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Original Article

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

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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.

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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 could induce POD, patients with 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.

Suvorevant (Belsomura, Merck Sharp & Dohme, Tokyo, Japan) has been sold since November 2014 in Japan, so we have administered Suvorevant 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 genera ward in our institute.

Table 1 Demographic characteristics of all patients before interventions

	N group (n = 52)	S group (n = 36)	p value
Age (year)	70.0 ± 8.9	68.3 ± 10.4	0.418
Sex (male)	44 (92.3%)	32 (88.9%)	0.571
Prevalence			
Hypertension			
Dyslipidemia	45 (84.6%)	33 (91.7%)	0.462
DM	39 (75.0%)	31 (86.1%)	0.208
CKD	28 (53.8%)	20 (55.6%)	0.876
Smoking within a month	3 (5.8%)	2 (5.6%)	0.967
Hb (g/dL)	10 (19.2%)	9 (25.0%)	0.523
	13.3 ± 1.7	13.2 ± 1.9	0.833

DM: diabetes mellitus; CKD: chronic kidney disease; Hb: hemoglobin; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease (excluded patients with hemodialysis).

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 (excluded 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**,

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 (□)	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

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.

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.[1,2)]

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

Table 5 Multivariate logistic regression analysis for POD

Variables	Odds ratio (95% confidence interval)	P value
Preoperative characteristics		
Male	2.35 (0.24–22.70)	0.461
Age >75 years	3.85 (1.00–14.70)	0.049
Surgical intervention		
Use of IABP	1.03 (0.17–6.13)	0.972
OPCAB	0.93 (0.16–5.51)	0.994
Postoperative complication		
Re-stenotomy	3.34 (0.12–9.30)	0.477
Mediastinitis	1.54 (0.33–7.33)	0.585
Atrial fibrillation	1.04 (0.27–4.03)	0.953
Renal failure (Cre >1.5 mg/dL)	1.55 (0.33–7.21)	0.575
Re-intubation	3.34 (0.12–9.30)	0.477
Use of Suvorexant	0.42 (0.18–0.98)	0.028

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

of all aspects of perioperative care of cardiac surgery are now much safer than ever past.[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%.[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.[10]

The mechanism of POD following CABG still remains unclear. Several factors are related to cerebral ischemia-reperfusion injury, endothelial dysfunction,[11] neuro-inflammation,[12] and neuro-transmitter imbalances.[13,14] Intraoperative brain injuries are caused by hypo-perfusion, arrhythmia, rapid rewarming, and systemic inflammation.[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.[2] 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.[18] Renal dysfunction is studied as the most important patient characteristics when performing endovascular aortic repair.[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,[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.[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.[22,23]

A lot of past studies have proved that statins had the capability to improve perioperative neuronal protection.[24] Statins have important pleiotropic effects, such as anti-inflammatory, immunomodulatory, and antithrombotic properties. Statin administration has reduced POD[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.[27–28] Suvorevant also has demonstrated improvement in both sleep and maintenance, and does not need to be adjusted for renal impairment.[28] Recently, the ability of Suvorexant to prevent delirium in ICU[29] and postoperative patients[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.

References

1) Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc 2010; **58**: 643-9.
2) Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011; **112**: 1202-11.
3) Trabold B, Metterlein T. Postoperative delirium: risk factors, prevention, and treatment. J Cardiothorac Vasc Anesth 2014; **28**: 1352-60.
4) Pisani MA, Murphy TE, Van Ness PH, et al. Characteristics associated with delirium in older patients in a medical intensive care unit. Arch Intern Med 2007; **167**: 1629-34.
5) Belsomra [package insert]. Kenilworth, NJ: Merck & Co., Inc; Revised August 2014.
6) Sessler CN, Gosnell MS, Grap MJ, et al. The richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; **166**: 1338-44.
7) 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**: 2258-63.
8) Bergeron N, Dubois MJ, Dumont M, et al. Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med 2001; **27**: 859-64.
9) Selnes OA, McKhann GM, Borowicz LM, et al. Cognitive and neurobehavioral dysfunction after cardiac bypass procedures. Neurol Clin 2006; **24**: 133-45.
10) Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012; **367**: 30-9.
11) Hughes CG, Morandi A, Girard TD, et al. Association between endothelial dysfunction and acute brain dysfunction during critical illness. Anesthesiology 2013; **118**: 631-9.
12) Cerejeira J, Firmino H, Vaz-Serra A, et al. The neuroinflammatory hypothesis of delirium. Acta Neuropathol 2010; **119**: 737-54.
13) Young BK, Camicioli R, Ganzini L. Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. Drugs Aging 1997; **10**: 367-83.
14) Hshieh TT, Fong TG, Marcantonio ER, et al. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. J Gerontol A Biol Sci Med Sci 2008; **63**: 764-72.
15) Newman MF, Mathew JP, Grocott HP, et al. Central nervous system injury associated with cardiac surgery. Lancet 2006; **368**: 694-703.
16) McKhann GM, Grega MA, Borowicz LM Jr, et al. Stroke and encephalopathy after cardiac surgery: an update. Stroke 2006; **37**: 562-71.
17) Grocott HP. Pharmacologic neuroprotection: the search continues. J Extra Corpor Technol 2007; **39**: 296-301.
18) Martin BJ, Buth KJ, Arora RC, et al. Delirium: a cause for concern beyond the immediate postoperative period. Ann Thorac Surg 2012; **93**: 1114-20.
19) Kawatani Y, Nakamura Y, Hayashi Y, et al. Development of delirium in the intensive care unit in patients after endovascular aortic repair: a retrospective evaluation of the prevalence and risk factors. Crit Care Res Pract 2015; **2015**: 405817.
20) Gaudreau JD, Gagnon P, Roy MA, et al. Association between psychoactive medications and delirium in hospitalized patients: a critical review. Psychosomatics 2005; **46**: 302-16.
21) Al Tmimi L, Van de Velde M, Herijgers P, et al. Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial. Trials 2015; **16**: 449.
22) Ma D, Yang H, Lynch J, et al. Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. Anesthesiology 2003; **98**: 690-8.
23) Deng J, Lei C, Chen Y, et al. Neuroprotective gases–fantasy or reality for clinical use? Prog Neurobiol 2014; **115**: 210-45.

24) Sironi L, Cimino M, Guerrini U, et al. Treatment with statins after induction of focal ischemia in rats reduces the extent of brain damage. Arterioscler Thromb Vasc Biol 2003; **23**: 322-7.
25) Page VJ, Davis D, Zhao XB, et al. Statin use and risk of delirium in the critically ill. Am J Respir Crit Care Med 2014; **189**: 666-73.
26) Morandi A, Hughes CG, Thompson JL, et al. Statins and delirium during critical illness: a multicenter, prospective cohort study. Crit Care Med 2014; **42**: 1899-909.
27) Sun H, Kennedy WP, Wilbraham D, et al. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. Sleep 2013; **36**: 259-67.
28) Hoyer D, Jacobson LH. Orexin in sleep, addiction and more: is the perfect insomnia drug at hand? Neuropeptides 2013; **47**: 477-88.
29) Hatta K, Kishi Y, Wada K, et al. Preventive effects of suvorexant on delirium: a randomized placebo-controlled trial. J Clin Psychiatry 2017; **78**: e970-9.
30) Booka E, Tsubosa Y, Matsumoto T, et al. Postoperative delirium after pharyngolaryngectomy with esophagectomy: a role for ramelteon and suvorexant. Esophagus 2017; **14**: 229-34.