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Risk factors for postoperative delirium on oxygen delivery-guided perfusion

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Abstract

Background: Studies have demonstrated the efficacy of oxygen delivery-guided perfusion (ODGP) in preventing postoperative acute kidney injury, but the benefit of ODGP for delirium has not been confirmed. We retrospectively investigated the risk factors for postoperative delirium in patients who underwent ODGP (with oxygen delivery index [DO₂i] > 300 mL/min/m²).

Methods: Consecutive patients who underwent on-pump cardiovascular surgery with ODGP from January 2018 to December 2020 were retrospectively analyzed. In addition to examining patients' DO₂i during cardiopulmonary bypass (CPB), we quantified the two primary DO₂ components-hematocrit (Hct) and pump flow. Delirium was defined based on the Intensive Care Delirium Screening Checklist (ICDSC). Patients were divided into three groups: no delirium (ICDSC score = 0), subsyndromal delirium (ICDSC score = 1–3), and clinical delirium (ICDSC score ≥ 4).

Results: Multivariate analysis identified only the number of red blood cell (RBC) units transfused, intubation time, and the cumulative time below the Hct threshold of 25% as predictive factors of postoperative delirium. Although patients with higher ICDSC scores had greater hemodilution during CPB, ODGP resulted in a higher pump flow, and DO₂i was maintained above 300 mL/min/m², with no significant difference between the three groups.

Conclusions: A low Hct level during CPB with ODGP, the number of RBC units transfused, and intubation time were associated with postoperative delirium. Further investigations are needed to determine the ability of ODGP to prevent low Hct during CPB.

Keywords: Cardiopulmonary bypass, Optimal perfusion, Goal directed perfusion, Oxygen delivery, Hemodilution

Background

Postoperative delirium is a common complication after cardiac surgery, with a reported frequency of 3% to 31% [1]. Postoperative delirium is associated with short- and long-term adverse outcomes, including longer length of hospital stay, greater prevalence of falls after surgery, and postoperative stroke and death [2, 3]. Moreover, strategies to prevent these adverse outcomes of postoperative

delirium are lacking [4]. Although postoperative delirium has been attributed to age, diabetes, pre-existing cerebrovascular disease, peripheral vascular disease, blood transfusion, renal insufficiency, and postoperative ventilation time [1, 3], many of these risk factors are unmodifiable.

Recently, many studies have directly examined the relationship between oxygen delivery (DO₂) during cardiopulmonary bypass (CPB) and postoperative acute kidney injury (AKI) [5–11]. Moreover, the relationship between low DO₂ during CPB and postoperative delirium has also been reported [12], and CPB management using DO₂ as an index of perfusion flow has received increased attention as a new concept regarding optimal perfusion flow. In a previous study, we reported that oxygen

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delivery-guided perfusion (ODGP), preventing a DO_2 index (DO_{2i}) of <300 mL/min/m² during CPB, reduced the incidence of postoperative AKI.¹³ Since then, we have performed ODGP (maintaining $DO_{2i} > 300$ mL/min/m² through pump flow adjustments during CPB) to prevent postoperative AKI. Studies have demonstrated the efficacy of ODGP in preventing postoperative AKI [10, 13], but the benefits of ODGP for delirium have not been confirmed. We aimed to retrospectively investigate the risk factors for postoperative delirium in patients who underwent ODGP (with $DO_{2i} > 300$ mL/min/m²).

Methods

Patient population

This retrospective study included 216 adult patients who underwent on-pump cardiovascular surgery with ODGP at Juntendo University Hospital from January 2018 to December 2020. The exclusion criteria were emergency surgery, requirement for circulation arrest, presence of severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) preoperatively, discontinuation of ODGP because of poor venous drainage, and incomplete preoperative or postoperative data. The study was approved by the institutional review board of Juntendo University Hospital (17–184).

Anesthesia and cardiopulmonary bypass procedure

Anesthesia was induced with midazolam, fentanyl, and rocuronium, and maintained with sevoflurane and remifentanyl before CPB, and with propofol and remifentanyl during and after CPB. After the surgery, remifentanyl was discontinued, and fentanyl was administered. Propofol was continued until extubation in the intensive care unit (ICU).

CPB was performed under normothermic conditions (≥ 35 °C). We maintained a DO_{2i} value of >300 mL/min/m² through pump flow adjustments during CPB. The minimum pump flow was set as 2.6 L/min/m². Red blood cell (RBC) transfusion during CPB was considered when hemoglobin (Hb) values were <7 g/dL. Roller pumps (LivaNova, Munich, Germany) were used for CPB. Mean arterial pressure (MAP) levels of 60 mmHg were maintained with intermittent intravenous phenylephrine administration. The CDI[®] Blood Parameter Monitoring System 500 (Terumo, Tokyo, Japan) was recalibrated every 20 min using ABL800 FLEX blood gas analyzer (Radiometer Medical ApS, Denmark). Oxygen-related measurements, including hematocrit (Hct) and DO_{2i} values, were performed using the LivaNova CONNECT data management system (LivaNova), which recorded data every 20 s.

Data collection and definitions

The collected demographic data included age, sex, body habitus, comorbidities, previous transient ischemic attack/cerebral vascular accident (TIA/CVA), left ventricular ejection fraction, eGFR, preoperative Hct, preoperative albumin, and Euro SCORE II.

Intraoperative variables included the type of surgery, pump time, nadir DO_{2i} , median DO_{2i} , area under the curve below the 300 mL/min/m² DO_{2i} threshold ($AUC < DO_{2i}^{300}$), cumulative time below the 300 mL/min/m² DO_{2i} threshold ($time < DO_{2i}^{300}$), median perfusion index (PI), nadir Hct, AUC below the 60 mmHg MAP threshold ($AUC < MAP^{60}$), cumulative time below the 60 mmHg MAP threshold ($time < MAP^{60}$), number of RBC units transfused, nadir cerebral oxygen saturation (ScO_2) during CPB, AUC below the 80% of baseline ScO_2 ($AUC < ScO_2^{80\%bas}$), and cumulative time below the 80% of baseline ScO_2 ($time < ScO_2^{80\%bas}$). These nadir points were defined as the lowest points during the measurement. Postoperative variables included intubation time, systolic blood pressure, blood glucose, sodium, and chloride. Systolic blood pressure, blood glucose, sodium, and chloride data were collected the day after surgery. DO_{2i} was calculated according to the equation: DO_{2i} (mL/min/m²) = pump flow (L/min) \times [Hct/2.94 (g/dL) \times 1.36 \times SaO₂ (%) + PaO₂ (mmHg) \times 0.003] \times 10 / BSA (m²), where SaO₂ is oxygen saturation in the arterial blood, PaO₂ is partial pressure of oxygen in the arterial blood, and BSA is body surface area.

In addition to examining the patients' DO_2 during CPB, we quantified the two primary DO_2 components – Hct and pump flow. To quantify hemodilution during CPB, the AUC below the 21%, 23%, and 25% Hct thresholds ($AUC < Hct^{21}$, $AUC < Hct^{23}$, and $AUC < Hct^{25}$) and the cumulative time below the 21%, 23%, and 25% Hct thresholds ($time < Hct^{21}$, $time < Hct^{23}$, and $time < Hct^{25}$) were calculated. Similarly, to quantify pump flow during CPB, the AUC below the 2.6, 2.7, and 2.8 L/min/m² PI thresholds ($AUC < PI^{2.6}$, $AUC < PI^{2.7}$, and $AUC < PI^{2.8}$) and the cumulative time below the 2.6, 2.7, and 2.8 L/min/m² PI thresholds ($time < PI^{2.6}$, $time < PI^{2.7}$, and $time < PI^{2.8}$) were calculated.

Definition of delirium

Delirium was defined based on the Intensive Care Delirium Screening Checklist (ICDSC) [14]. ICDSC is an eight-item checklist that produces a score between 0 and 8. The ICDSC scores were calculated once every 8 h by nurses. The score during ICU stay within 48 h postoperatively was categorized into three groups. No delirium was defined as the non-manifestation of any of the eight items

(ICDSC score 0). Subsyndromal delirium was defined as the manifestation of some of the eight items (ICDSC score 1–3) without reaching the diagnostic criteria for clinical delirium. Clinical delirium was defined as the manifestation of at least four of the eight items (ICDSC score ≥ 4). Patients who did not permit evaluation with the ICDSC throughout their ICU stay (postoperative 48 h) were excluded.

Statistical analysis

Continuous and categorical variables are expressed as mean \pm standard deviation (SD) or median (interquartile range) and numbers (%), respectively. Continuous variables were compared between the three groups using a one-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference test if the one-way ANOVA was significant. For continuous variables with skewed distribution, the nonparametric Kruskal–Wallis test was used, followed by the Steel–Dwass test in the case of significant findings. Categorical variables were analyzed using the Pearson chi-squared test. These tests were used to comprehensively evaluate the associations between perioperative variables and ICDSC scores; thus, candidate predictors of delirium were selected. Subsequently, a multivariate ordered logistic regression analysis was performed to identify significant predictors of delirium. Moreover, a multivariate ordered logistic regression model was built based on previously reported independent risk factors (age, diabetes, previous TIA/

CVA, eGFR, preoperative albumin, number of RBC units transfused, intubation time, systolic blood pressure, blood glucose, and sodium) for delirium [1, 15–17]. Statistical significance was set at $p < 0.05$. The Holm method was used to adjust the p-values for multiple comparisons of categorical variables. To make the presentation simpler, we compared the p-value adjusted with 0.05 to determine whether a particular test result was statistically significant after adjustment. All analyses were performed using JMP14 software (SAS Institute. Cary, NC, USA).

Results

Patient characteristics

The characteristics of the 225 patients are shown in Table 1. Those in the study population who were diagnosed with no delirium, subsyndromal delirium, and clinical delirium during the postoperative 48 h were 53 (23.6%), 163 (72.4%), and 9 (4.0%), respectively. There were significant differences in BSA, diabetes, preoperative Hct, and Euro SCORE II values. Patients who developed clinical delirium were more likely to have smaller BSA, diabetes, lower preoperative Hct, and higher Euro SCORE II.

Perioperative data

Table 2 shows the perioperative data in the three groups. Although no significant differences were found in nadir DO_{2i} , median DO_{2i} , $AUC < DO_{2i}^{300}$, and $time < DO_{2i}^{300}$, median PI, nadir Hct, number of RBC

Table 1 Demographic characteristics of patients in the groups with no delirium, subsyndromal delirium, and clinical delirium

| Variable | No delirium n = 53 (23.6%) | Subsyndromal delirium n = 163 (72.4%) | Clinical delirium n = 9 (4.0%) | P value | | | |
|-----------------------------------|-------------------------------|---|-----------------------------------|---------|-----------|-----------|-----------|
| | | | | Overall | ND vs. SD | ND vs. CD | SD vs. CD |
| Age (years) | 64.7 \pm 14.2 | 67.5 \pm 12.1 | 71.9 \pm 8.7 | 0.193 | | | |
| Male | 35 (66.0%) | 97 (59.5%) | 4 (44.4%) | 0.424 | | | |
| BSA (m ²) | 1.68 \pm 0.19 | 1.62 \pm 0.19 | 1.51 \pm 0.14 | 0.014 | 0.06 | 0.033 | 0.246 |
| BMI (kg/m ²) | 23.6 \pm 3.6 | 22.7 \pm 3.2 | 21.8 \pm 2.3 | 0.163 | | | |
| Hypertension | 26 (49.1%) | 79 (48.5%) | 6 (66.7%) | 0.568 | | | |
| Diabetes | 8 (15.1%) | 19 (11.7%) | 4 (44.4%) | 0.020 | 0.511 | 0.078 | 0.015 |
| Peripheral vascular disease | 0 | 1 (0.6%) | 0 | 0.826 | | | |
| Previous TIA/CVA | 11 (20.8%) | 30 (18.4%) | 4 (44.4%) | 0.162 | | | |
| LVEF (%) | 62.9 \pm 10.7 | 62.5 \pm 11.0 | 62.7 \pm 12.8 | 0.976 | | | |
| eGFR (mL/min/1.73m ²) | 71.0 \pm 19.7 | 69.8 \pm 19.7 | 56.9 \pm 20.4 | 0.138 | | | |
| Preoperative Hct (%) | 38.9 \pm 4.3 | 38.4 \pm 4.8 | 34.0 \pm 4.4 | 0.016 | 0.793 | 0.012 | 0.018 |
| Preoperative albumin (g/dL) | 4.0 \pm 0.5 | 4.0 \pm 0.3 | 3.9 \pm 0.6 | 0.816 | | | |
| Euro SCORE II | 1.50 (0.85–3.06) | 1.95 (1.01–3.40) | 6.68 (2.33–11.50) | 0.005 | 0.471 | 0.006 | 0.01 |

Continuous and categorical data are expressed as means \pm standard deviations or medians (interquartile ranges), and numbers (%), respectively

BMI body mass index, BSA body surface area, CD clinical delirium, CVA cerebral vascular accident, eGFR estimated glomerular filtration rate, Euro SCORE European System for Cardiac Operative Risk Evaluation, Hct hematocrit, LVEF left ventricular ejection fraction, ND no delirium, SD subsyndromal delirium, TIA transient ischemic attack

Table 2 Perioperative data in the groups with no delirium, subsyndromal delirium, and clinical delirium

| Variable | No delirium (n = 53) | Subsyndromal delirium (n = 163) | Clinical delirium (n = 9) | P value | | | |
|---|----------------------|---------------------------------|---------------------------|---------|-----------|-----------|-----------|
| | | | | Overall | ND vs. SD | ND vs. CD | SD vs. CD |
| Surgical procedure | | | | 0.986 | | | |
| Valve | 41 (77.4%) | 127 (77.9%) | 8 (88.9%) | | | | |
| Valve + TA replacement | 6 (1.3%) | 20 (12.3%) | 1 (11.1%) | | | | |
| TA replacement | 1 (1.9%) | 3 (1.8%) | 0 | | | | |
| Adult congenital | 1 (1.9%) | 5 (3.1%) | 0 | | | | |
| Cardiac tumor | 4 (7.6%) | 8 (4.9%) | 0 | | | | |
| Pump time (min) | 127 (105–167) | 128 (103–177) | 173 (135–213) | 0.110 | | | |
| Nadir DO ₂ i (mL/min/m ²) | 292.2 ± 28.4 | 286.1 ± 28.5 | 278.3 ± 18.6 | 0.251 | | | |
| Median DO ₂ i (mL/min/m ²) | 341.8 ± 20.9 | 339.9 ± 24.4 | 349.1 ± 25.9 | 0.488 | | | |
| AUC < DO ₂ i ³⁰⁰ | 42 (0–159) | 68 (0–516) | 265 (6–658) | 0.246 | | | |
| Time < DO ₂ i ³⁰⁰ (min) | 2.3 (0–6.8) | 2.3 (0–11.7) | 8 (0.5–10.7) | 0.519 | | | |
| Median PI (L/min/m ²) | 2.72 (2.63–2.80) | 2.78 (2.68–2.85) | 2.86 (2.69–2.92) | 0.012 | 0.025 | 0.118 | 0.415 |
| Nadir Hct (%) | 23 (21–24) | 22 (21–23) | 21 (20.5–22) | 0.048 | 0.096 | 0.161 | 0.481 |
| AUC < MAP ⁶⁰ | 571 (285–795) | 620 (348–1151) | 368 (235–729) | 0.065 | | | |
| Time < MAP ⁶⁰ (min) | 28.9 ± 31.5 | 31.7 ± 25.6 | 24.4 ± 19.7 | 0.635 | | | |
| Units of RBC transfused (u) | 2.1 ± 4.1 | 2.4 ± 3.4 | 6.6 ± 3.7 | 0.003 | 0.872 | 0.003 | 0.003 |
| Nadir ScO ₂ (%) | 51 (43–58) | 50 (42–56) | 47.5 (41.5–55) | 0.519 | | | |
| AUC < ScO ₂ ^{80%bas} | 0 (0–4.5) | 0 (0–28.6) | 2.3 (0.0–114.9) | 0.247 | | | |
| Time < ScO ₂ ^{80%bas} (min) | 0 (0–2.4) | 0 (0–15.2) | 1.6 (0.1–40.8) | 0.094 | | | |
| Intubation time (h) | 6.7 (5.0–9.4) | 6.2 (4.2–9.4) | 15.2 (4.8–57.3) | 0.123 | | | |
| Systolic blood pressure (mmHg) | 118.7 ± 18.9 | 115.1 ± 21.1 | 123.9 ± 26.2 | 0.604 | | | |
| Blood glucose (mg/dL) | 128 (110–148) | 135 (118–152) | 144 (131–187) | 0.039 | 0.465 | 0.285 | 0.417 |
| Sodium (mEq/L) | 141.9 ± 3.4 | 142.7 ± 0.3 | 144.8 ± 2.7 | 0.026 | 0.283 | 0.045 | 0.162 |
| Chloride (mEq/L) | 107.0 ± 4.3 | 107.3 ± 4.2 | 109.2 ± 4.3 | 0.321 | | | |

Continuous and categorical data are expressed as means ± standard deviations or medians (interquartile ranges), and numbers (%), respectively. Nadir points were defined as the lowest points during measurement. The type of thoracic aortic replacement was ascending aortic replacement (excluded circulatory arrest under hypothermia). Systolic blood pressure, blood glucose, sodium, and chloride data were collected the day after surgery. AUC < MAP⁶⁰, area under the curve below the 60 mmHg mean arterial pressure thresholds; AUC < DO₂i³⁰⁰, area under the curve below the 300 mL/min/m² oxygen delivery thresholds; AUC < ScO₂^{80%bas}, area under the curve below the 80% of baseline cerebral oxygen saturation

Time < MAP⁶⁰, cumulative time below the 60 mmHg mean arterial pressure thresholds; Time < DO₂i³⁰⁰, cumulative time below the 300 mL/min/m² oxygen delivery thresholds; Time < ScO₂^{80%bas}, cumulative time below the 80% of baseline cerebral oxygen saturation

CD clinical delirium, DO₂i oxygen delivery index, Hct hematocrit, ND no delirium, PI perfusion index, RBC red blood cell, ScO₂ cerebral oxygen saturation, SD subsyndromal delirium, TA thoracic aortic

units transfused were significantly different between the three groups. Patients with higher ICDSC scores tended to have a higher median PI, lower nadir Hct, a greater number of RBC units transfused, higher blood glucose, and higher sodium.

The relationships between the two primary DO₂ components during CPB and delirium are presented in Table 3. Time < Hct²³, AUC < Hct²⁵, and time < Hct²⁵ were significantly different between the three groups. Patients with higher ICDSC scores were more likely to have greater hemodilution during CPB. However, there was no significant difference in pump flow between the three groups, but there was a trend toward higher pump flow in those with higher ICDSC scores.

Perioperative variables predicting delirium

Twelve perioperative variables (BSA, diabetes, preoperative Hct, Euro SCORE II, median PI, nadir Hct, units of RBC transfused, blood glucose, sodium, time < Hct²³, AUC < Hct²⁵, and time < Hct²⁵) were significantly associated with delirium ($p < 0.05$ each). Variables related to hemodilution, including nadir Hct, time < Hct²³, AUC < Hct²⁵, and time < Hct²⁵, were correlated with each other; thus, time < Hct²⁵ was selected as a candidate predictor of delirium because time < Hct²⁵ was more significantly associated with delirium compared to nadir Hct, time < Hct²³, and AUC < Hct²⁵. Multivariate ordered logistic regression analysis for the ICDSC score was performed by entering nine variables, including time < Hct²⁵,

Table 3 The two primary DO₂ components during CPB and delirium

| Variable | No delirium (n = 53) | Subsyndromal delirium (n = 163) | Clinical delirium (n = 9) | P value | | | |
|--------------------------------|----------------------|---------------------------------|---------------------------|---------|-----------|-----------|-----------|
| | | | | Overall | ND vs. SD | ND vs. CD | SD vs. CD |
| AUC < Hct ²¹ | 0 (0–0) | 0 (0–0) | 0 (0–6.5) | 0.268 | | | |
| Time < Hct ²¹ (min) | 0 (0–0) | 0 (0–0) | 0 (0–2.2) | 0.308 | | | |
| AUC < Hct ²³ | 0 (0–33.5) | 6 (0–60) | 35 (10.5–122) | 0.055 | | | |
| Time < Hct ²³ (min) | 0 (0–8.2) | 2 (0–16) | 9.3 (2.7–20.9) | 0.049 | 0.096 | 0.117 | 0.540 |
| AUC < Hct ²⁵ | 60 (17.5–221.5) | 154 (22–421) | 205 (94.5–562.5) | 0.048 | 0.084 | 0.153 | 0.587 |
| Time < Hct ²⁵ (min) | 18.3 (5.5–43.9) | 31.7 (7–75.3) | 58 (23.3–125.7) | 0.021 | 0.081 | 0.055 | 0.271 |
| AUC < PI ^{2.6} | 0.79 (0.26–3.88) | 0.44 (0.04–2.50) | 0.12 (0.02–2.90) | 0.223 | | | |
| Time < PI ^{2.6} (min) | 3.3 (1.7–26.8) | 3 (0.7–11.0) | 5 (0.9–10.2) | 0.344 | | | |
| AUC < PI ^{2.7} | 8.6 (2.3–22.4) | 3.8 (1.3–14.3) | 4.0 (2.0–20.4) | 0.097 | | | |
| Time < PI ^{2.7} (min) | 41 (14.2–99) | 20.3 (7.3–66) | 15.3 (8.8–80.9) | 0.086 | | | |
| AUC < PI ^{2.8} | 30.6 (13.3–61) | 16.1 (6.5–42.1) | 10.8 (5.7–48.2) | 0.081 | | | |
| Time < PI ^{2.8} (min) | 91 (42.3–132.5) | 62.7 (21.7–116) | 44.7 (14.7–134) | 0.065 | | | |

AUC < Hct²¹, area under the curve below the 21% hematocrit thresholds; AUC < Hct²³, area under the curve below the 23% hematocrit thresholds; AUC < Hct²⁵, area under the curve below the 25% hematocrit thresholds; AUC < PI^{2.6}, area under the curve below the 2.6 perfusion index thresholds; AUC < PI^{2.7}, area under the curve below the 2.7 perfusion index thresholds; AUC < PI^{2.8}, area under the curve below the 2.8 perfusion index thresholds; CD, clinical delirium; CPB, cardiopulmonary bypass; DO₂, oxygen delivery; Hct, hematocrit; ND, no delirium; SD, subsyndromal delirium; Time < Hct²¹, cumulative time below the 21% hematocrit thresholds; Time < Hct²³, cumulative time below the 23% hematocrit thresholds; Time < Hct²⁵, cumulative time below the 25% hematocrit thresholds; Time < PI^{2.6}, cumulative time below the 2.6 perfusion index thresholds; Time < PI^{2.7}, cumulative time below the 2.7 perfusion index thresholds; Time < PI^{2.8}, cumulative time below the 2.8 perfusion index thresholds; Time < PI^{2.8}, cumulative time below the 2.8 perfusion index thresholds

Table 4 Multivariate ordered logistic regression analysis for ICDSC score

| Variable | Coefficient | Standard error | Chi-Square | P value |
|------------------------------------|-------------|----------------|------------|---------|
| <i>Model 1</i> | | | | |
| BSA (m ²) | 0.84 | 1.27 | 0.44 | 0.508 |
| Diabetes | – 0.52 | 0.33 | 2.47 | 0.116 |
| Preoperative Hct (%) | – 0.05 | 0.05 | 1.07 | 0.301 |
| Euro SCORE II | – 0.11 | 0.07 | 2.91 | 0.088 |
| Median PI (L/min/m ²) | – 2.09 | 1.42 | 2.16 | 0.141 |
| Number of RBC units transfused (u) | – 0.12 | 0.08 | 2.05 | 0.153 |
| Blood glucose (mg/dL) | – 0.00 | 0.01 | 0.04 | 0.526 |
| Sodium (mEq/L) | – 0.01 | 0.06 | 0.01 | 0.907 |
| Time < Hct ²⁵ (min) | – 0.01 | 0.00 | 5.51 | 0.019 |
| Overall model fit | | AIC = 217.7 | | 0.002 |
| <i>Model 2</i> | | | | |
| Age (years) | – 0.01 | 0.02 | 0.36 | 0.547 |
| Diabetes | – 0.23 | 0.28 | 0.65 | 0.419 |
| Previous TIA/CVA | 0.21 | 0.25 | 0.76 | 0.384 |
| eGFR (mL/min/1.73m ²) | 0.00 | 0.01 | 0.07 | 0.789 |
| Preoperative albumin (g/dL) | – 0.65 | 0.53 | 1.50 | 0.220 |
| Number of RBC units transfused (u) | – 0.16 | 0.07 | 5.56 | 0.018 |
| Intubation time (h) | – 0.05 | 0.02 | 4.64 | 0.031 |
| Time < Hct ²⁵ (min) | – 0.01 | 0.00 | 5.88 | 0.015 |
| Systolic blood pressure (mmHg) | 0.01 | 0.01 | 1.22 | 0.269 |
| Blood glucose (mg/dL) | – 0.01 | 0.01 | 1.73 | 0.189 |
| Sodium (mEq/L) | – 0.00 | 0.05 | 0.00 | 0.991 |
| Overall model fit | | AIC = 244.1 | | 0.003 |

Results of the multivariate ordered logistic regression are given as coefficient, standard error, and chi-square. As multivariate ordered logistic regression analyses for the ICDSC score, Model 1 incorporated nine significant variables to identify independent predictors of delirium, Model 2 incorporated time < Hct²⁵ that was independent predictor in model 1 together with previously reported independent risk factors

into the model. This analysis revealed that $\text{time} < \text{Hct}^{25}$ remained a significant independent predictor of the ICDSC score ($p=0.019$) (Table 4, model 1). In model 2, only the number of RBC units transfused, intubation time, and $\text{time} < \text{Hct}^{25}$ were independently associated with the ICDSC score ($p=0.018$, $p=0.031$, and $p=0.015$, respectively) (Table 4, model 2).

Discussion

In the present study, we investigated the risk factors for postoperative delirium in patients who underwent ODGP (maintaining $\text{DO}_2\text{i} > 300 \text{ mL/min/m}^2$ through pump flow adjustments during CPB). $\text{Time} < \text{Hct}^{25}$ was an independent predictor of the ICDSC score in model 1, and the number of RBC units transfused, intubation time, and $\text{time} < \text{Hct}^{25}$ were independent predictors of the ICDSC score in model 2. Although patients with higher ICDSC scores had greater hemodilution during CPB, ODGP resulted in a higher PI, and DO_2i was maintained above 300 mL/min/m^2 , with no significant difference between the three groups. These results suggest that the increase in pump flow due to ODGP could not compensate for the decreased Hct or prevent postoperative delirium. Further exploration is needed in larger populations to determine whether suppressing the decrease in Hct during CPB can prevent delirium following cardiac surgery.

Postoperative delirium is a common neurologic complication of cardiac surgery and is associated with short-term and long-term morbidity and mortality [2, 3]. While it is important to diagnose, treat, and manage delirium, it is also important to prevent its onset. In this study, the ICDSC score was used to divide the patients into three groups: non-delirium, subsyndromal delirium, and delirium. Subsyndromal delirium is an intermediate state between delirium and non-delirium, but the risk of developing delirium is high in this state, and the prognosis is also intermediate between delirium and non-delirium [18, 19]. The study reported that the ICU mortality rates were 2.4% in the non-delirium, 10.6% in the subsyndromal delirium, and 15.9% in the clinical delirium ($p < 0.001$, overall) [18]. Since the more delirium-related symptoms appear on the ICDSC, the higher the score; this may indicate not only the "presence" of delirium, but also the "severity" of delirium. Therefore, it is important to not only prevent the onset of delirium but also to suppress the symptoms of delirium.

Regarding preoperative risk factors, there was an association between BSA, diabetes, preoperative Hct, and Euro SCORE II and postoperative delirium, which is influenced by preoperative comorbidities. Low preoperative Hct, followed by low intraoperative Hct and number of RBC units transfused, were associated with postoperative delirium, suggesting the importance of perioperative

hemodilution (Hct level) management. Hct during CPB tended to be lower in patients with higher ICDSC scores, and $\text{time} < \text{Hct}^{25}$ was identified as an independent predictor of ICDSC score by two multivariate models. Perioperative low Hb or Hct and anemia have been identified as risk factors for delirium [20–22], but not in systematic reviews or meta-analyses [1, 23]. When evaluating hemodilution in cardiac surgery with CPB, it is generally necessary to analyze the lowest value during CPB or the difference between the preoperative value and the lowest value during CPB. The Hct or Hb level is dynamic, suggesting that analyzing data from a specific point in time cannot accurately evaluate hemodilution. Some studies [24, 25] have focused on the AUC to show the relationship between ScO_2 and cognitive decline or delirium after cardiac surgery. The AUC of ScO_2 accounts for both the depth and duration of oxygen debt below the threshold. Such results have presented both depth and duration of oxygen debt as the AUC rather than absolute values, which are more relevant in predicting organ ischemia. Therefore, the differences in the assessment of hemodilution during CPB (e.g., with or without AUC) might explain why variables related to hemodilution were identified or not identified as risk factors for delirium. We selected variables in the multivariate analysis based on $\text{time} < \text{Hct}^{25}$ instead of $\text{AUC} < \text{Hct}^{25}$ in this study because $\text{time} < \text{Hct}^{25}$ was more significantly associated with delirium compared to nadir Hct, $\text{time} < \text{Hct}^{25}$, and $\text{AUC} < \text{Hct}^{25}$.

In the present study, there were no differences in the DO_2 parameters between the three groups since ODGP maintained a $\text{DO}_2\text{i} > 300 \text{ mL/min/m}^2$ through pump flow adjustments during CPB. Increased cumulative time and AUC below the DO_2 thresholds have been noted to be independently associated with elevations in brain injury biomarker (ubiquitin C-terminal hydrolase L1) level [26]. Our preliminary results suggest the importance of optimizing DO_2 management during CPB. A recent study reported that although DO_2 parameters, such as AUC of DO_2i , were clearly associated with delirium, DO_2 could not be identified as an independent predictor of postoperative delirium [12]. However, unlike DO_2 parameters, the evaluation of hemodilution was performed only at specific points in these studies. The lowest Hb on CPB just failed to reach significance but tended to be lower in patients with delirium (9.29 ± 1.27 vs. 8.89 ± 1.27 ; $p=0.053$) [12]. It is likely that the hemodilution was not correctly assessed, and the results may have been different if a comprehensive method for assessing hemodilution, such as AUC, was used. A low Hct during CPB may reflect the severity of delirium, which cannot be modified by increasing the pump flow. Considering the two primary DO_2 components, pump flow and Hb, as opposed

to the increase in pump flow due to ODGP compensating for the decreased Hct and preventing postoperative AKI [13, 27], low Hct was an independent risk factor for delirium in this study. This indicates that the pump flow, Hb, or both should be adjusted to maintain DO₂ during CPB depending on the target organs for oxygenation (e.g., renal oxygenation due to increased pump flow or cerebral oxygenation due to increased Hb, among others). The ability to prevent a low Hct during CPB might preclude the symptoms of delirium after cardiac surgery.

Limitations

This study has some limitations. Because this relatively small study was conducted retrospectively, the measurement of variables may have been inconsistent and have selection and treatment bias, which may have influenced the analysis. Although evidence strongly suggests that previous TIA/CVA is an independent predictor of postoperative delirium in cardiac surgery, it was not identified as a risk factor in this study. The lack of consistency or reproducibility of risk factors indicates that the observed associations resulted from bias, confounding, or a statistical model. In this study, we emphasized the consideration of the two primary DO₂ components, pump flow and Hct. Even though the sample size of the study is small, the low Hct during CPB still has an important predictive role in the development of postoperative delirium.

Other limitations of this study are the lack of known risk factors, such as reduced hearing, reduced visual acuity, comprehensive assessment of preoperative psycho-emotional status, cognitive status, and sleep deprivation. Moreover, the differences in ODGP, the assessment of hemodilution, or both may have been affected. Additionally, the small number of delirium occurrences limited our ability to develop comprehensive multivariable models. Thus, we considered the use of ICDSC to define postoperative delirium as appropriate; however, the ICDSC evaluation was performed within only the first 48 h postoperatively to minimize the influence of postoperative factors, which may have affected the present study.

Conclusion

This study revealed that low Hct during CPB with ODGP, number of RBC units transfused, and intubation time were significantly associated with postoperative delirium following cardiac surgery. The efficacy of ODGP in increasing pump flow could not compensate for decreased Hct levels and prevent postoperative delirium. The ability of ODGP to increase Hct, which consequently prevents postoperative delirium, remains unproven. Further studies are needed to determine whether suppressing the decrease in Hct during CPB with ODGP can

prevent delirium following cardiac surgery and to clarify the mechanism of delirium via low Hct following CPB.

Abbreviations

DO₂: Oxygen delivery; CPB: Cardiopulmonary bypass; AKI: Acute kidney injury; ODGP: Oxygen delivery-guided perfusion; DO₂i: Oxygen delivery index; eGFR: Estimated glomerular filtration rate; ICU: Intensive care unit; RBC: Red blood cell; MAP: Mean arterial pressure; TIA: Transient ischemic attack; CVA: Cerebral vascular accident; Hct: Hematocrit; AUC: Area under the curve; SaO₂: Arterial oxygen saturation; PaO₂: Arterial partial pressure of oxygen; BSA: Body surface area; PI: Perfusion index; Hb: Hemoglobin; ICDSC: Intensive Care Delirium Screening Checklist; ScO₂: Cerebral oxygen saturation; SD: Standard deviation; ANOVA: Analysis of variance.

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Author contributions

HM, SM, YM, GS, MU, RK, and TA designed the study. HM, SM, YM, GS, MU, and RK contributed to data collection and analysis. HM, SM, TA, and AA were major contributors to writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Data will not be shared because of institutional policy.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of Juntendo University Hospital (17-184), and informed consent from the patients was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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