear to reduce incident delirium regardless of etiology. Future studies will be needed to elucidate further groups that may or may not benefit from administration of melatonin/ramelteon (36). Current Society of Critical Care Pain, Agitation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines for adult ICU patients do not recommend the use of pharmacologic preventative agents for delirium, and our findings align with these recommendations (37). Finally, we were agnostic to the mechanism of action by which ramelteon might affect delirium, either by promotion of sleep versus maintenance of circadian rhythm. If the latter, there may be some individuals for whom our chosen timing of drug administration may have upset their endogenous circadian rhythm. That is, some individuals who are phase advanced or phase delayed might be harmed, whereas others might be helped based on the timing of the intervention relative to the endogenous circadian rhythm.

Interestingly, delirium rates were lower in this study compared with prior literature, especially when we excluded the occurrence of short-term, sedation-related delirium which may not convey serious additional morbidity and mortality. Although this reduction could be due to a number of factors—for example, improved operative and postoperative care techniques, early mobilization, and reduction in the use of benzodiazepines—we note this important finding because it confirms that, to some degree, delirium is preventable without additional pharmacological therapy. For now, adherence to guidelines with proven benefit should remain the mainstay of efforts to reduce delirium. The inclusion of sleep in the latest PADIS guidelines reflects both a growing interest in sleep in the ICU but also a number of uncertainties (37). At the least, sleep in the ICU is perceived to be poor by most patients and causes distress (38–40). Relevant to our investigation, it has been hypothesized that sleep and circadian rhythm disturbances during ICU admission might affect ICU outcomes (41, 42). Similarly, a number of medications such as melatonin and propofol have been proposed to improve sleep, but generally with low-quality evidence, leading to a call for RCTs of sleep-promoting medications. In our study, the melatonin receptor agonist ramelteon—which in other settings can improve sleep and circadian timing—was not associated with reduced rates of ICU delirium.

We note several important limitations to our work. First, this was a single-center trial, although this limitation must be balanced by less variability in operative, perioperative, and ICU care which could affect delirium rates. Second, we did not follow patients after discharge to the general wards, potentially missing new-onset delirium. However, given the clinical improvement that allowed discharge to the floor, we believe this to be very uncommon. Third, the duration of delirium for our subjects was relatively short, although this was similar to the study by Nishikimi et al (24). Notably, we also tried to examine the impact of ramelteon on only those with longer durations of delirium, which has not been done by others. Finally, we approached only about half of the patients admitted for PTE over the study period due to investigator availability (see Methods). However, our study protocol called for assessments by a study physician and nightly monitoring of study drug administration. Although delirium rates may change over time based on secular trends in postoperative care, the likelihood of this occurring over the relatively brief study period is low and would have been addressed with the blocked randomization scheme.

Strengths of our study include a homogenous population as all participants underwent the same operative procedure by one of two surgeons and select group of anesthesiologists, and all received perioperative care by the same clinicians. Furthermore, patients had similar opportunity for sleep prior to the procedure, in contrast to other studies where patients are admitted to the hospital with acute illness and may have sleep deprivation preceding ICU admission. Thus, we believe our reasonably large study population provided a good model in which to study the efficacy of ramelteon in delirium prevention without multiple confounders. Second, delirium frequency was assessed rigorously by trained and experienced physicians using a widely used and validated scale. Finally, the study protocol was closely adhered to with few missing interventions or assessments.

In conclusion, we did not find that ramelteon prevented delirium in patients undergoing elective cardiopulmonary bypass surgery. Conversely, the drug did not increase sedation levels and overall appeared safe. Thus, although we do not currently (36, 43) recommend the routine use of ramelteon to prevent delirium, it could be used in individuals at high risk of ICU delirium. However, we clearly recommend further efforts to identify effective strategies to prevent delirium.

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