Preventive Effect of Suvorexant for Postoperative Delirium after Coronary Artery Bypass Grafting

Kiyoshi Tamura, MD, PhD, Toshiyuki Maruyama, MD, and Syogo Sakurai, MD

Objective: Suvorexant is an orexin receptor antagonist and is effective in inducing sleep. We hypothesized that Suvorexant would reduce the incidence of postoperative delirium (POD) after coronary artery bypass grafting (CABG).

Methods: We reviewed 88 patients (12 women, mean age: 69.3 ± 2.5 years) who were undergone CABG alone. Patients were divided into two groups; patients received Suvorexant (S group, n = 36), patients not received Suvorexant (N group, n = 52), and the following data were analyzed and compared between two groups.

Results: Intensive Care Unit Delirium Screening Checklist Score was significantly lower in S group compared with N group (N:S = 2.0 ± 1.7:0.8 ± 1.0, p = 0.0003). Although POD was present in 11 of 52 patients (21.2%) in N group, one patient (2.8%) developed in S group (p = 0.008). In S group, both intensive care unit stay (N:S = median 6:5 days, p = 0.001) and hospital stay (N:S = median 23:20 days, p = 0.035) were significantly shorter than in N group.

Conclusions: Suvorexant might reduce incidence of POD in patients undergone CABG.

Keywords: Suvorexant, orexin receptor antagonist, postoperative delirium, coronary artery bypass grafting

Introduction

Postoperative delirium (POD) remains a common complication following coronary artery bypass grafting (CABG) with incidences ranging from 37% to 52%.1,2 Generally, POD is defined as an acute deterioration of brain function and is characterized by fluctuating mental condition with both inattention and disturbances in consciousness.3 The development of POD affected the patient’s outcome through prolonged hospital stays and increased complications.4 So, it is important to prevent POD after CAGB.

Sleep disorder is one of eventual causes of POD. So, soporific drugs have possibilities for improving POD. Suvorexant is known as a novel orexin receptor antagonist and was developed for sleep disorders and more specifically insomnia.5 Although the orexin neuropeptide signal system supports wakefulness, Suvorexant inhibits the binding of orexin neuropeptides to receptors and suppresses the wake drives. However, few studies have reported the effect of Suvorexant for POD.

The purpose of this study was to investigate the availability of Suvorexant for POD after CABG and evaluate the effect of Suvorexant for operative outcome.

Subjects and Methods

This retrospective study was approved by the institutional review board of Soka municipal hospital.
A total of 102 consecutive patients undergone elective CABG from February 2013 to January 2018 in our institution. We investigated the patients excluded patients with mental disorder, sleep disorder, and dementia patient. And the patients with emergency operation and/or with hemodialysis were excluded. Because benzodiazepine sedative-hypnotic agent for insomnia after CABG were excluded, too. So, 88 patients (12 women, mean age: 69.3 ± 2.5 years) were intended.

Induction and maintenance of anesthesia were similar for all patients and consisted of weight-related doses of fentanyl, midazolam, and pancuronium bromide.

So, normal dosage propofol was dispensed as sedative agent until extubation in all patients. Avoiding over suppression, the sedation levels of all patients were controlled by The Richmond Agitation-Sedation Scale (RASS)\(^6\) from 0 to 2 points. For pain control, acetaminophen was used in all cases controlled by Behavioral pain scale (BPS)\(^7\) under 5 points. In our hospital, extubation was not on the day of operation under consideration for medical safety. After extubation, postoperative rehabilitation program was started from the first postoperative day.

Suvorexant (Belsomura, Merck Sharp & Dohme, Tokyo, Japan) has been sold since November 2014 in Japan, so we have administered Suvorexant after extubation for all the target patients since March 2016 (S group, n = 36). As a reference, the consecutive target patients undergone CABG before the due day (from February 2013 to February 2016) were N group (n = 52). So, total 88 patients were researched in this study, mean age was 69.3 ± 2.5 years (41–83 years), 12 were women (13.6%). Because all data are collected at the point of care and serve to create both medical reports and a scientific data base, the quality of the primary data is reliable.

The basic dosing of oral Suvorexant was 20 mg daily, but the patients over 75-year old were adjusted to 15 mg daily. After extubation, Suvorexant was scheduled from just before falling asleep in intensive care unit (ICU) at night. Suvorexant was prescribed during hospitalization.

PODs were diagnosed by the attending physicians along the lines with the Intensive Care Unit Delirium Screening Checklist (ICDSC).\(^8\) The ICDSC scoring routinely was performed after cardiac surgery in all the patients including the patients without POD. POD was defined as more three score in ICDSC. Whenever POD occurs, pharmacological treatment based on our institutional standards of care will be administered. Patients with POD were administered Haloperidol. Once standard discharge criteria will be met, the patients will be transferred from ICU to the general ward. Patients with drain, central venous catheter, and use of catecholamine cannot be transferred from ICU to general ward in our institute.

Diabetes mellitus (DM) was defined as the recent use of antidiabetic drugs, fasting blood glucose >126 mg/dL, and/or hemoglobin A\(_1c\) >6.5%. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <50 mL/min/1.73m\(^2\).

Continuous data are expressed as mean ± SD with ranges when appropriate. Parametric data were compared using a student’s t-test. Non-parametric Mann-Whitney U-test was used. Parametric data were examined with contingency tables, with Fisher’s exact test, as appropriate. A Chi-squared test to examine with 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 (CIs). Differences were considered significant at p <0.05.

### Results

There were data before interventions for all patients in Table 1. There was no significant difference among groups in age, sex, hypertension, dyslipidemia, chronic obstructive pulmonary disease, and CKD (excluding patients with hemodialysis), smoking within a month, and hemoglobin value. In operative factors, there was no difference between both groups (Table 2). In Table 3,
there was no difference between both groups in postoperative complications (re-stenotomy, mediastinitis, atrial fibrillation, renal failure, and re-intubation).

In our hospital, extubation was not on the day of operation under consideration for medical safety. So, intubation time was longer than usual. In Table 4, there was no significant different in intubation time between two groups. ICDSC was much lower in S group compared with N group (N:S = 2.0 ± 1.7:0.8 ± 1.0, p = 0.0003).

And then, although POD was present in 11 of 52 patients (21.2%) in N group, only one patient (2.8%) developed in S group (Table 4, p = 0.008). The patient with POD in S group was 83-year-old male and was performed with off-pump bypass. Patients with drain, central venous catheter, and use of catecholamine cannot be transferred from ICU to genera ward in our institute. So, the length of ICU stay was longer than usual. In S group, both ICU stay (N:S = median 6:5 days, p = 0.001) and hospital stay (N:S = median 23:20 days, p = 0.035) were significantly decreased compared with N group.

The results of multivariate logistic models of logistic regression analysis for POD are shown in Table 5. Use of Suvorexant (OR: 0.42, 95% CI: 0.18–0.98) and older age (>75 years old) (OR: 3.85, 95% CI: 1.00–14.70) were identified as independent predictors of POD.

### Table 2 Surgical intervention

|                        | N group (n = 52) | S group (n = 36) | p value |
|------------------------|-----------------|-----------------|---------|
| OPCAB                  | 7 (13.4%)       | 9 (25.0%)       | 0.219   |
| Operative time (min)   | 436.2 ± 103.9   | 391.7 ± 139.4   | 0.090   |
| Circulation time (min) | 210.3 ± 74.7    | 231.4 ± 119.7   | 0.392   |
| Minimum rectum temperature (°C) | 35.1 ± 0.8 | 34.9 ± 1.2 | 0.584 |
| Use of IABP            | 4 (7.7%)        | 1 (2.7%)        | 0.513   |

OPCAB: off-pump coronary artery bypass grafting; IABP: intra-aortic balloon pumping

### Table 3 Postoperative complication

|                          | N group (n = 52) | S group (n = 36) | p value |
|--------------------------|-----------------|-----------------|---------|
| Re-stenotomy             | 1 (1.9%)        | 2 (5.6%)        | 0.362   |
| Mediastinitis            | 2 (3.8%)        | 2 (5.6%)        | 0.709   |
| Atrial fibrillation      | 17 (32.7%)      | 7 (19.4%)       | 0.174   |
| Renal failure (Cre >1.5 mg/dL) | 10 (19.2%) | 5 (13.9%) | 0.518  |
| Re-intubation            | 1 (1.9%)        | 1 (2.8%)        | 0.794   |

POD: postoperative delirium

### Table 4 Clinical outcome

|                          | N group (n = 52) | S group (n = 36) | p value |
|--------------------------|-----------------|-----------------|---------|
| Intubation time (hour)   | 24.0 ± 25.3     | 17.2 ± 8.2      | 0.120   |
| ICDSC                    | 2.0 ± 1.7       | 0.8 ± 1.0       | 0.0003  |
| POD (ICDSC >4)           | 11 (21.2%)      | 1 (2.8%)        | 0.008   |
| ICU stay (day)           | 6 (3–12)       | 5 (3–8)         | 0.001   |
| Hospital stay (day)      | 23 (14–41)     | 20 (12–29)      | 0.035   |
| Hospital death           | 0 (0%)         | 0 (0%)          |         |

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

### Discussion

The present study showed that Suvorexant reduced the incidence of POD in patients after CABG, and that Suvorexant shortened length of ICU and hospital stay. One of the strong risk factors for delirium is arterial sclerosis, and all patients underwent with CABG are affected with arterial sclerosis. So, POD remains a common complication following CABG.¹²

Neurologic complication after cardiac intervention is a complex problem, and perioperative factors may be responsible for this neurologic injury. Although the complexity of surgical procedures and the population increasing high ages are as part of causes, significant advances
of all aspects of perioperative care of cardiac surgery are now much safer than ever past.\textsuperscript{9)} Despite improvements of surgical and anesthetic techniques, POD remains a major complication following CABG. The incidence of POD was reported widely among studies, ranging from 37\% to 52\%\textsuperscript{1,2)} It is associated with short-term complications including increase in mortality, morbidity, costs, and length of stay. And POD is also associated with long-term outcomes, such as the development of persistent cognitive deficits, loss of independence, and increased mortality within 2 years\textsuperscript{10)}.

The mechanism of POD following CABG still remains unclear. Several factors are related to cerebral ischemia-reperfusion injury, endothelial dysfunction\textsuperscript{11)} neuro-inflammation\textsuperscript{12)} and neuro-transmitter imbalances.\textsuperscript{13,14)} Intraoperative brain injuries are caused by hypo-perfusion, arrhythmia, rapid rewarming, and systemic inflammation.\textsuperscript{15–17)} Preventing such brain injury is to prevent these events occurring. In this study, additionally, the individual baseline risk to develop POD is determined by a lot of causative factors such as high age, male gender, psychiatric illness, cognitive impairment, and atherosclerotic diseases.\textsuperscript{19)} However, no significant difference in the operative factors was observed between both groups in our study (Tables 1 and 2).

Martin et al. reported that renal dysfunction was one of the risk factors for POD development after CABG.\textsuperscript{18)} Renal dysfunction is studied as the most important patient characteristics when performing endovascular aortic repair.\textsuperscript{19)} In the present study, we investigated patients excluded dialyzed patients, and there was no significant difference in perioperative prevalence of CKD (Tables 1 and 3).

Many drugs were reported to be associated with delirium. Benzodiazepine\textsuperscript{20)}, steroid, drugs for Parkinsonism, antidepressant agent, and H2 blocker may be a risk factor for development of delirium. Especially, use of benzodiazepine caused delirium. In our study, patients with benzodiazepine sedative-hypnotic agent for insomnia after CABG were excluded.

There were a few studies to reduce the incidence of POD. Tmimi et al. reported general anesthesia with xenon significantly reduced the incidence of POD in old patients undergoing elective cardiac surgery with the use of cardiopulmonary bypass.\textsuperscript{21)} The noble gas xenon has effected neuro-protection in in-vitro and in-vivo models of neuronal injury, including neurocognitive dysfunction after cardiac surgery.\textsuperscript{22,23)}

A lot of past studies have proved that statins had the capability to improve perioperative neuronal protection.\textsuperscript{24)} Statins have important pleiotropic effects, such as anti-inflammatory, immunomodulatory, and antithrombotic properties. Statin administration has reduced POD\textsuperscript{25,26)} although counter results have been reported after cardiac surgery.

Suvorexant is reported to be the most advanced dual orexin receptor antagonist. Clinical data have collected in various population of young and elderly insomnia patients, of both sexes.\textsuperscript{27–28)} Suvorexant also has demonstrated improvement in both sleep and maintenance, and does not need to be adjusted for renal impairment.\textsuperscript{28)} Recently, the ability of Suvorexant to prevent delirium in ICU\textsuperscript{29)} and postoperative patients\textsuperscript{30)} was reported. However, it has not been reported whether Suvorexant improves POD after cardiac surgery yet. In the present study, we demonstrated Suvorexant was...
useful for preventing for POD (Tables 4 and 5). We investigated that almost POD involved within the 3 days after CABG (data not shown). So we do not think the incidence of POD will be reduced without Suvorexant, if ICU stay was 2 days long. Unfortunately, mechanism in action of Suvorexant was unclear in our study, but its improvement for POD could be associated with good sleep (data not shown) that created sustainable postoperative care. Further studies are needed to confirm our results.

The results of this study should be interpreted in certain limitations. First, our study is a retrospective study. Second, the present study was a single-center experience, and as a result was limited by the relatively small number of patients included. Therefore, further prospective studies with a large group are expected.

Conclusion

Suvorexant could improve sleep and reduce incidence of POD in patients after CABG. This orexin receptor antagonist is thought to be a useful medication used in ICU after CABG.

Disclosure Statement

There is no conflict of interest for this article.

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