Safety of Orexin Receptor Antagonist on Cardiac and Respiratory Function in Patients who Underwent Off-pump Coronary Artery Bypass Grafting

Kiyoshi Tamura, Toshiyuki Maruyama, and Shogo Sakurai

Objective: We assessed the safety of Suvorexant, an orexin receptor antagonist, on cardiac and respiratory function in patients who underwent off-pump coronary artery bypass grafting (OPCAB) retrospectively.

Materials and methods: We investigated 66 patients including 16 women (mean age 71.6 ± 8.1 years) who underwent OPCAB alone at our hospital. Patients were categorized as those received orexin receptor antagonist after OPCAB (S-group, n=35) or without orexin receptor antagonist (N-group, n=31), and the following data were analyzed between both groups. Results: The incidence of postoperative delirium was significantly lesser in the S-group than in the N-group (N vs. S = 32.3 % vs. 8.6 %, p=0.004). Intensive care unit stay was also significantly shorter in the S-group compared with the N-group (N vs. S = 4.6 ± 1.1 vs. 4.1 ± 0.8 days, p=0.040). No significant intergroup difference was observed in arterial blood gas measurement (mean the potential of hydrogen, partial pressure of oxygen, the partial pressure of carbon dioxide, base excess, and respiratory rate) and circulation statement (systolic arterial blood pressure, pulmonary artery wedge pressure, heart rate, cardiac index, and mixed venous oxygen saturation) before and after the administration of Suvorexant. Conclusion: Orexin receptor antagonists didn’t worsen the cardiac function and the respiratory function in patients who underwent OPCAB.

KEY WORDS: cardiac function, coronary artery bypass grafting, orexin receptor antagonist, respiratory function

I. Introduction

Suvorexant is an orexin receptor antagonist for the treatment of insomnia, and many studies reported the effect\(^1\). Suvorexant improved sleep as assessed by the Insomnia Severity Index, and improved the impact of insomnia on daytime function/quality-of-life, too\(^2\). Additionally, the recent studies reported that Suvorexant had the efficacy for the prevention of delirium during acute hospitalization\(^3,4\). There are a few reports about the respiratory effect of Suvorexant\(^5,6\). Though Shitara et al.\(^6\) reported that Suvorexant could be used in heart failure patients without affecting their sleep-disordered breathing, there were few studies to investigate the respiratory effect of Suvorexant after cardiac surgery. Additionally, there were few reports to demonstrate whether Suvorexant affected the cardiac functions. So, this study aims to examine the effect on the respiratory and the cardiac function of Suvorexant in patients who underwent off-pump coronary artery bypass grafting (OPCAB).

II. Materials and methods

This retrospective study was approved by the Institutional Review Board of Soka Municipal Hospital, and written informed consent was obtained from all of the patients included in this study.

A total of 187 consecutive patients undergoing elective coronary artery bypass grafting (CABG) at our hospital between February 2013 and June 2020. In our hospital, as a unit policy weaning from a respirator was not performed on the day of operation. We excluded patients who underwent an emergency operation, and those with a mental disorder, a sleep disorder and dementia. Though artificial heart-lung apparatus affects postoperative respiratory function, 66 patients who underwent OPCAB (16 women, mean age 71.6 ± 8.1 years) were included.

Induction and maintenance of anesthesia were similar in all patients who received weight-related doses of fentanyl, midazolam, and pancuronium bromide.
After CABG, all patients received the usual dosage of propofol for sedation until they were weaned from a respirator. To avoid over-sedation, sedation levels were controlled using The Richmond Agitation-Sedation Scale scores\(^{(10)}\), which were maintained between 0 and 2 points in all patients admitted to the intensive care unit (ICU). Acetaminophen was used for pain control; the Behavioral Pain Scale scores\(^{(11)}\) were maintained at < 5 points in all patients. As per our unit policy, weaning from the respirator was not performed on the day of operation. After weaning from the respirator, the postoperative rehabilitative program was initiated on the first postoperative day.

All patients who fulfilled the standard discharge criteria were transferred from the ICU to the general ward, except patients with indwelling drains and central venous catheters and those who required catecholamine administration.

Suvorexant (Belsomara\(^*\), Merck Sharp & Dohme, Chiyoda-ku, Tokyo, Japan) is one of the sleep medications and has been prescribed since November 2014 in Japan. In our institution, we have administered Suvorexant for patients who had a symptom of insomnia from March 2016. The patients who were prescribed Suvorexant were the S group (n=35). As a reference, the consecutive target patients without Suvorexant were the N group (n=31). 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.

The basic dosing of oral Suvorexant was 20 mg daily, but the patients over seventy-four years old were adjusted to 15 mg daily. After weaning from the respirator, Suvorexant was scheduled from just before falling asleep in ICU at night. Suvorexant was prescribed during hospitalization.

The arterial blood gas was obtained from a catheter placed into the radial artery. Cardiac function was measured with a Swan-Ganz catheter placed into the right internal jugular vein. Maximum blood concentration is attained 90 minutes after the administration of Suvorexant. So, the measures of arterial blood gas and cardiac function were done before and 90 minutes after the administration of Suvorexant.

Postoperative delirium (POD) was diagnosed by the attending physicians and along with the Intensive Care Unit Delirium Screening Checklist (ICDSC)\(^{(12)}\) every day during ICU stay. The ICDSC scorings routinely were performed after CABG in all the patients including the patients without POD. POD was defined as greater than or equal to four scores in ICDSC. When 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 were attained, the patients were 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 A\(_1c\) >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±standard deviation (SD) with ranges. Non-Parametric data were analyzed using contingency tables; the Mann-Whitney U test was used. Parametric data were compared using the Student’s t-test. The chi-squared test was used to analyze data presented in a contingency table. Repeated measured 2-way ANOVA was used to analyze data for the change of cardiac function and respiratory function before and after the administration of Suvorexant. A p-value <0.05 was considered statistically significant. The Stat View for Windows soft, version 6.0 (SAS Institute Inc, Cary, NC) was used for all statistical analyses.

III. Results

The study groups were matched about pre-operative characteristics (Table 1). No statistically significant intergroup differences were observed in the operative characteristics (Table 2).

As per our unit policy, weaning from the respirator was not performed on the day of operation. So, intubation time was longer than usual. In Table 3, there was no significant difference in intubation time between the two groups. There was no patient who performed re-intubation in this study.

The incidence of postoperative delirium was significantly lesser in the S-group than in the N-group (N vs. S =32.3 % vs. 8.6 %, p=0.004).

All patients who fulfilled the standard discharge criteria were transferred from the ICU to the general ward, except patients with indwelling drains and central venous catheters and those who required catecholamine administration. So, the length of ICU stay might be longer than another institute. But, ICU stay was significantly shorter in the S-group than the N-group (N vs. S=4.6 ±1.1 vs. 4.1 ±0.8 days, p=0.040). No significant intergroup differences were observed in the indwelling length of drains and central venous catheters, and no significant intergroup difference was observed in the length of catecholamine use (data not shown).

There was postoperative arterial blood gas measurement before and after the administration of Suvorexant in Table 4. No significant intergroup differences were observed in the mean potential of hydrogen (PH), the partial pressure of oxygen (PO\(_2\)), the partial pressure of carbon dioxide (PCO\(_2\)), base excess (BE) before and after the administration of Suvorexant between both groups. Though the mean dose of oxygen (O\(_2\)) didn’t change before and after the administration of Suvorexant, no significant

— 54 —
Table 1  Demographic characteristics of all patients before interventions

|                      | N-group (n=31) | S-group (n=35) | P value |
|----------------------|----------------|----------------|---------|
| Age (year)           | 70.6 ± 9.0     | 72.5 ± 7.3     | 0.380   |
| Sex (female)         | 8 (25.8%)      | 8 (22.9%)      | 0.784   |
| BMI (kg/m²)          | 23.5 ± 3.2     | 23.7 ± 3.9     | 0.829   |
| Prevalence           |                |                |         |
| Hypertension         | 30 (96.8%)     | 33 (94.3%)     | 0.643   |
| Dyslipidemia         | 27 (82.4%)     | 32 (91.4%)     | 0.575   |
| DM                   | 22 (71.0%)     | 25 (71.4%)     | 0.968   |
| COPD                 | 6 (19.4%)      | 5 (14.3%)      | 0.949   |
| CKD                  | 8 (25.8%)      | 5 (14.3%)      | 0.247   |
| Smoking within a month| 5 (16.1%)     | 6 (17.1%)      | 0.914   |
| Hb (g/dl)            | 13.1 ± 1.8     | 13.1 ± 2.3     | 0.967   |
| CRP (mg/dl)          | 0.7 ± 2.1      | 0.8 ± 1.3      | 0.735   |
| EF (%)               | 58.8 ± 10.7    | 58.9 ± 13.1    | 0.979   |
| Euro score II (%)    | 1.6 ± 0.8      | 1.7 ± 1.0      | 0.626   |

BMI: body mass index, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, PAD: peripheral artery disease, Hb: hemoglobin, CRP: C-reactive protein, EF: ejection fraction

Table 2  Operative characteristics

|                      | N-group (n=31) | S-group (n=35) | P value |
|----------------------|----------------|----------------|---------|
| Number of bypass     | 2.8 ± 1.0      | 3.0 ± 0.8      | 0.410   |
| Operative time (min) | 340.5 ± 89.6   | 315.9 ± 77.1   | 0.235   |
| Use of IABP          | 0 (0%)         | 1 (2.9%)       | 0.351   |
| Use of blood transfusion | 14 (45.2%)   | 20 (57.1%)     | 0.339   |

OPCAB: off-pump coronary artery bypass grafting; SVG: saphenous vein graft, AVR: aortic valve replacement, IABP: intra-aortic balloon pumping

Table 3  Postoperative characteristics

|                      | N-group (n=31) | S-group (n=35) | P value |
|----------------------|----------------|----------------|---------|
| Intubation time (hr) | 16.1 ± 3.6     | 16.9 ± 1.2     | 0.241   |
| Re-stenotomy         | 0 (0%)         | 0 (0%)         |         |
| Mediastinitis        | 0 (0%)         | 1 (2.9%)       | 0.351   |
| Atrial fibrillation  | 9 (29.0%)      | 5 (14.3%)      | 0.148   |
| Re-intubation        | 0 (0%)         | 0 (0%)         |         |
| Delirium             | 10 (32.3%)     | 3 (8.6%)       | 0.004   |
| ICU stay (day)       | 4.6 ± 1.1      | 4.1 ± 0.8      | 0.040   |
| Hospital stay (day)  | 19.7 ± 4.6     | 18.0 ± 4.8     | 0.170   |
| Hospital death       | 0 (0%)         | 0 (0%)         |         |

ICU: intensive care unit

Table 4  The arterial blood gas data before and after the administration of Suvorexant

|                      | N-group (n=31) | S-group (n=35) | P value |
|----------------------|----------------|----------------|---------|
| PH                   | 7.44 ± 0.04    | 7.45 ± 0.03    | 7.46 ± 0.07 | 7.46 ± 0.05 | 0.555 |
| PO₂                  | 88.0 ± 15.5    | 82.4 ± 18.6    | 88.3 ± 13.7 | 80.5 ± 13.0 | 0.181 |
| PCO₂                 | 34.1 ± 5.0     | 35.4 ± 4.4     | 32.2 ± 5.0 | 34.5 ± 5.0 | 0.282 |
| BE                   | -0.9 ± 1.8     | 0.2 ± 1.7      | -0.5 ± 1.2 | 0.2 ± 1.4 | 0.298 |
| Respiratory rate (l/min) | 21.4 ± 3.7    | 20.8 ± 3.6     | 22.3 ± 3.8 | 22.3 ± 2.6 | 0.194 |

PH: potential of hydrogen, PO₂: partial pressure of oxygen, PCO₂: partial pressure of carbon dioxide, BE: base excess
intergroup differences were observed in respiration rate in both groups, too. During the administration of Suvorexant, no significant intergroup differences were observed in the applied dose of O2 (data not shown).

No significant intergroup differences were observed in the circulation statement (systolic blood pressure, pulmonary wedge pressure, heart rate, cardiac index, and mixed venous oxygen saturation) before and after the administration of Suvorexant (Table 5). During the administration of Suvorexant, no significant intergroup differences were observed in the applied dose of catecholamine (data not shown).

IV. Discussion

In this study, we observed no significant differences in the respiratory and cardiac statements before and after the administration of Suvorexant in patients who underwent OPCAB. Compared with the N-group, the S-group showed a significantly lesser incidence of postoperative delirium. Moreover, the length of ICU stay was significantly shorter in the S-group than in the N-group.

Suvorexant has been prescribed since November 2014 in Japan and has been taken up since March 2016 in our hospital. Suvorexant is reported to improve sleep quality and the impact of insomnia on daytime function/quality-of-life. Kario et al.14 demonstrated that Suvorexant administered to elderly patients admitted for acute care provided protection against delirium. And so, Masuyama et al.16 presented that Suvorexant was associated with a lesser 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 antipsychotics10. However, there are a few reports on whether Suvorexant is effective to prevent delirium after cardiac surgery9. The present study showed that the incidence of POD in patients taking Suvorexant was significantly lower than that in patients without Suvorexant (Table 3), suggesting preventive effects of Suvorexant on delirium after CABG.

The respiratory effect of Suvorexant was reported in a few studies6-8,9. In healthy subjects with Suvorexant, the mean saturation of percutaneous oxygen (SpO2) was >96% for all treatments during total sleep time and during both non-REM and REM sleep6. Additionally, Shitara et al.8 presented that Suvorexant could be used in heart failure patients without affecting their sleep-disordered breathing. Sun et al.7,9 reported that no increase in mean apnea-hypopnea index was observed after a 40 mg dose of Suvorexant versus placebo and there was no treatment effect on mean SpO2 during total sleep time in patients with obstructive sleep apnea. However, there were few studies for the respiratory effects of Suvorexant in patients who underwent cardiac surgery. Our data did not suggest an overt respiratory depressant effect with Suvorexant in patients who underwent OPCAB and this orexin receptor antagonist might be generally safe in many situations.

There were few reports to investigate the effect of Suvorexant on cardiac functions. Kario et al.14 reported that Suvorexant had no overall effect on blood pressure in patients with treated hypertension. In our study, no significant intergroup differences were observed in the circulation statement before and after the administration of Suvorexant (Table 5). The orexin receptor antagonist might be safe and useful after cardiac surgery because it would not affect cardiac function. However, further randomized clinical trials are required to definitively establish the safety and effectiveness of Suvorexant.

A retrospective, the small-scale single-center study design is a limitation of this study. Further prospective studies that include a large number of patients are warranted to gain a deeper understanding of this subject.

Table 5 The circulation statement before and after the administration of Suvorexant

|                        | N-group (n=31) | S-group (n=35) | P value |
|------------------------|---------------|---------------|---------|
| Systolic arterial blood pressure (mmHg) | Before administration | After administration | Before administration | After administration | 0.092 |
| Pulmonary wedge pressure (mmHg) | 127.7 ± 14.9 | 126.1 ± 12.6 | 128.6 ± 11.4 | 128.4 ± 12.4 |
| Heart rate (b/min) | 9.2 ± 3.0 | 9.7 ± 2.5 | 8.9 ± 3.4 | 9.4 ± 3.5 | 0.937 |
| Cardiac index (L/m²) | 93.0 ± 12.7 | 92.7 ± 12.5 | 92.8 ± 13.2 | 91.3 ± 10.8 | 0.337 |
| SVO2 (%) | 3.0 ± 0.6 | 3.0 ± 0.5 | 3.2 ± 0.7 | 3.2 ± 0.6 | 0.439 |
| SVO2: mixed venous oxygen saturation | 70.1 ± 11.0 | 68.8 ± 11.9 | 68.1 ± 8.9 | 67.4 ± 10.5 | 0.647 |
V. Conclusion

Orexin receptor antagonists didn’t worsen the respiratory and cardiac functions of patients undergoing OPCAB. Suvorexant is thought to be a useful medication used in ICU and during hospitalization after CABG.

Conflicts of interest

There is no conflict of interest for this article.

References

1) Herring WJ, Connor KM, Snyder E, et al: Effects of suvorexant on the Insomnia Severity Index in patients with insomnia: analysis of pooled phase 3 data. Sleep Med 2019; 56: 219–223
2) Takeuchi Y, Sano H, Asai Y, et al: Real-world evidence of the safety and efficacy profile of suvorexant in elderly patients with insomnia: A sub-analysis of the post-marketing drug-use results survey in Japan. Curr Med Res Opin 2020; 36: 465–471
3) Adams AD, Pepin MJ, Brown JN: The role of suvorexant in the prevention of delirium during acute hospitalization: A systematic review. J Crit Care 2020; 59: 1–5
4) Kawada K, Ohta T, Tanaka K, et al: Addition of suvorexant to ramelteon therapy for improved sleep quality with reduced delirium risk in acute stroke patients. J Stroke Cerebrovasc Dis 2019; 28: 142–148
5) Tamura K, Maruyama T, Sakurai S: Preventive effect of suvorexant for postoperative delirium after coronary artery bypass grafting. Ann Thorac Cardiovasc Surg 2019; 25: 26–31
6) Shitara J, Kasa T, Sato A, et al: Effects of suvorexant on sleep apnea in patients with heart failure: A protocol of crossover pilot trial. J Clin Cardiol 2019; 74: 90–94
7) Sun H, Palcza J, Card D, et al: Effects of suvorexant, an orexin receptor antagonist, on respiration during sleep in patients with obstructive sleep apnea. J Clin Sleep Med 2016; 12: 9–17
8) Uemura N, McCrea J, Sun H, et al: Effects of the orexin receptor antagonist suvorexant on respiration during sleep in healthy subjects. J Clin Pharmacol 2015; 55: 1093–1100
9) Sun H, Palcza J, Rosenberg R, et al: Effects of suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with chronic obstructive pulmonary disease. Respir Med 2015; 109: 416–426
10) Sessler CN, Gosnell MS, Grap MJ, et al: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166: 1338–1344
11) Payen JF, Bru O, Bosson JL, et al: Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001; 29: 2258–2263
12) Bergeron N, Dubois MJ, Dumont M, et al: Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001; 27: 859–864
13) Hatta K, Kishi Y, Wada K, et al; DELIRIA-J Group: Preventive effects of suvorexant on delirium: A randomized placebo-controlled trial. J Clin Psychiatry 2017; 78: e970–e979
14) Masuyama T, Sanui M, Yoshida N, et al: Suvorexant is associated with a low incidence of delirium in critically ill patients: A retrospective cohort study. Psychogeriatrics 2018; 18: 209–215
15) Kario K, Yamazaki K, Yagi K, et al: Effect of suvorexant on nighttime blood pressure in hypertensive patients with insomnia: The SUPER-i study. J Clin Hypertens (Greenwich) 2019; 21: 896–903