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Risk Factors for Postoperative Delirium in Type A Aortic Dissection Patients: A Retrospective Study

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Background: Postoperative delirium (POD) is a common complication in cardiac surgery among adult patients. This retrospective study was designed to identify the risk factors associated with POD of type A aortic dissection patients.

Material/Methods: Clinical data of 148 patients with type A aortic dissection in the Department of Critical Care Medicine was retrospectively analyzed. All these patients underwent Sun's procedure with anesthetic treatment. The confusion assessment method for intensive care unit (CAM-ICU) was adapted to evaluate the delirium status of these patients. They were divided into 2 groups: the delirium group and the control group. Univariate analysis and multivariate logistic regression were performed in succession to determine the independent risk factors for POD.

Results: The average age of these patients was 54.41±11.676 years old. Among the 148 patients, POD was detected in 68 patients, with an incidence of 45.95%. According to univariate analysis, age, irritability, alcohol use, extracorporeal circulation duration (cardiopulmonary bypass, CPB time), antegrade selective cerebral perfusion (ASCP) time, lowest partial pressure of oxygen (lowest PO_2), mechanical ventilation time, blood loss, low PO_2 and oxygenation index, hemoglobin (Hb), Intensive Care Unit (ICU) stay, and dihydroxyphenylalanine (DEX) were associated with higher odds of POD among type A aortic dissection patients. According to further analysis of multivariate logistic regression, ASCP time and irritability were confirmed as the independent factors for POD of type A aortic dissection patients.

Conclusions: We determined 2 independent risk factors for POD: ASCP time and irritability. Identifying and adjusting these risk factors are very important in reducing the incidence of POD among type A aortic dissection patients.

MeSH Keywords: Aortic Diseases • Delirium • Risk Factors

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Background

Aortic dissection (AD) is a common disease associated with high mortality [1]. AD occurs when injury to the innermost layer of the aorta allows blood to flow between the layers of the aortic wall, forcing the layers apart [2]. AD can quickly result in death due to lack of blood flow and rupture of the aorta or the heart. Stanford type A dissection is an emergency surgery, with rapid progress and poor prognosis. In clinical practice, surgery is the most effective therapeutic method for type A aortic dissection. In recent years, progress has been made in investigating and supervising different surgery procedures [2,3]. However, there are still many potential complications after surgery [4].

Delirium is an acute mental disorder, which is an organic decline from previous baseline levels of mental function. It usually includes other psychiatric characteristics, such as cognitive deficits, arousal (hyperactivity, low activity, or mixing), perceptual deficits, sleep-wake cycle changes, hallucinations, and delusions. Postoperative delirium (POD) is an acute change in mental function characterized by inattention and fluctuating conscious, occurring within 30 days after surgery [5,6]. POD is also associated with high patient morbidity and mortality, with an incidence of up to 72% [7].

POD leads to prolonged recovery time, postoperative care difficulties, prolonged ICU time and hospital stay, and higher mortality [8–10]. The main purpose of our study was to identify the risk factors associated with POD of type A aortic dissection patients.

Material and Methods

Study design

Data on patients who underwent cardiac surgery of type A aortic dissection in Hospital were collected in our retrospective analysis. Ethics approval for our retrospective study was provided by the Institutional Review Board of our hospital. We retrospectively studied 148 patients with type A aortic dissection who underwent Sun operation in the cardiac surgery ICU. Written informed consent was obtained from all patients who were involved in this retrospective study.

Setting and participants

Data on 163 patients who underwent Sun's procedure of type A aortic dissection in our hospital recorded from January 2015 to December 2017 were retrospectively analyzed. Fifteen patients were excluded from the analysis because of death or discharge from hospital. There were 148 patients involved in the retrospective analysis. POD was assessed using the Confusion Assessment Scale (CAM) [11]. Patients were divided into 2 groups: a POD group and a non-POD group. Demographic data included gender, age, and body mass index (BMI).

Assessment for irritability

The assessment of the irritability of patients were performed by using a clinical scale including 5 questions. Patients were asked to answer these questions for the assessment of irritability: 1) do you sometimes or often lose temper and shout or snap at others, 2) are you hardly ever patient with other people, 3) do you often angry with yourself, 4) do you sometimes feel you might lose control and hit or hurt someone, and 5) do you sometimes or often feel like slamming doors or banging about when others upset you. Positive answers were considered to indicate irritability.

Assessment of POD

Two researchers assessed delirium on the first and second days after the operation. The assessment was performed twice to assess any fluctuations of in mental state.
First, the sedation level was assessed using the diagnostic tool Richmond Assessment Sedation Scale (RASS score), which enables health professionals to assess bedside sedation or agitation levels after discontinuation of sedative infusion [12]. If patients respond to pain/physical stimuli but do not open their eyes (RASS score –4), they will be defined as comatose. An RASS score of –5 indicates they did not respond to physical/verbal stimuli. Delirium can be screened by CAM-ICU diagnostic tools if the patient has a negative score (>–3 to +4) [13]. The purpose of CAM is to record 4 specific characteristics of delirium: 1) An acute change in mental state over a period of time, 2) Decrease of concentration, 3) Change of consciousness level, and 4) Confusion of thinking structure. As long as the patient present either features of 1) and 2) or 3) and 4), the score of delirium assessment should be defined as positive.

Data collection

Fifty-two potential risk factors for POD were collected retrospectively. These potential risk factors were adopted from previous research in the cardiovascular field. The factors were divided into 3 categories: preoperative, intraoperative, and postoperative factors. We used 25 preoperative risk factors, including demographic data (gender and age), cerebral hemorrhage history, cerebral infarction/TIA, diabetes mellitus, hypertension, smoking (tobacco use 3 months before surgery), chronic obstructive pulmonary disease (COPD), major surgery history, coronary disease, constipation, dyssomnia, stone, irritability, myocardial infarction and hyperlipemia, body mass index, alcohol use (3 months before surgery), white blood cell,

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Table 1. Univariate analysis of perioperative risk factors for POD in patients with type A aortic dissection.

Preoperative variables	POD (n=68)	No POD (n=80)	*P* value
Gender (Male, n, %)	44 (64.75)	58 (72.5)	0.0591
Age (mean ±SD)	59.90±10.17	50.73±12.57	0.0169
Cerebral hemorrhage history (n, %)	4 (85.88)	9 (11.25)	0.5719
Cerebral infarctio/TIA (n, %)	1 (20.15)	9 (11.25)	0.0576
Diabetes mellitus (n, %)	6 (8.82)	9 (11.25)	0.8642
Hypertension (n, %)	38 (55.88)	65 (81.25)	0.6112
COPD (n, %)	1 (1.47)	3 (3.75)	0.5867
Major surgery history (n, %)	19 (27.94)	29 (36.25)	0.7733
Coronary disease (n, %)	4 (5.88)	15 (18.75)	0.1085
Constipation (n, %)	4 (5.88)	8 (10)	0.7541
Dyssomnia (n, %)	4 (5.88)	8 (10)	0.7541
Calculus (n, %)	9 (13.24)	9 (11.25)	0.2373
Irritability (n, %)	29 (42.65)	24 (30)	0.0007
Myocardial infarction (n, %)	0 (0)	2 (2.5)	0.2646
Hyperlipemia (n, %)	4 (5.88)	5 (6.25)	0.6789
Smoking (n, %)	20 (29.41)	29 (36.25)	0.604
Alcohol use (n, %)	20 (29.41)	19 (23.75)	0.0405
Body Mass Index	25.80±3.44	25.36±3.34	0.4747
White blood cell (×10)	11.89±3.99	10.99±3.48	0.1832
Hemoglobin (g/L)	135.00 (IQR, 122.00–146.50)	132.00 (IQR,125.00–140.80)	0.324
Creatinine (μmol/L)	72.00 (IQR, 62.00–87.00)	69.00 (IQR, 57.25–82.00)	0.318
Albumin (g/L)	37.09±3.51	36.42±0.58	0.3039
Ejection fraction (%)	63.00 (IQR, 62.00–64.00)	62.00 (IQR, 61.00–64.00)	0.041
D-Dimer (μg/mL)	3.35 (IQR, 2.32–5.55)	2.96 (IQR, 1.72–4.44)	0.078
DEX (n, %)	36 (52.94)	57 (71.25)	0.785

COPD – chronic obstructive pulmonary disease; IQR – interquartile.

hemoglobin, creatinine, albumin, ejection fraction, D-dimer, and DEX. There were 16 intraoperative risk factors, including blood transfusion, crystal quantity, colloid quantity, liquid equilibrium, hemorrhage, surgery duration, high mean artery pressure (MAP), ΔMAP, low MAP, extracorporeal circulation, aortic cross-clamping duration, ASCP time, DHCA time, lactic acid (LAC), ΔLAC, and low PO_2. The following 22 postoperative variables included Acute Physiology and Chronic Health Evaluation (APACHE) value, mechanical ventilation time, PO_2, oxygenation index, LAC, hypernatremia, hemoglobin, white blood cell, N terminal pro B type natriuretic peptide (NT-proBNP), blood transfusion, ejection fraction, creatinine, fever, blood glucose, D-dimer, arrhythmia, ICU stay, hospital stay, propofol, and dihydroxyphenylalanine (DEX).

Statistical analysis

Statistical Product and Service Solutions (SPSS) 19.0 (IBM, Armonk, NY, USA) software was used to perform the analyses. Demographic variables are shown as mean ± SD and categorical variables are shown as the number/ratio. Quantile-quantile plots were created to check the normal distribution of continuous data. Demographic variables conforming to normal distribution were analyzed using the *t* test, whereas other variables

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Table 2. Univariate analysis of intraoperative risk factors for POD in patients with type A aortic dissection.

Intraoperative variables	POD (n=68)	No POD (n=80)	*P* value
Blood transfusion (mL)	3300 (IQR, 2700–3800)	2900 (IQR, 2431–3500)	0.069
Crystal quantity (mL)	1300 (IQR, 1000–1500)	1250 (IQR, 1000–1500)	0.549
Colloid quantity (mL)	2000 (IQR, 1500–2500)	2000 (IQR, 1500–2500)	0.352
Liquid equilibrium (mL)	3279±1383	4335±1583	0.5707
Blood loss (mL)	1800 (IQR, 1300–2200)	1350 (IQR, 1000–1738)	0.001
Surgery duration (min)	505.00 (IQR, 477.50–552.50)	502.50 (IQR, 450.00–543.80)	0.498
Highest MAP (mmHg)	73.98±10.69	73.41±10.90	0.7731
ΔMAP (mmHg)	49.14±12.95	47.78±10.88	0.5207
Lowest MAP (mmHg)	24.00 (IQR, 20.00–28.00)	25.00 (IQR, 21.00–29.00)	0.497
Extracorporeal Circulation duration (min)	202.00 (IQR, 184.00–243.00)	186.00 (IQR, 169.30–210.00)	0.001
Aortic cross-clamping duration (min)	114.00 (IQR, 105.00–138.00)	116.50 (IQR, 103.30–138.00)	0.900
ASCP time (min)	23.00 (IQR, 20.65–26.60)	20.30 (IQR, 18.23–23.58)	0.001
DHCA time (min)	19.45±2.77	18.92±3.58	0.3751
LAC (mmol/L)	4.90 (IQR, 4.40–6.10)	4.30 (IQR, 2.93–5.20)	0.071
ΔLAC (mmol/L)	3.90 (IQR, 3.25–4.65)	3.00 (IQR, 1.70–4.00)	0.062
Lowest PO_2 (mmHg)	72.30 (IQR, 64.05–81.40)	81.15 (IQR, 72.30–91.23)	0.001

MAP – mean artery pressure; ASCP – antegrade selective cerebral perfusion; DHCA – deep hypothermic circulatory arrest; LAC – lactic acid; Lowest PO_2 – lowest partial pressure of oxygen; IQR – interquartile.

were analyzed by Mann-Whitney U test. Demographic variables conforming to normal distribution are shown as mean ±SD, whereas other variables are shown as interquartile (IQR). For categorical variables, the chi-square test or Fisher exact test were performed. For factors that were significant for univariate analysis ($P<0.05$), a multivariate logistic regression analysis was conducted. $P<0.05$ showed a statistically significant difference.

Results

Preoperative risk factors of POD

According to the univariate analysis of perioperative risk factors for POD in type A aortic dissection patients, we found that age, irritability, and alcohol use were significantly associated with POD (Table 1).

Intraoperative risk factors of POD

Results of the univariate analysis of intraoperative risk factors for POD in type A aortic dissection patients showed that CPB time, ASCP time, and lowest PO_2 were significantly associated with the occurrence of POD (Table 2).

Postoperative risk factors of POD

According to the univariate analysis of postoperative risk factors for POD in type A aortic dissection patients, we found that mechanical ventilation time, low PO_2, oxygenation index, hemoglobin, ICU stay, and DEX were significantly associated with POD (Table 3).

Multivariate logistic regression analysis

An analysis of multiple logistic regression was performed with POD occurrence as a dependent covariate. These potential risk factors associated with POD were used in the multiple logistic regression analysis. ASCP time and irritability were confirmed as the independent risk factor of POD, with OR (95% CI) of 5.947 (1.200–29.465) and 4.773 (1.711–13.312) (Table 4).

Discussion

POD is a common and serious complication in patients after aortic dissection, and it has a high incidence rate [3]. The exact cause of POD, however, remains unclear [14,15]. In addition, there are no currently available drugs to effectively prevent and treat POD [16].

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Table 3. Univariate analysis of postoperative risk factors for POD in patients with type A aortic dissection.

Postoperative variables	POD (n=68)	No POD (n=80)	*P* value
APACHE II score	15.00 (IQR, 13.00–17.50)	13.00 (IQR, 11.00–17.00)	0.094
mechanical ventilation time (h)	78.30(IQR, 55.65–106.00)	38.09 (IQR, 18.00–81.67)	0.001
PO_2 (mmHg)	84.70 (IQR, 76.70–94.95)	98.00 (IQR, 83.85–112.80)	0.001
Oxygenation index	130.70 (IQR, 80.10–175.60)	189.70 (IQR, 135.30–247.20)	0.001
LAC (mmol/L)	3.70 (IQR, 2.95–5.30)	3.30 (IQR, 1.80–4.65)	0.063
Hypernatremia (n, %)	32 (47.06)	43 (53.75)	0.1966
Hemoglobin (g/L)	88.00 (IQR, 81.50–100.00)	95.00 (IQR, 84.00–105.80)	0.029
White blood cell ($\times 10^9$)	10.28 (IQR, 8.02–12.65)	9.38 (IQR, 7.50–12.19)	0.308
NT-proBNP (pg/mL)	218.00 (IQR, 107.00–337.50)	168.00 (IQR, 119.30–360.00)	0.835
Blood transfusion (mL)	500.00 (IQR, 175.00–1088.00)	600.00 (IQR, 331.30–1244.00)	0.413
Ejection fraction (%)	61.00 (IQR, 60.00–63.00)	61.00 (IQR, 59.00–62.00)	0.644
Creatinine (μmol/L)	103.00 (IQR, 82.00–126.50)	86.50 (IQR, 67.00–113.50)	0.055
Fever (38°C) (n, %)	33 (48.53)	44 (64.71)	0.165
Blood glucose(mg/mL)	10.60 (IQR, 9.40–12.45)	10.25 (IQR, 9.20–11.55)	0.301
D-Dimer (μg/mL)	2.15 (IQR, 1.60–3.32)	1.80 (IQR, 1.22–3.16)	0.216
Arrhythmia (n, %)	15 (22.06)	26 (38.24)	0.823
ICU stay (n, %)	7 (IQR, 5–10)	4 (IQR, 3–6)	0.001
Hospital stay	21 (IQR, 18–27)	19 (IQR, 16–24)	0.061
DEX	42 (61.76)	55 (80.88)	0.030
Propofol	43 (63.24)	52 (76.47)	0.054
Dihydroxyphenylalanine-nine	40 (58.82)	42 (61.76)	0.576

APACHE – Acute Physiology and Chronic Health Evaluation; ICU stay – Intensive Care Unit stay; DEX – dihydroxyphenylalanine; IQR – interquartile.

Table 4. Multivariate logistic regression analysis of independent predictors of POD.

Variable	Regression Coefficient	OR	95% CI	*P* value
ASCP time	1.783	5.947	1.200–29.465	0.044
Irritability	1.563	4.773	1.711–13.312	0.003

ASCP – antegrade selective cerebral perfusion; OR – odds ratio; CI – confidence interval.

Recently, risk factors for POD have been investigated by a number of studies [16,17]. A retrospective study by Liu et al. revealed that cerebrovascular disease history, surgery and cardiopulmonary bypass duration, postoperative hypoxia, and intubation time are independently associated with the development of delirium [18]. These studies elucidate the risk factors of POD after type A aortic dissection surgery and present helpful ideas for the prevention of POD. The main purpose of our study was to identify the risk factors associated with POD of type A aortic dissection patients. We investigated the association more precisely with more samples and risk factors. This might be helpful for the early detection of patients at high risk of delirium and provide effective measures to prevent the occurrence of POD [1,19]. The cause of POD is still unclear, and it is currently considered to be the result of the combined effects of multiple factors [2,13,20]. The results of our study showed that ASCP time and irritability were the independent risk factors of POD, confirming that POD is caused by multiple factors during the perioperative period.

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To investigate the risk factors associated with POD, we first performed bivariate analysis. Among preoperative variables, age, irritability, and alcohol use were the preoperative risk factors of POD. CPB time, ASCP time, and low PO_2 were the intraoperative risk factors of POD. Mechanical ventilation time, low PO_2, oxygenation index, hemoglobin, and ICU stay were the postoperative risk factors of POD. Multivariate logistic regression analysis was performed on POD variables. The variables used in the logistic regression model are the results of the bivariate analysis before multivariate analysis; the variables that showed a statistically significant association with the occurrence of delirium ($P<0.05$) were used in the model. Our results show that ASCP time and irritability are independent risk factor of POD, with OR (95% CI) of 5.947 (1.200–29.465) and 4.773 (1.711–13.312). These results should be of use in preventing POD.

Several studies have shown that aging is an independent risk factor for delirium, which may be related to increased neuronal apoptosis, degeneration of brain tissue, and decrease of central neurotransmitter content in the elderly [5,21]. These patients need to be well cared for, and they may need psychological attention.

Alcohol use has been shown to be an independent risk factor for delirium in several studies [8]. Our research confirms the conclusion that alcohol use should not be allowed during treatment.

Our analysis shows that hypoxia increases the risk of POD. Due to the complexity and difficulty of acute aortic dissection surgery, and because these patients are always in a state of severe stress, they easily suffer significant shock. There is also a higher risk of lung injury, which leads to hypoxia and subsequent problems. In the citric acid cycle, synthesis of glutamate, acetylcholine, and acetyl coenzyme A is inhibited by hypoxia, with decreased cerebral activity of glutamatergic and cholinergic neurons. Hypoxia thus leads to a higher risk of delirium.

In terms of mechanical ventilation time, longer mechanical ventilation time was associated with higher risk of POD. Recent research reported that the incidence of POD is increased by about 10% by prolonged mechanical ventilation time. During mechanical ventilation, patients need to maintain the state of analgesia or conscious sedation. Drugs are needed to achieve this state, and these drugs can damage the function of the neurons and result in the genesis of POD.

We found that increased CPB time contributes to the development of delirium, and it is speculated that increased release of inflammatory mediators after prolonged CPB may lead to cerebral vasoconstriction, thus inhibiting cerebral blood flow and altering brain function [22].

Delirium is associated with prolonged ICU time. Limb restraint, indwelling catheterization, and sleep deprivation often occur in the ICU, so delirium is prone to occur. Our findings also confirm that ICU duration is an independent risk factor for postoperative delirium.

Recent studies have shown that DEX can help prevent POD. Su et al. [23] reported that DEX decreases the incidence of delirium in elderly patients after non-cardiac surgery. Ji et al. [24] found that perioperative DEX use was associated with a decrease in postoperative mortality for up to 1 year and decreased the incidence of postoperative complications and delirium in patients undergoing cardiac surgery. These studies revealed that use of DEX was helpful in decreasing the incidence of POD. Djaiani et al. [25] found that, compared with propofol, DEX sedation reduced the incidence, delayed onset, and shortened duration of POD in elderly patients after cardiac surgery. In recent years, DEX has been shown to reduce delirium by blocking a single neurotransmitter, providing sedation without respiratory depression, coordinating sedation with other sedatives, and facilitating a more physiological sleep-wake cycle. In ischemic animal models, DEX has been shown to inhibit nerve damage and thus effectively prevent focal cerebral ischemia. The neuroprotective properties of DEX are related to the ultra-early regulation of the balance between pro-apoptotic and anti-apoptotic proteins. Therefore, the use of DEX sedation and early rapid extubation can prevent postoperative delirium. The reasons for the absence of statistically significant differences in DEX in the present study may be the greater brain damage in aortic dissection surgery than in other operations, inadequate DEX dosage, and insufficient frequency of delirium assessment, which is sometimes omitted.

ASCP time was an independent risk factor of POD. Delirium was associated with neurological dysfunction resulting from decreased or interrupted cerebral blood flow. The duration of ASCP in our study was not long, but there were significant differences between the delirium group and non-delirium group, suggesting that there might be insufficient cerebral perfusion even if the management of selective cerebral perfusion was strengthened. This was because normal blood pressure fluctuates within a certain range, and it can regulate cerebrovascular resistance and maintain stable cerebral blood flow. However, diabetes and hypertension, especially in those with definite cerebrovascular diseases, decrease self-regulation of the cerebrovascular system, so that cerebral blood flow is more dependent on selective cerebral perfusion pressure. Therefore, the surgery should be kept as simple as possible, and ASCP time and operation time should be short.

Irritability was another independent risk factor of POD according to our analysis. There are many potential psychological problems in irritable people. In the field of nursing psychology,

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irritability refers to a group of symptoms caused by long-term mental tension, excessive psychological pressure, anger, and mental stimulation. Its main symptoms are emotional instability, irritability, and anxiety, and such patients may be unable to watch TV when upset or even hear words spoken to them. They feel uncomfortable, panicky, angry, nervous, fearful, sensitive, suspicious, grieving, pessimistic, and disappointed. Irritable people have trouble feeling pleasure, cannot enjoy conversation and take no interest in activities. In addition, aortic dissection often has an acute onset. The stress caused by disease and the unfamiliar of treatment methods aggravate the emotional fluctuations of such patients. During the preoperative waiting period, the patient needs to be absolutely confined to bed, hemodynamic parameters are monitored closely, an artificial catheter is inserted throughout the body to perform the surgical drainage, and physical restraint is required. These requirements may lead to delusions of victimization, violent agitation, and even excessive use of sedatives, affecting mental judgment in irritable patients. It is suggested that we should strengthen the psychological counseling of irritable patients and seek to alleviate their negative emotions. In severe cases, medication such as DEX can be used. Thus, regulating the mood of patients in treatment is important in treating disease and preventing POD.

Limitations of the present study are that it was a single-center retrospective study, and only early postoperative POD patients in the ICU were included. In addition, the observation period was relatively short, the sample size was limited, and some risk factors may not have been included in the analysis. Multi-center prospective studies with large sample sizes are needed to further clarify the risk factors for POD.

Conclusions

According to our analysis of multiple logistic regression, ASCP time and irritability were confirmed as the independent risk factor of POD. ASCP time of POD patients in the operation was longer than in non-POD patients. This suggests that longer ASCP time elevates the risk of POD. Our results suggest that we should simplify operation as far as possible, so as to shorten the ASCP time and operation time. Irritability is another independent risk factor of POD according to our analysis. This shows that we should strengthen the psychological counseling of irritable patients and alleviate their negative emotions to prevent POD. Our study provides helpful guidance for prevention of POD among type A aortic dissection patients. In addition, more patients and more risk factors will be investigated in our future research to clarify the risk factors more precisely and provide more useful guidance.

Conflict of interest

None.

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