I. Introduction

Postoperative delirium (POD) represents a disturbance in attention, awareness, and cognition that develops over the postoperative period. The prevalence of POD after coronary artery bypass grafting (CABG) is reported from 37 to 52%.

Some medicines were reported to reduce the incidence of POD. Ramelteon, as a melatonin receptor agonist, regulates the sleep cycle and improves subjective sleep quality of patients with chronic insomnia. Ramelteon also is reported to reduce the occurrence of delirium in patients admitted to the intensive care unit (ICU).

Recently, Suvorexant, as a new type of sleep medication as an orexin receptor antagonist, is noted for subjective measures of sleep onset and maintenance. The orexin neuropeptide signal system supports wakefulness, but Suvorexant inhibits the binding of orexin neuropeptides to receptors and suppresses the wake drives. Recently, a few studies reported the effect of Suvorexant for delirium.

The purposes of this study were to investigate the availability of Suvorexant for POD after CABG and to evaluate the effect of Suvorexant for the operative outcome.
After CABG, normal dosage Propofol was administered as a sedative drug until weaning from a respirator in all patients. Avoiding over suppression, the sedation levels of all patients were controlled by The Richmond Agitation-Sedation Scale (RASS)\(^\text{10}\) from 0 to 2 points. For pain control, acetaminophen was used in all cases controlled by Behavioral pain scale (BPS)\(^\text{11}\) under 5 points. In our institution, weaning from respirator wasn’t on the day of operation under consideration for the standpoint of medical safety. After weaning from the respirator, postoperative rehab program was started from the first postoperative day.

Suvorexant (Belsomura\(^\text{®}\), Merck Sharp & Dohme, Chiyoda-ku, Tokyo, Japan) is a relatively new sleep medication and has been prescribed since November 2014 in Japan. In our institution, we have administered Suvorexant after weaning respirator for the target patients from March 2016 to May 2018 (S-group, n=45). Besides, Ramelteon (Rozerem\(^\text{®}\), Takeda Pharmaceutical Co., Ltd., Chyuo-ku, Osaka, Japan) is reported to decrease in the occurrence rate of delirium in elderly patients\(^\text{6}\). In our institution, Ramelteon has been employed since June 2018, so we have put the target patients on Ramelteon from June 2018 (R-group, n=26). As a reference, the consecutive target patients underwent CABG before the due day (from February 2013 to February 2016) were N-group (n=67). So, a total of 138 patients was searched in this study, the mean age was 69.7 ± 3.4 years (41 – 84 years), twenty-nine were women (21.0%). Because all data are collected at the point of care and services to create both medical reports and a scientific database, the quality of the primary data is reliable.

| Table 1 Demographic characteristics of all patients before interventions |
|:------------------|:------------------|:------------------|:------------------|:------------------|
| Age (year) | 70.2 ± 8.7 | 68.0 ± 10.1 | 59.4 ± 12.3 | 0.475 |
| Sex (female) | 13 (19.4%) | 8 (17.8%) | 67.6 ± 10.4 | 0.406 |
| Prevalence | | | 8 (30.8%) | |
| Hypertension | 59 (88.1%) | 42 (93.3%) | 22 (84.6%) | 0.506 |
| Dyslipidemia | 51 (76.1%) | 40 (88.9%) | 22 (84.6%) | 0.277 |
| DM | 39 (58.2%) | 26 (57.8%) | 22 (84.6%) | 0.811 |
| CKD | 11 (16.4%) | 5 (11.1%) | 17 (65.4%) | 0.608 |
| Smoking within a month | 12 (17.9%) | 9 (20.0%) | 5 (19.2%) | 0.972 |
| Hb (g/dl) | 12.9 ± 1.9 | 13.2 ± 1.8 | 5 (19.2%) | 0.564 |
| EF (%) | 58.8 ± 11.5 | 59.4 ± 12.3 | 13.2 ± 1.5 | 0.37 |

Table 1 Demographic characteristics of all patients before interventions

DM: diabetes mellitus, CKD: chronic kidney disease, Hb: hemoglobin, EF: ejection fraction

There is no full-time psychiatrist in our institution. So, POD was diagnosed by the ICU doctors and the attending physicians and along the lines with the Intensive Care Unit Delirium Screening Checklist (ICDSC)\(^\text{12}\) every day during ICU stay. The ICDSC scorings routinely were performed after cardiac surgery for all the patients. POD was defined as a more three scores in ICDSC. Whenever POD occurs, pharmacological treatment based on our institutional standards of care will be administered. Haloperidol was administered in patients who developed POD. Once standard discharge criteria will be attained, the patients will be transferred from the intensive care unit (ICU) to the general ward. Patients were transferred from ICU to the general ward after removing drains, central venous catheters, and catecholamine in our hospital.

Diabetes mellitus (DM) was defined as the recent use of anti-diabetic drugs, fasting blood glucose >126 mg/dl and/or hemoglobin A1c >6.5%. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <50 ml/min/1.73 m\(^2\).

Continuous data are expressed as mean ± SD with ranges when appropriate. Parametric data were compared using Student t-test. A Chi-squared test to examine with a contingency table was used. The associated variables were included in the stepwise backward selection method in the multivariable model to identify the independent predictors of POD, presented as odds ratio (OR) with 95% confidence intervals (CI). Differences were considered significant at p<0.05.

III. Results

There were preoperative characteristics for all patients in Table 1. There was no significant difference among every group in age, sex, prevalence (hypertension, dyslipidemia, diabetes mellitus, and chronic kidney disease), smoking within a month, hemoglobin value, and ejection fraction.

Inoperative characteristics, there was no difference between the three groups (Table 2). In Table 3, there was no difference
among the three groups in postoperative complications (re-sternotomy, mediastinitis, postoperative atrial fibrillation, re-intubation, and cerebral infarction).

In our institution, respirator weaning wasn’t on the day of operation under consideration for medical safety. So, intubation time was longer than usual. In Table 4, there was no significant difference for intubation time in three groups. ICDSC was much lower in S-group compared with N and R-group (N: 2.4 ± 2.0;  S:  0.9 ± 1.1;  R=2.2 ± 1.4, p<0.001). And then, although the patients with POD were 20 of 67 patients (29.9%) in the N-group and 7 of 26 patients (26.9%) in the R-group, only two patients (4.4%) developed in S-group (p=0.002). Patients were transferred from ICU to the general ward after removing drains, central venous catheters, and catecholamine in our hospital. So, the length of ICU stay might be longer than another institute. Therefore, there was not significantly different for ICU stay in three groups. However, hospital stay was significantly decreased in S-group compared with N and R-group (N: 23.6 ± 8.9:  S:  18.8 ± 2.9:  R=20.7 ± 4.4 days, p=0.005).

The result of multivariate logistic models of logistic regression analysis for POD is shown in Table 5. In this analysis, use of Suvorexant (OR ; 0.10, 95% CI ; 0.03–0.37, p<0.001) was identified as an only independent predictor of POD prevention.

IV. Discussion

The present study showed that Suvorexant reduced the incidence of POD in patients after CABG. And then, Suvorexant has indicated the potency shortening length of hospital stay in our study. Suvorexant has been released since November 2014 in Japan and has been taken up since April 2016 in our institute. Although we started to prescribe Suvorexant for postoperative insomnia from May 2016, we had found POD decreasing in patients with Suvorexant for a while. So, we investigated the availability of Suvorexant for POD after CABG. However, the present study was a single-center experience, and there were only a few studies of Suvorexant for delirium.

By contrast, Ramelteon had been reported to reduce the occurrence of delirium in many studies previously. Such as, we had prescribed Ramelteon since June 2018, and had studied the incidence of the POD on Suvorexant in comparison with on Ramelteon. We couldn’t indicate the efficiency of Ramelteon for POD decreasing but could present the impact of Suvorexant. Suvorexant is reported to be a new type of sleep medication that has no affinity for an alpha-aminobutyric acid receptor (GABAR), and can be safely used for the treatment of insomnia in older adults. In addition, Suvorexant is reported to be associated with a low incidence of delirium in ICU patients. Hatta et al reported that Suvorexant administered to elderly patients admitted for acute care provided protection against delirium. Also, Masuyama et al presented that Suvorexant was associated with a lower incidence of delirium with ICU patients using multivariable logistic regression analysis. The mechanism for the preventive effects of Suvorexant on delirium was thought to be associated with anti-dopaminergic activity like antipsychotics.
However, there are a few reports on whether Suvorexant is effective to prevent delirium after cardiac surgery\(^9\). The present study showed that the incidence of POD in patients taking Suvorexant was significantly lower than that in patients without Suvorexant (including patients taking Ramelteon, Table 4), suggesting preventive effects of Suvorexant on delirium after CABG. In univariate and multivariable logistic regression analysis, Suvorexant was indicated to be one of the predictor associated with a lower incidence of delirium with patients who underwent CABG (Table 5). Regrettably, the mechanism of Suvorexant for delirium was unsure in the present study, but the decrease of POD with Suvorexant could be associated with good sleep (data not shown) that created sustainable postoperative care. Further studies are hoped to confirm our results.

Inouye et al\(^{14}\) reported that the delirium was associated with an increase in the length of hospital stay because POD was associated with increased short-term complications. In Table 4, we presented there was significantly more decrease in-hospital stay in patients prescribing Suvorexant. Continuation of POD after transferring to the general ward might affect hospital stay, too. So, the preventive effect of Suvorexant on delirium might decrease hospital stay.

Ramelteon is an agonist binding to melatonin (MT1 and MT2) receptors in the central nervous system\(^{15}\). And so, the previous

### Table 4  Clinical outcome

|                      | N-group (n=67) | S-group (n=45) | R-group (n=26) | P value |
|----------------------|---------------|---------------|---------------|--------|
| Intubation time (hour) | 20.4 ± 15.1   | 17.1 ± 7.4    | 21.7 ± 16.7   | 0.306  |
| ICDSC                | 2.4 ± 2.0     | 0.9 ± 1.1     | 2.2 ± 1.4     | <0.001 |
| POD (ICDSC>3)        | 20 (29.9%)    | 2 (4.4%)      | 7 (26.9%)     | 0.002  |
| ICU stay (day)       | 6.5 ± 3.2     | 4.7 ± 0.8     | 5.0 ± 0.8     | 0.219  |
| Hospital stay (day)  | 23.6 ± 8.9    | 18.8 ± 2.9    | 20.7 ± 4.4    | 0.005  |
| Hospital death       | 0 (0%)        | 0 (0%)        | 0 (0%)        |        |

POD: postoperative delirium, ICDSC: intensive care delirium screening checklist, ICU: intensive care unit

### Table 5  Multivariate logistic regression analysis for POD

|                          | Odds ratio (95% confidence interval) | P value |
|--------------------------|-------------------------------------|--------|
| Preoperative characteristics |                                     |        |
| Male                     | 0.92 (0.32-2.71)                     | 0.884  |
| Age>75 years             | 2.21 (0.85-5.76)                     | 0.103  |
| Hypertension             | 1.95 (0.35-10.9)                     | 0.448  |
| Dyslipidemia             | 2.00 (0.55-7.20)                     | 0.29   |
| DM                       | 2.51 (0.96-6.57)                     | 0.061  |
| CKD                      | 1.42 (0.38-5.37)                     | 0.602  |
| Surgical intervention    |                                     |        |
| OPCAB                    | 1.13 (0.39-3.29)                     | 0.819  |
| Postoperative complication |                                     |        |
| Re-stenotomy             | 1.32 (0.06-28.10)                    | 0.859  |
| Mediastinitis            | 0.19 (0.01-3.18)                     | 0.246  |
| Atrial fibrillation      | 0.81 (0.29-2.27)                     | 0.692  |
| Renal failure            | 0.66 (0.16-2.68)                     | 0.56   |
| (Creatinine>1.5mg/dl)    | 0.35 (0.02-5.98)                     | 0.466  |
| Re-intubation            | 0.10 (0.03-0.37)                     | <0.001 |
| Use of Suvorexant        | 0.48 (0.14-1.57)                     | 0.222  |
| Use of Ramelteon         |                                     |        |

DM: diabetes mellitus, CKD: chronic kidney disease, OPCAB: off-pump coronary artery bypass grafting
studies reported Ramelteon had a preventive effect on delirium in elderly inpatients. In relation to POD, Booka et al. indicated that the use of Ramelteon was the preventive factor of POD after esophagus surgery. Miyata et al. demonstrated that Ramelteon reduced the incidence and intensity of delirium after surgery for lung cancer in elderly patients. Though Ramelteon didn’t reduce the incidence of POD compared with Suvorexant in our study (Table 4), further studies are needed to validate the effect of Ramelteon.

The prevalence of POD after CABG was previously reported from 37 to 52%. The recent studies reported POD occurred 4.2% to 17% after CABG. In our study, the patients with POD were 20 of 67 patients (29.9%) in the N-group, 7 of 26 patients (26.9%) in the R-group, and two patients (4.4%) developed in S-group. The cause of the frequent development of POD in this study might be associated with the prolonged duration of intubation and ICU stay. Fast-track protocols for cardiac surgery have been reported in the past. Non-pharmacologic strategies are thought to be a first-line component of management. We have been revising the unit policy and attempted early weaning from a respirator and short ICU stay.

This present study has several limitations. Firstly, our study was a retrospective design. Secondly, the present study was a single-center experience and was limited by the relatively small number of patients included. And, the groups compared were performed in different time periods. Therefore, further prospective studies with a large group are expected.

Conclusion

Suvorexant has shown positive outcomes in the prevention of delirium after CABG. This orexin receptor antagonist, not melatonin receptor agonist, is thought to be a useful medication used in ICU and during hospitalization after CABG. Large trials are necessary to further comparing the efficacy of Suvorexant to other sleep modulating options.

Conflicts of interest

There is no conflict of interest for this article.

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