

The Efficacy of Risperidone in Reducing the Incidence of Postoperative Delirium in Vascular Surgery Patients: Preliminary Report of a Randomized Controlled Trial

Orawan Pongraweevan¹, Panate Pukrittiyakamee^{2,3}, Tachawan Jirativanont¹, Aphichat Suphathamwit¹, Pimpisa Konateerakul¹, Phatcharakamon Mahothorn¹

¹Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

²Department of Psychiatry, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

³Integrated Perioperative Geriatric Excellent Research Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: Postoperative delirium (POD) increases postoperative morbidity, mortality, and health care costs. POD has many risk factors, such as old age, preoperative cognitive impairment, alcohol abuse, malnutrition, multiple comorbidities, and vascular disease. Risperidone has been reported as effective in POD prevention and treatment. This study investigated the effectiveness of risperidone in reducing the incidence of POD in vascular patients.

Materials and Methods: Patients undergoing vascular surgery were assigned randomly to two groups. Those in the risperidone group received sublingual disintegrating risperidone (1 mg) within one hour after surgery, while the placebo-group patients received a sublingual Listerine strip. All patients were evaluated for POD using the CAM-ICU twice daily for seven days, with the DSM-5 delirium criteria being used to confirm POD by a psychiatrist blinded to the group allocations. The possible risk factors for POD were recorded.

Results: The study unfortunately needed to be terminated early as supplies of orally disintegrating risperidone became unavailable in Thailand. Of the 35 participating vascular surgery patients, 17 were in the risperidone group, and 18 in the control. One patient (5.6%) in the former group and one individual (5.9%) in the latter were diagnosed with POD. The overall POD incidence was 5.7%. The groups demonstrated no statistically significant differences in baseline characteristics, possible risk factors, or lengths of hospital stay.

Conclusion: The study could not demonstrate the impact of orally disintegrating risperidone (1 mg) on the incidence of POD among vascular-surgery patients due to the very low incidence and inadequate sample size.

Keywords: CAM-ICU, disintegrating risperidone, postoperative delirium, sublingual, vascular surgery

วิทยุสาร 2564; 47(1): 23-29. • Thai J Anesthesiol 2021; 47(1): 23-29.

Introduction

Postoperative delirium (POD) is characterized by an onset which is sudden; a varying clinical course; an abnormal level of consciousness; inattention; disorientation to person, place and time; and perceptual and sleep-wake-cycle disturbances.¹ The incidence of

POD in old-age vascular patients is 29%-39%.²⁻⁴ POD in patients who underwent open thoracoabdominal aortic aneurysm surgery has been reported to be as high as 55.6%.² POD in surgical patients is associated with increased incidences of mortality as well as multiple complications, such as falls, fractures, and infections.

Correspondence to: Orawan Pongraweevan, M.D., Email: Orawan.pon@mahidol.ac.th

Received 13 Mar 2020, Revised 20 June 2020, Accepted 21 June 2020

The length of hospital and intensive care stay is also longer for delirium patients.^{5,6}

The risk factors for POD are a patient age > 65 years; preoperative cognitive impairment; alcohol abuse; malnutrition; multiple comorbidities; and the undergoing of open heart, vascular or hip-fracture surgery.⁷ The pathophysiology of POD remains unclear. One hypothesis for its pathogenesis is related to a deficiency in serotonin levels caused by a depletion of tryptophan and a rise in phenylalanine.² Although the large majority of patients recover completely after several days, some may experience long-term cognitive dysfunction.⁵

Risperidone is an atypical antipsychotic drug that has similar effects to haloperidol, but with a smaller incidence of adverse neurological effects. A study by Prakarnrattana et al. demonstrated that sublingual disintegrating risperidone reduces the incidence of POD after cardiac surgery.⁸

The objective of the present study is to compare the efficacies of risperidone and a placebo in lowering the incidence of POD among vascular surgery patients.

Materials and Methods

This prospective, single-blinded, randomized, and placebo-controlled trial was conducted at Siriraj Hospital, Bangkok, Thailand, between April 2017 and April 2018. The study was approved by the Institutional Review Board of the Faculty of Medicine, Mahidol University (Si 165/2017) and registered with the Thai Clinical Trials Registry (TCTR 20170724002).

Written, informed consent was obtained from each participant the day before surgery. The inclusion criteria were patients aged > 60 years who were undergoing elective vascular surgery with an operative time > 2 hours. The exclusion criteria were patients with cognitive impairment (a Thai Mental State Examination score < 24); evidence of alcohol abuse, alcohol ingestion occurring in the 14-day period preceding the surgery; preoperative delirium (shown by a positive result with the Confusion Assessment Method for the Intensive Care Unit, CAM-ICU); severely impaired renal

function (demonstrated by a creatinine clearance < 0 mL/min/1.72 m²); hepatic impairment (a Child Pugh score ≥ 10); an allergy to risperidone; and neuroleptic malignant syndrome.

All participants received premedication based on their underlying disease. Benzodiazepine was avoided at any time from the first preoperative day to the seventh postoperative day. The anesthesia techniques comprised general anesthesia (GA) for carotid surgery, aortic surgery, and a peripheral arterial bypass; intravenous sedation plus local anesthesia for percutaneous endovascular revascularization; and either regional anesthesia or GA for endovascular abdominal aortic aneurysm (AAA) repair. The GA participants received intravenously administered fentanyl (1-2 mg/kg) and propofol (1-2 mg/kg). Endotracheal intubations employed using cisatracurium (0.15 mg/kg) when the train-of-four count equaled 0. The anesthesia level was maintained with desflurane, fentanyl, and cisatracurium. The ventilator settings were set for a low tidal volume (6-8 mL/kg, PEEP 5 cmH₂O), and the rate of respiration was varied to ensure the end-tidal carbon dioxide was maintained at 35-40 mmHg. The bispectral index was maintained between 40 to 60 mmHg. At the conclusion of the operation, neostigmine (2.5 mg) and glycopyrrolate (0.4 mg) were administered. All participants were extubated when the standard extubation criteria were obtained and the train-of-four ratio was ≥ 0.9. The IV sedation participants received fentanyl (1-2 mcg/kg) to maintain a mild to moderate sedation level and a numeric rating pain score < 5. The mean arterial pressure was kept > 60 mmHg and the temperature > 35 degrees Celsius, and packed red cells were administered when the hematocrit level was < 25%.

Within the first hour after surgery, sealed envelopes were used to randomly allocate participants to one of the two trial groups. Upon patients regaining consciousness, a nurse anesthetist gave sublingual disintegrating risperidone tablet (1 mg) to the individuals in the risperidone arm and group sublingual Listerine strip to second group. That nurse was not involved in the

subsequent POD detection process. All participants were evaluated for POD by using the CAM-ICU by the research assistants, who had been well trained in CAM-ICU testing and were blinded to the group allocations. The CAM-ICU is an algorithm that diagnoses four key POD characteristics: an acute onset of POD or a fluctuating clinical course, an inability to maintain attention, a lack of organization in thinking, and changes in a patient's consciousness level. POD evaluations using the CAM-ICU were performed on all participants twice daily for seven days. A psychiatrist who was blinded to the group allocations was informed whenever a participant's CAM-ICU result was positive. Confirmation of the POD diagnosis was made by the psychiatrist using the criteria detailed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Participants diagnosed with POD then received treatment in accordance with hospital protocols. The results of the treatment and any postoperative complications were recorded.

Unfortunately, after 37 participants had participated in the study, the research team was informed that the orally disintegrating risperidone tablet was no longer available in Thailand. The team decided to stop the project and produce a preliminary report. The future planned project is using the risperidone oral solution instead of the orally disintegrating form.

Statistical analysis

The sample size was predetermined. A power analysis was performed using an estimated POD incidence of 48% for the participants in the placebo arm. A reduction from 50% was considered clinically significant, with a 5% type-one error ($\alpha = 0.05$) and a power ($1 - [\text{beta}]$) of 80%. Assuming a 12% dropout rate, the sample size needed for each study arm was 62 patients. Hence, the total size was calculated to be 150 patients, or 75 patients per group.

Continuous variables were compared using the independent Student t-test and Mann-Whitney U test, while the chi-square test was employed for categorical variables. All analyses were performed using SPSS

Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

This study had to be terminated early because the orally disintegrating risperidone preparation did not available in Thailand. Of the 67 initial potential participants, 30 were excluded because either they declined to participate or the inclusion criteria were not met. A 2 enrolled participants (one in each study arm) were absent for the POD test (Figure 1). That 35 participants who completed the analysis (17 in the risperidone arm, and 18 in the placebo group).

The baseline characteristics of the participants (Table 1), patient age sex, body mass index, ASA classification, presenting disease, and preoperative laboratory were not significant different. The characteristics of the two study arms did not significantly differ.

In addition, the relevant operative and postoperative data of the groups were not statistically significantly different. However, the anesthesia, surgery duration, the amount of urine output and blood loss were slightly higher for the risperidone group than the placebo group (Table 2).

The delirium and length of hospital stay are displayed in Table 3. A provisional diagnosis of POD was made using the CAM-ICU and subsequently confirmed by a psychiatrist using the DSM-5 criteria. One patient (5.6%) in the risperidone arm and another (5.9%) in the placebo arm were diagnosed as having POD; the incidence for the total cohort was 5.7%.

One of the two participants diagnosed as having POD was a male, aged 69, who had an AAA with no comorbidities. He underwent a right internal iliac artery embolization procedure and received a placebo postoperatively. The other participant was a 74-year-old male AAA patient with hypertension and dyslipidemia. He underwent an endovascular AAA repair under general anesthesia and was administered orally disintegrating risperidone after the procedure.

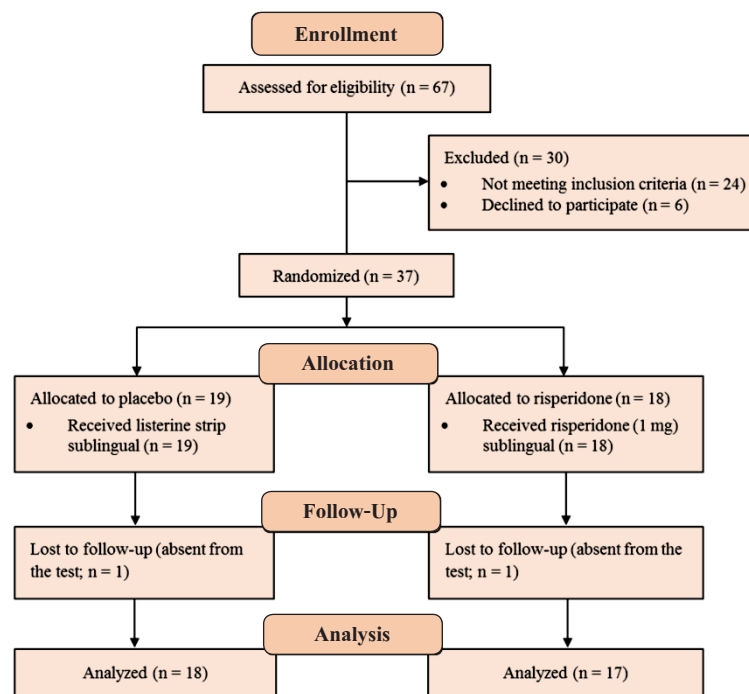


Fig 1 Flowchart outlining patient enrollment, randomization, follow-up, and analysis.

Table 1 Demographic and preoperative data

Variable	Risperidone Group (n = 17)	Placebo Group (n = 18)	P-value
Gender:			0.228
Male	12 (70.6)	16 (88.9)	
Female	5 (29.4)	2 (11.1)	
Age (years)	71.4 ± 6.2	70.7 ± 6.3	0.747
BMI	22.6 ± 3.7	22.3 ± 2.8	0.733
ASA class:			0.443
II	3 (17.6)	6 (33.3)	
III	14 (82.4)	12 (66.7)	
Underlying:			
Hypertension	8 (47.1)	14 (77.8)	0.086
Diabetes mellitus	5 (29.4)	3 (16.7)	0.443
Chronic Kidney Disease	4 (23.5)	1 (5.6)	0.177
Chronic renal failure	6 (35.3)	3 (16.7)	0.264
Laboratory data			
Hct	33.1 ± 11.7	35.2 ± 7.2	0.534
Hb	16.2 ± 9.3	13.5 ± 6.1	0.317
Na	138.6 ± 3.6	137.8 ± 4.5	0.530
K	4.1 ± 0.4	4.0 ± 0.3	0.391
Cl	95.4 ± 20.1	99.3 ± 4.5	0.442
H ₂ CO ₃	26.8 ± 3.0	25.4 ± 2.7	0.156
BUN	15.1 ± 5.8	15.5 ± 5.7	0.811
Cr	1.1 ± 0.3	1.1 ± 0.4	0.892

Data presented as mean ± SD or number (%); ASA: American Society of Anesthesiologists; BMI: body mass index; HCT: Hematocrit; Hb: Hemoglobin; Na: Sodium; K: Potassium; Cl: Chloride; H₂CO₃: Carbonic acid; BUN: blood urea nitrogen; Cr: Creatinine

Table 2 Operative and postoperative data

Variable	Risperidone Group (n = 17)	Placebo Group (n = 18)	P-value
Operation:			
Endovascular AAA repair	11 (61.1)	7 (41.2)	0.543
Percutaneous endovascular revascularization	2 (11.1)	3 (17.6)	
Iliac embolization	2 (11.1)	1 (5.9)	
Peripheral arterial bypass	2 (11.1)	1 (5.9)	
Carotid endarterectomy	1 (5.6)	3 (17.6)	
Open AAA repair	0	2 (11.8)	
Duration of anesthesia (hr)	4.45 ± 2.52	4.25 ± 1.31	0.685
Duration of surgery (hr)	3.50 ± 2.39	3.19 ± 1.19	0.489
Anesthesia technique:			0.437
General anesthesia	8 (47.1)	12 (66.7)	
TIVA/IV sedation	3 (17.6)	2 (11.1)	
Analgesics in recovery room			0.258
Fentanyl	3 (17.6)	1 (5.6)	
Morphine	2 (11.8)	4 (22.2)	
Pethidine	2 (11.8)	0	
Blood loss (mL)	200 (100-700)	200 (75-500)	0.934
Urine (mL)	650 (450-1000)	562 (300-750)	0.116
Low blood pressure (SBP < 90 mmHg/MAP < 60 mmHg)	8 (50.0)	13 (72.2)	0.291

Data presented as mean ± SD or number (%) or median (IQR)

Table 3 Outcomes

Variable	Risperidone Group (n = 17)	Placebo Group (n = 18)	P-value
Delirium	1 (5.9)	1 (5.6)	1.000
Hospital: Length of stay (days)	4.4 ± 1.4	5.0 ± 1.3	0.414

Data presented as mean ± SD or number (%)

Discussion

The DSM-5 defines delirium as a set of neurocognitive disorders and syndromes whose primary symptom is an acquired cognitive dysfunction. The DSM-5 criteria specify that the disorder is characterized by fluctuating disturbances in a patient's attention, an awareness level which has declined from baseline, and evidence of a cognitive dysfunction. The

condition presents in one of several states: hyperactive (increased psychomotor activity, agitation, and mood lability); hypoactive (reduced psychomotor activity and lethargy); or mixed (either the psychomotor activity fluctuates between the hyperactive and hypoactive states or, more rarely, there is normal psychomotor activity with disordered attention and awareness). The current investigation established an overall POD

incidence of 5.7%, which was lower than the corresponding figures reported by several studies of vascular patients.²⁻⁴ The differences in the reported incidences may stem from different study populations, different age groups, the confounding factors, and the diagnostic criteria. A systematic review by Raats et al. found the POD incidence among elective vascular surgery patient ranged from 0%-65%; endovascular AAA repair had the lowest incidence, and open aortic repair the highest.⁹ In the present study, a slight majority of vascular patients (n = 18, 51.4%) underwent endovascular AAA repair, with a POD incidence of 5.56%. Two patients who underwent open AAA repair did not have POD. The mean age of all participants in the current study was 71 years; an older age has been reported as a risk factor for POD.^{3,9}

In order to control confounding factors, the present study avoided benzodiazepines, used the bispectral index as a guide to the anesthetic depth, controlled the hematocrit levels, and avoided hypotension. All of these are risk factors for POD, and they could explain the low incidence of POD found in this study. Risperidone, a second-generation antipsychotic, has an affinity for the D2, 5-HT2A, alpha1, alpha 2, and H1 receptors, with the ability to block the D2 and 5-HT2A receptors.¹⁰ Risperidone reaches its mean peak plasma concentration approximately an hour after its administration (orally, either in tablet or solution form), making it suitable for prophylaxis administration. In a randomized, placebo-controlled trial, the POD incidence dropped from 31.7% to 11.1% following the administration of orally disintegrating risperidone (1 mg) given after cardiac surgery.⁸ In contrast, the current study saw no difference in the incidence of POD in the risperidone and placebo groups.

One possible factor contributing to variations in the reported incidences of POD is the methodology employed for delirium assessment. Using the Neelon and Champagne (NEECHAM) confusion scale, Katznelson et al. reported a POD incidence of 22% among vascular surgery patients (excluding carotid surgery).¹¹ However, the NEECHAM delirium scale is

not suitable intubated patients, and it still lacks validation against the DSM criteria for delirium.¹² In comparison, the CAM-ICU is a practical tool which can be readily utilized by trained nurses and physicians, and assessments can be performed within 5 minutes with high inter-rater reliability.¹³ Moreover, the CAM-ICU has been validated against the gold standard, DSM-4.^{14,15} The present study used the CAM-ICU to detect possible incidents of POD, and a psychiatrist subsequently confirmed the diagnosis using the DSM-5 criteria as the gold standard.

Limitations: The trial was terminated early because the orally disintegrating risperidone preparation became unavailable, resulting in an inadequate sample size. In addition, the incidence of POD was very low. That may have been because prospective patients were excluded if they had a severe renal impairment (35% of the eligible participants), which is a high risk factor for postoperative POD. The future proposed study referred to earlier will be based on the risperidone oral solution and may include patients with severe renal impairments. If they are, the risperidone dosage will be reduced to avoid overdose, in accordance with the pharmaceutical company recommendations.¹⁶

Conclusion

The current study could not demonstrate the effect of sublingual disintegrating risperidone (1 mg) on the incidence of postoperative delirium in vascular patients.

Acknowledgements

This research project was facilitated by the faculty's Integrated Perioperative Geriatric Excellence Research Center. The authors thank Suthipol Udompanthurak of the faculty's Clinical Epidemiology Unit for the statistical analysis. We also gratefully acknowledge the administrative assistance provided by Miss Chayan Tanakiattiwibun and Miss Nipaporn Sangarunakul.

Funding: This work was supported by the Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand (reference: [IO] R016034010).

References

1. Kolh P. The burden of postoperative delirium after vascular surgery. *Eur J Vasc Endovasc Surg* 2011;42:831-2.
2. Bohner H, Hummel TC, Habel U, et al. Predicting delirium after vascular surgery: a model based on pre- and intraoperative data. *Ann Surg* 2003;238:149-56.
3. Sasajima Y, Sasajima T, Uchida H, et al. Postoperative delirium in patients with chronic lower limb ischaemia: what are the specific markers? *Eur J Vasc Endovasc Surg* 2000;20:132-7.
4. Schneider F, Bohner H, Habel U, et al. Risk factors for postoperative delirium in vascular surgery. *Gen Hosp Psychiatry* 2002;24:28-34.
5. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443-51.
6. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004;32:955-62.
7. Benson RA, Ozdemir BA, Matthews D, Loftus IM. A systematic review of postoperative cognitive decline following open and endovascular aortic aneurysm surgery. *Ann R Coll Surg Engl* 2017;99:97-100.
8. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care* 2007;35:714-9.
9. Raats JW, Steunenbergh SL, de Lange DC, van der Laan L. Risk factors of post-operative delirium after elective vascular surgery in the elderly: A systematic review. *Int J Surg* 2016;35:1-6.
10. Leysen JE, Janssen PM, Megens AA, Schotte A. Risperidone: a novel antipsychotic with balanced serotonin-dopamine antagonism, receptor occupancy profile, and pharmacologic activity. *J Clin Psychiatry* 1994;55 Suppl:5-12.
11. Katznelson R, Djaiani G, Mitsakakis N, et al. Delirium following vascular surgery: increased incidence with preoperative beta-blocker administration. *Can J Anaesth* 2009;56:793-801.
12. Kallenbach TF, Amado LA. Assessment of delirium in the intensive care unit. *South Afr J Anaesth Analg* 2017;23:57-63.
13. Tomasi CD, Grandi C, Salluh J, et al. Comparison of CAM-ICU and ICDSC for the detection of delirium in critically ill patients focusing on relevant clinical outcomes. *J Crit Care* 2012;27:212-7.
14. Gusmao-Flores D, Salluh JI, Chalhub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care* 2012;16:R115.
15. Neto AS, Nassar AP, Jr., Cardoso SO, et al. Delirium screening in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2012;40:1946-51.
16. Ward S, Roberts JP, Resch WJ, Thomas C. When to adjust the dosing of psychotropics in patients with renal impairment. *Current Psychiatry* 2016;15:60-6.