The Efficacy of Oral Risperidone Solution to Reduce the Incidence and Severity of Postoperative Delirium After Vascular Surgery: A Randomized Controlled Trial

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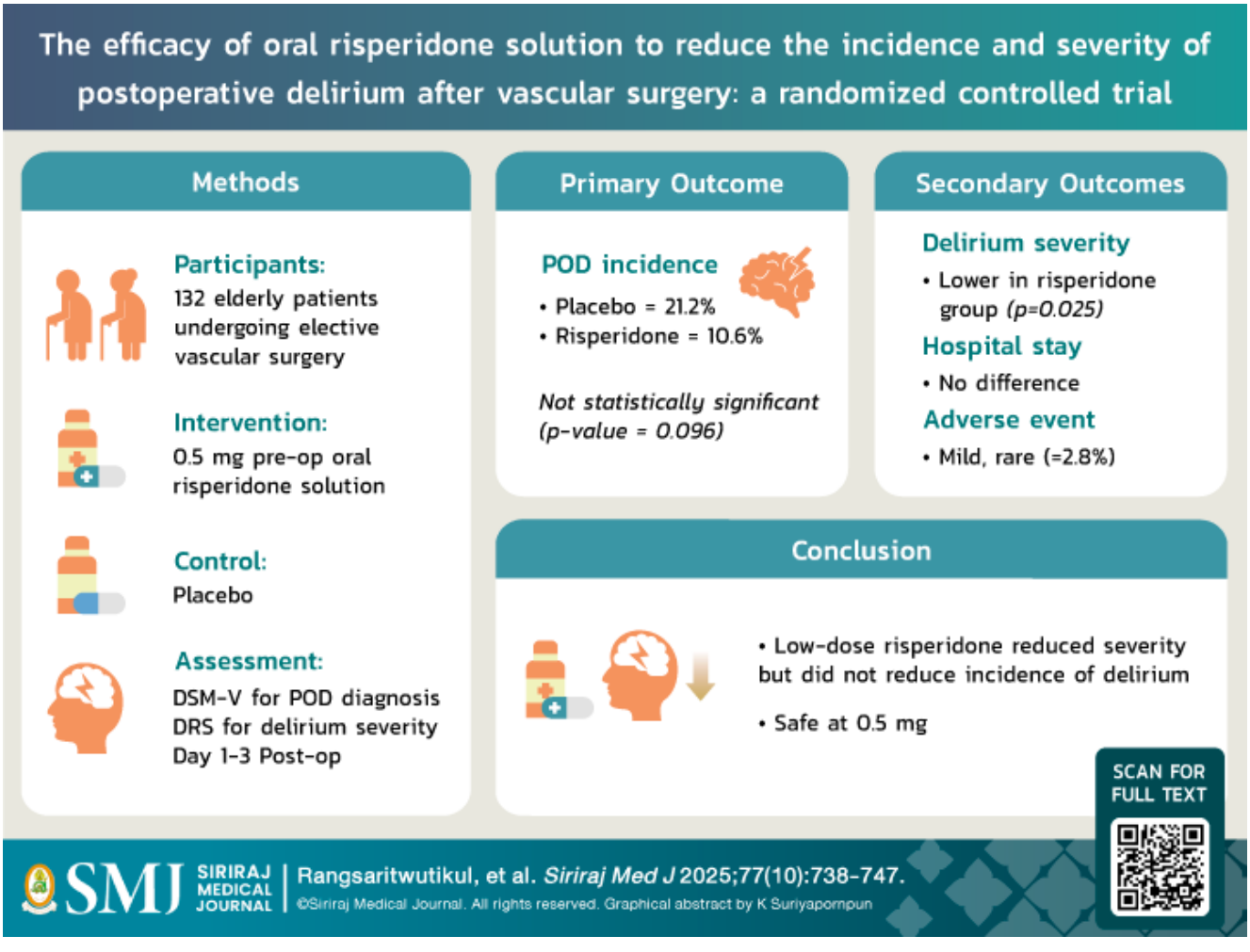

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ABSTRACT

Objective: To determine the efficacy of the preoperative oral solution of risperidone in preventing Postoperative delirium (POD) and reducing the severity of POD in patients with geriatric vascular disease.

Materials and Methods: Randomized, double-blind, placebo-controlled trial. A total of 140 elderly patients scheduled for vascular surgery were enrolled and randomly assigned to either the risperidone group (0.5 mg oral solution of risperidone within 1 hour before surgery) or the placebo group.

Results: POD was assessed daily using the DSM-5 criteria, and its severity was measured with the Delirium Rating Scale (DRS) for the first three days after surgery. The incidence and severity of POD were compared between the two groups. Potential side effects of risperidone, and the length of hospital stay were also recorded. There were no statistical differences in demographic data between the two groups. The incidence of POD was 10.6% compared to 21.2 % in the intervention group without statistical significance (p-value=0.096). However, the severity of POD, measured by the DRS, was significantly lower in the risperidone group (2.0 vs. 6.0, p-value=0.025). The length of hospital stay did not show significant differences between the two groups.

Conclusions: The overall incidence of POD in this study without intervention was 21.2%. Preoperative administration of oral risperidone (0.5mg) reduced the severity of POD, but did not affect the incidence of POD or the length of hospital stay in this population.

Keywords: Vascular surgery; postoperative delirium; risperidone (Siriraj Med J 2025; 77: 738-747)

INTRODUCTION

Postoperative delirium (POD) is a form of delirium that occurs in patients who received surgical procedures and anesthesia. It is common among geriatric surgical patients, and its etiology is not fully understood. For vascular surgical patients alone, the incidence of POD ranges from 33 to 54 %.[1-3] Since this world is becoming an aging society, more geriatric patients undergo surgeries each year. The impact of POD is becoming more significant for perioperative care.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the diagnosis of delirium includes an acute disturbance in attention, cognition, and / or awareness that is not explained by another medical condition or substance intoxication or toxin.[1] Unlike dementia, POD has an acute onset and fluctuates throughout the day. It typically appears during the first three postoperative days.[2] Common risk factors for postoperative delirium include the elderly, preexisting cognitive impairment, history of prior delirium, hip surgery, cardiac surgery, vascular surgery, use of benzodiazepine, alcohol withdrawal, etc.[3]

POD is associated with significant morbidities, increased length of hospitalization, worse surgical outcome, and higher healthcare costs.[4-6] Prevention of POD in this patient group can enhance patient recovery, reduce morbidity and mortality, and hospital fee. The proposed preventive methods include the identification of patients who are at higher risk, the prevention of risk factors, and pharmacological management. Previous studies have found that some medications show benefits for delirium prevention, including some antipsychotic agents and dexmedetomidine.[7,8] However, frail elderly patients can develop significant side effects, including hypotension, hypertension, and bradycardia due to dexmedetomidine.[9]

Antipsychotic agents that were studied for the prevention of POD include haloperidol and risperidone. Haloperidol, a typical antipsychotic, showed conflicting results for postoperative delirium prevention in previous studies.[10-13] Risperidone is an atypical antipsychotic agent with less extrapyramidal side effects such as dyskinesia, dystonia, or Parkinsonism compared to typical antipsychotics. It is also cheap and very accessible and does not have interactions with anesthetic agents. Previous studies showed promising results in preventing POD in patients undergoing elective cardiac surgery with cardiopulmonary bypass.[14,15]

The study by Prakanrattana et al. found that 1 mg of risperidone administered sublingually after awakening on the postoperative ward reduced the incidence of postoperative delirium from 31.7% in the placebo group to 11.1% in the intervention group.[14] Another study by Hakin et al. showed the effectiveness of 0.5 mg of risperidone when given orally every 12 hours in patients with subsyndromal delirium after on-pump cardiac surgery reduced the incidence of delirium from 34% to 13.7%.[15] An adverse effect of risperidone was reported as a mild extrapyramidal syndrome in two patients of the intervention group (3.9%).

We decided to give risperidone preoperatively,

contrary to previous studies, due to its long duration of action and ease of administration. When given at a low dose of 0.5 mg, we expected risperidone to have minimal side effects, while still being effective.[16]

Objectives

The primary objective of this study is to determine the efficacy of preoperative oral risperidone solution 0.5mg for reducing the incidence of POD in surgical vascular patients compared to placebo.

Secondary objectives include demonstrating the incidence of POD in vascular surgical patients, its efficacy in reducing delirium severity and length of hospital stay, and reporting adverse side effects observed in this study.

MATERIALS AND METHODS

Study design

This study is a prospective, double-blind, randomized, placebo-controlled trial conducted at the tertiary-care university hospital. After the study was authorized by the institutional review board. All patients signed an informed consent before enrollment.

Study population

Patients more than 60 years-old who were admitted for an elective aorta, carotid or peripheral vascular surgery and were expected to be under anesthesia for more than 2 hours were included in the study. Exclusion criteria were patients with delirium prior to surgery positive Confusion Assessment for Intensive Care Unit (CAM-ICU) (Thai version) or severe cognitive impairment Thai Mental State Examination (TMSE less than 10)[17,18] history of alcoholic abuse or alcohol ingestion within the 14-day period preceding surgery, history of psychiatric illness, receiving antipsychotic drugs, physical disabilities that limit the evaluation of delirium such as blindness, deafness or mute, liver impairment with Child-Turcotte-Pugh score more than or equal to 10, history of allergy to risperidone, risk of adverse effects from risperidone such as history of neuroleptic malignant syndrome, Parkinson's disease, Parkinsonism or prolongation of QTc, and patients who refused to participate. This study withdrawal or termination criteria included patients who developed cardiac arrest during surgery and patients who received dexmedetomidine or benzodiazepine during the perioperative period.

Sample size calculation

The formula used to calculate the sample size of this study was made with n4 studies program. The formula used is as follow.

$$n = \frac{(Z_1 - \alpha/2\sqrt{2\bar{p}(1-\bar{p})} + Z_1 - \beta\sqrt{p_1(1-p_2) + p_2(1-p_2)})^2}{(p1-p2)^2}$$

Assumptions: we used a two-sided $\alpha = 0.05$ and 80% power ($\beta = 0.2$)

Incidence rates: According to previous studies, the incidence of postoperative delirium in patients undergoing vascular surgery was between 33-54%; we assumed P1 (control incidence) =48% as a mid-range estimate.

Expected effect size: From the study by Prakanrattana et al., risperidone reduced the incidence of postoperative delirium in cardiac surgery patients from 31.7% to 11% compared to placebo. In this study, we hypothesized a 50% relative reduction (P2=24%) with prophylactic risperidone. This estimate was based on prior trials that show a substantial risk reduction. While the dose, timing and population differences might influence effect size; we chose this conservative but clinically meaningful reduction to ensure adequate study power.

The calculated sample size is equal to 62 for each group. Allowing for 10% dropout for protocol deviation and loss to follow-up, we increase the sample size to: treatments = 70, controls = 70. Therefore, the sample size for this study was 70 in each group. The total sample size was 140.

The study outcomes

The primary outcome of this study is the efficacy of risperidone in reducing the incidence of POD in elderly vascular surgical patients. Secondary outcomes include the incidence of POD in this group of patients, the delirium rating scale, and the length of hospital stay.

Study process

Participants who met the inclusion criteria will be recruited from the surgical ward by anesthesiology residents. After written informed consent was obtained from eligible participants, they were screened for severe cognitive impairment and delirium by trained anesthesiology residents using TMSE and CAM-ICU screening tools.

All participants received a preanesthetic evaluation the day before surgery and were premedicated based on their underlying disease. Benzodiazepines were omitted during the perioperative period. The participants were randomized into a 1:1 ratio to the intervention or the control group using simple randomization. A random sequence was generated in advance, and allocation was concealed using sequentially numbered, sealed, and opaque envelopes. A research assistant, who was not involved in patient care or outcome assessment, opened the next enveloped in sequence to assign each participant after

enrollment. The risperidone group received a 0.5ml solution containing 0.5 mg of risperidone while the control group received 0.5 ml of sterile water within 1 hour before surgery (Fig 1). The risperidone and sterile water were prepared by a pharmacist and the solution were labeled by trial name and participations' randomization number. A nurse anesthetist, who did not participate in this study and blinded to the randomization, was assigned to administer these per oral solutions according to the participant's randomization number. Both risperidone and sterile water were matched in volume, color and transparency. However, a blinding test for both solutions was not conducted. Non-invasive blood pressure, EKG and oxygen saturation were monitored before the operation. The attending anesthesiologist selected the type of anesthesia, including general anesthesia (GA), intravenous sedation, regional or local anesthesia.

For the GA technique, participants received fentanyl (1-2 µg/kg) and propofol (1-2 mg/kg) intravenously. Endotracheal intubations were facilitated with cis-atracurium (0.15 mg/kg) when the train-of-four count was equal to 0. The level of anesthesia was maintained with desflurane, fentanyl (1-2 µg/kg/h) and cis-atracurium (1-3 µg/kg/min). The TOF count was maintained between 1 and 2 during the surgery. The anesthesiologist adjusted the concentration of desflurane with the air : oxygen

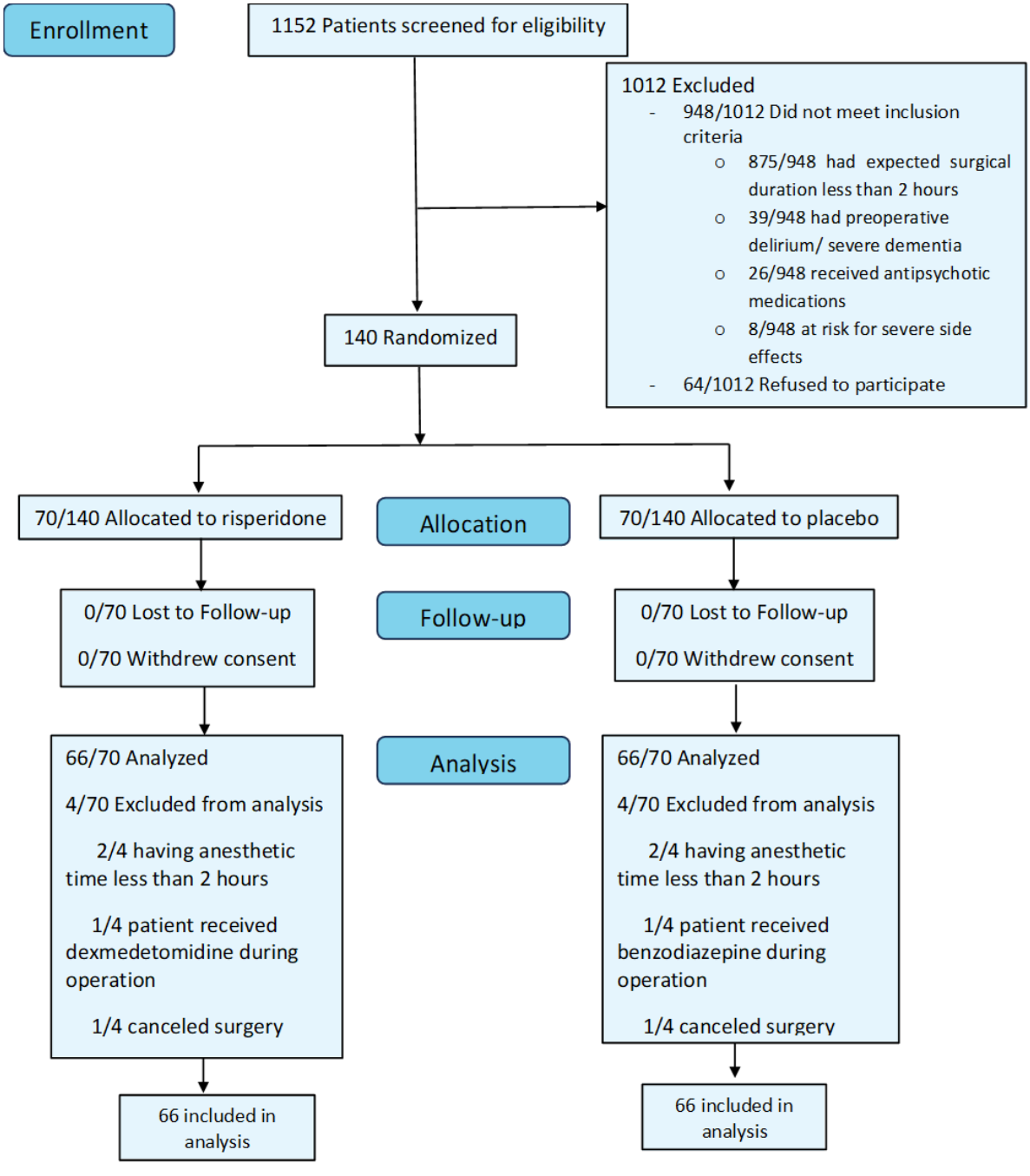

Fig 1. Consort flow diagram.

mixture. Ventilator settings were set for low tidal volume (6-8 ml/kg, PEEP 5 cm H_2O). The respiratory rate was adjusted to keep the end tidal CO_2 between 35 and 40 mmHg during surgery. At the end of the surgery, 2.5 mg of neostigmine and 0.4 mg of glycopyrrolate were administered and extubation was performed when the TOF ratio was greater than 90%.

Fentanyl infusion (1-2 μg/kg) and/or propofol was used to sedate the patients. 25 μg of fentanyl could be added during the operation when the pain score was greater than or equal to 5 or the patient was agitated. The patients received oxygen by cannula or mask. Benzodiazepines were avoided during the operation. The anesthesiologist determined the dose of anesthetic drugs and sedation drugs for regional anesthesia and the surgeon determined the concentration and volume of drugs for local anesthesia.

During surgery, noninvasive blood pressure or direct arterial pressure, electrocardiogram, pulse oximetry, end-tidal concentration of CO_2 and desflurane, body temperature, and neuromuscular monitoring were monitored and recorded. After the operation, the patients were transferred to the ward or the surgical critical care unit. They were assessed for postoperative delirium using the DSM-5 criteria by a psychiatrist who was blinded by allocation. They were reassessed for the first three days postoperatively by the same psychiatrist.

If postoperative delirium was detected, the severity of delirium would be further assessed using the Delirium Rating Scale.[19] Treatments for postoperative delirium were provided by the psychiatrist team. The researchers recorded all physical examination, treatment, and complication during the postoperative period.

Data collection

Preoperative data include general demographic characteristics, TMSE score, and preoperative laboratory results. Intraoperative data include anesthetic technique, surgical and anesthetic duration, amount of each medication administered, number of episodes of intraoperative hypotension, number of episodes of hypoxemia, amount of fluid and blood products administered, urine output, and estimated blood loss. Postoperative data include pain score in the recovery room or intensive care unit, adverse effects of risperidone, DSM-5 evaluation, and delirium rating scale in delirious patient.

Statistical analysis

All randomized patients who met the protocol eligibility criteria were included in the analysis with a modified intention-to-treat (mITT) approach. Patients who were excluded post-randomization due to protocol deviations were not included in the analysis.

Continuous variables were reported according to data distribution. Normally distributed data are presented as mean ± SD and compared using the student's *t*-test. Skewed data are reported as median (interquartile range [IQR]) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequency and percentage and were compared using Chi-square test. A two-sided $p < 0.05$ was considered statistically significant.

The primary analysis followed a modified intention-to-treat approach, excluding patients who were randomized but not treated due to protocol-related reasons. A total of 140 patients were randomized, of whom 132 patients were included in the modified intention-to-treat analysis (Intervention =66, Control = 66).

Delirium Rating Scale (DRS) was compared among patients who developed POD and was reported as median with IQR. Comparison was conducted using Mann-Whitney U test.

Subgroup analyses based on TMSE scoring and hypotensive events were conducted as post-hoc exploratory analyses.

Statistical analysis was conducted using IBM Statistic SPSS for Windows version 21.0.

RESULTS

The recruitment took place from September 2020 to January 2023. During the study period, 1,152 elective vascular patients were evaluated for eligibility, 1,012 patients were excluded mainly due to expected anesthesia time less than 2 hours, followed by preoperative delirium, receiving antipsychotic medications preoperatively, age less than 60 years, having a prolonged QT interval in preoperative ECG, and declining participation.

A total of one hundred and forty participants were eligible and were randomized to the placebo group (n=70) and the risperidone group (n=70). After exclusions for protocol deviations (n=8), 132 patients were included in the modified intention-to-treat (mITT) analysis. In each group, two patients (2.8%) had anesthetic time less than 2 hours, and a patient had her operation cancelled by the surgeon. A patient in the placebo group received benzodiazepine during the operation and was excluded from the analysis. A patient in the risperidone group received dexmedetomidine and was withdrawn from the analysis (Fig 1).

The baseline clinical characteristics and intraoperative variables were balanced between the two groups and were demonstrated in Tables 1 and 2. Clinical outcomes are demonstrated in Table 3.

TABLE 1. Baseline patient characteristics.

Characteristics	Placebo Group (n=66)	Risperidone Group (n=66)	P value
Age, mean (SD), y	72.6 (7.4)	71.5 (7.3)	0.374
Gender			0.434
Female, No., %	16 (24.2%)	20 (30.3%)	
Male, No., %	50 (75.8%)	46 (69.7%)	
Body mass index, mean (SD)	22.8 (4.3)	23.8 (3.8)	0.165
Hematocrit, mean, %	34.0 (6.5)	36.0 (6.6)	0.076
eGFR, mean (SD)	58.5 (28.7)	58.4 (31.5)	0.993
Sodium level, mean (SD)	137.1 (4.3)	136.5 (4.0)	0.343
Comorbidity			
Stroke	10 (15.2%)	14 (21.2%)	0.367
Coronary artery disease	23 (34.8%)	24 (36.4%)	0.856
Diabetes	25 (37.9%)	36 (54.5%)	0.055
ASA classification			0.637
II	7 (10.6%)	7 (10.6%)	
III	55 (83.3%)	52 (78.8%)	
IV	4 (6.1%)	7 (10.6%)	

Abbreviations: eGFR: Estimated glomerular filtration rate, ASA: American Society of Anesthesiologists physical status classification.

TABLE 2. Intraoperative variables.

Intraoperative variables	Placebo Group (n=66)	Risperidone Group (n=66)	P value
Anesthesia techniques			0.186
GA or iv sedation	45 (68.1%)	52 (78.7%)	
RA or MAC	21 (31.8%)	14 (21.2%)	
Estimated blood loss, ml, IQR	125 (50-285)	100 (50-250)	0.532
Hypotensive events >5minutes, times, IQR	1 (0-4)	2 (0-4)	0.561
Supra-inguinal operation, no., %	36 (54.5%)	33 (50%)	0.601
Operative time, mean (SD), min	207.8 (123.5)	181.5 (98.9)	0.179
Anesthesia time, mean (SD), min	265.0 (141.3)	243.8 (120.1)	0.356

Abbreviations: *GA*: General anesthesia, *RA*: Regional anesthesia, *MAC*: Monitored anesthesia care, *IQR*: Interquartile range, *SD*: Standard deviation.

TABLE 3. Clinical outcomes during study drug administration.

Outcomes	Placebo Group (n=66)	Risperidone Group (n=66)	P value
Delirium, No., %	14 (21.2%)	7 (10.6%)	0.096
Subtype of delirium			0.174
Hypoactive, No, %	7 (50%)	6 (85.7%)	
Hyperactive, No, %	7 (50%)	1 (14.2%)	
Delirium rating scale. Median, IQR	6.0 (5.0-8.25)	2.0 (2.0-5.0)	0.025
Length of hospital stay. Median, IQR	5.0 (4.0-14.25)	7.0 (3.0-15.25)	0.922

Abbreviation: *IQR*: Interquartile range.

The incidence of postoperative delirium in the risperidone group was 10.6% compared to the control group 21.2% with no statistical significance (p = 0.096). In patients who developed postoperative delirium of each group, the incidence of hyperactive delirium in the risperidone group (14.2%) vs the placebo group (50%) was also not statistically different (p = 0.174). However, the DRS in the risperidone group was statistically lower at median of 2 (2-5) compared to the control group at median of 6 (5-8.25) (p = 0.025). There was no difference in hospital stay between the two groups (5.0 (4.0-14.25) vs 7.0 (3.0-15.25), p = 0.922).

In a subgroup analysis, we found that the risperidone group had a lower incidence of postoperative delirium in patients with hypotensive events (defined by mean arterial blood pressure < 20% of the baseline value or systolic blood pressure <90 mmHg) less than 3 times. We found no difference in postoperative delirium in patients with hypotensive events more than 3 times. We found no statistical differences between patients with mild cognitive impairment (TMSE scores <22) compared to patients with TMSE scores ≥ 22 (Table 4).

The side effects of risperidone included mild extrapyramidal symptoms (cogwheel rigidity) in one patient (1.4%) that resolved spontaneously and asymptomatic QT prolongation in one patient (1.4%). A patient developed cardiac arrest on postoperative day 3 due to acute heart failure and hypoxemia. We believe that this is unlikely to be due to risperidone which was administered 3 days prior to the event. After the incident, the patient's randomization to the risperidone group was quickly disclosed and reported to the IRB.

TABLE 4. Subgroup analysis of clinical outcomes.

Subgroup	Outcome	Placebo group (n=66)	Risperidone Group (n=66)	P value
Hypotension < 15 min	Delirium, No., %	11 (24.4%)	3 (7%)	0.025
Hypotension ≥ 15 min	Delirium, No., %	3 (14.3%)	4 (17.4%)	0.778
Preoperative TMSE score < 22	Delirium, No. %	5 (35.7%)	2 (18.2%)	0.332
Preoperative TMSE score ≥ 22	Delirium, No. %	9 (17.3%)	5 (9.1%)	0.258

Abbreviation: *TMSE*: Thai Mental State Examination.

DISCUSSION

We found that 0.5 mg of oral risperidone solution, when administered preoperatively, reduced the severity of delirium, but not the incidence of POD or the length of stay in the hospital. In a subgroup analysis, risperidone showed a benefit in reducing POD in patients with less than three hypotensive events.

In contrast to our hypothesis, this randomized controlled trial showed that 0.5 mg of risperidone oral solution administered preoperatively did not reduce the incidence of POD in elderly vascular patients (21.2% VS 10.6%, p=0.096). We believe that this may be due to several factors.

First, the incidence of postoperative delirium in our placebo group (21.2%) was much lower than the incidence used for the calculation of the sample size (48%). This discrepancy may be due several factors including differences in patient characteristics, surgical techniques, perioperative practices, and intraoperative hemodynamic control. Our study also used DSM-5 criteria for diagnosis of delirium, which are highly specific but less sensitive than CAM-ICU, potentially missing milder or transient cases. Protocol related exclusions including patients with severe cognitive impairment, sedative use and patients having pre-operative delirium may resulted in a lower risk population.

Second, a single dose of 0.5 mg of risperidone used in this study may not be enough to reduce the incidence of POD. Previous studies used a higher dose (1 mg) or higher frequency (every 12 hours).[17,18]

The choice of a single 0.5 mg preoperative dose of risperidone in this study was based on concerns regarding tolerability and safety in elderly vascular patients, who often have multiple comorbidities and polypharmacy. Risperidone at low doses has been shown to treat postoperative delirium in elderly orthopedic patients with minimal side effects.[22] Pharmacokinetically, oral risperidone reaches peak plasma concentrations within 1–2 hours, with a mean elimination half-life of approximately 20 hours, and its active metabolite, 9-hydroxyrisperidone, has a half-life of 20–30 hours.[23] Therefore, we hypothesized that a single preoperative dose would provide an effect for least 48–72 hours, which is the period with the highest risk of POD. However, compared with prior studies using 1 mg or repeated dosing schedules, a single low dose regimen was insufficient in preventing POD. Future studies should explore the optimal dosing that balance efficacy with safety in this vulnerable population.

It is also important to consider some potential confounding factors that could influenced POD risk. Variables such as site of surgery (supra-inguinal surgery vs infra-inguinal surgery), duration of anesthesia and surgery, intraoperative hypotension, opioid exposure and baseline cognitive function (TMSE score) may affect delirium incidence and severity. Although randomization was intended to balance these factors, residual differences may contribute to variability in outcomes.

Regarding our secondary outcomes, risperidone showed a reduction in the severity of postoperative delirium defined by the Delirium Rating Scale (6 VS 2, p=0.025) but not hospital stay (5 VS 7, p=0.922). In contrast to a previous study[20], the reduced delirium severity found in risperidone group was not associated with a reduction in the length of hospital stay. Other worse clinical outcomes including higher 1-year mortality rate, greater in-hospital costs[20] and long-term cognitive decline[21] was also linked with delirium severity but were not studied in this research. There were few reported side effects of risperidone.

The external validity of our findings is limited. This was a single-center study focusing on elderly patients undergoing elective vascular surgery, with a benzodiazepine-avoidant anesthetic protocol. Therefore, results may not fully apply to other surgical populations, including non-vascular geriatric patients, or to centers with different perioperative practices. Future multicenter studies across diverse surgical settings are needed to determine the broader applicability of these findings.

Strengths of this study include the use of DSM-5 criteria for the diagnosis of delirium, a gold standard for the diagnosis of delirium, compared to previous studies using CAM-ICU. Assessment of all participants was done by only one psychiatrist and the assessment period is three consecutive days, which are the period with the highest incidence of delirium. All participants, researchers, and psychiatrists were blinded to the groups of patient allocation.

Limitations

Our study had some limitations. The assessment of delirium was performed once each day, which may have missed some cases of delirium due to its fluctuating course. The sample size was calculated using the incidence of delirium, which was the primary outcome. This may have reduced the power of our study to detect a statistically significant difference in the primary and secondary outcomes.

CONCLUSIONS

In this RCT, we observed that surgical vascular patients receiving 0.5 mg of risperidone before surgery

showed a reduction in severity but not incidence of POD compared to placebo. There were no differences in hospital stay between the two groups. Risperidone has low side effects.

Suggestions for future research include determining the proper sample size for other research outcomes, increasing the frequency of delirium assessment, and considering the appropriate dose of risperidone for effective postoperative delirium prevention.

Data Availability Statement

De-identified data were available from the corresponding author upon reasonable request.

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DECLARATIONS

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Conflict of Interest

The authors assert that they have no conflicts of interest to declare.

Registration Number of Clinical Trial

Registered at the Thai Clinical Trials Registry (TCTR ID: TCTR20190704003) on 4 July 2019.

Author Contributions

Conceptualization: O.P., P.P.; Data curation: V.R., T.C.; Formal analysis: V.R., T.C.; Methodology: O.P., P.P.; Supervision: O.P.; Writing – original draft: V.R., T.C.; Writing – review & editing: V.R., T.C., O.P., P.P., T.J., A.S. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

AI-based tools (ChatGPT, OpenAI) were used for language editing under author supervision.

Ethics Approval Statement

This study was authorized by the Siriraj Institutional Review Board (approval number: COA no. Si 381/2019), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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