

Predictors and Clinical Outcomes of Postoperative Delirium after Administration of Dexamethasone in Patients Undergoing Coronary Artery Bypass Surgery

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ABSTRACT

Background: Postoperative delirium (POD) is one of the important complications of cardiac surgery and it is assumed to provoke inflammatory responses. Theoretically, anti-inflammatory effects of dexamethasone can have an influence on the incidence and outcomes of POD. The aim of our study was to assess POD predictors and outcomes of dexamethasone administration after cardiac surgery.

Methods: Patients' mental status was examined by mini-mental status examination and psychiatric interviewing to diagnose delirium. Subsequently, authors analyzed the patient variables for identification of predictors and outcomes of POD.

Results: Between 196 patients who met the inclusion criteria, 34 (17.34%) patients were delirious. History of chronic renal failure, obstructive pulmonary disease, smoking, and addiction strongly predicted development of POD. Other predictors were intra-aortic balloon pump insertion, transfusion of packed cells, and atrial fibrillation rhythm. In our study, the administration of dexamethasone significantly reduced the risk for POD. Furthermore, delirium was associated with longer intensive care unit (ICU) stay.

Conclusion: Our study reports the predictors of POD, which patients commonly facing them in cardiac surgery ICU. Appropriate management and prevention of these predictors, especially modifiable ones, can decrease the incident of POD and improves cognitive outcomes of cardiac surgeries.

Key words: Cardiopulmonary bypass, coronary artery bypass, delirium

INTRODUCTION

Coronary artery bypass graft (CABG) is one of the most common procedures for increasing cardiac perfusion and improvement in cardiac function and mental and physical aspects of quality of life.^[1-3] In anyway, CABG relating with many further complications ranged from minor signs to fatal symptoms.^[4] Delirium is one of the most common CABG-associated complications and defined as global disturbance of memory and cognitive status, which characterized by memory deficiency,

altered level of consciousness, disorientation, inappropriate speech, hallucinations, and illusions/delusions.^[5,6] The incidence of postoperative delirium in cardiac surgery intensive care unit (ICU) is widely ranged from 8% to 50%.^[7] Generally, postoperative delirium is a serious catastrophe after cardiac surgery because it is associated with prolonged ICU and hospital length of stay (LOS).^[8]

Despite advancements in CABG procedure in recent years, insertion of cardiopulmonary bypass (CPB) still is responsible for neuropsychologic disorders.^[9,10] CPB through induction of systemic inflammatory response syndrome is associated with postoperative delirium.^[11,12] In detail, proinflammatory cytokines in collaboration with reactive oxygen species can damage cerebral tissue, leading to consequential brain edema.^[13-15]

There are a number of studies conducted with the aim of evaluation of postoperative delirium (POD) predictors and such studies are continued to recent years because of the importance of POD. Several factors known as predictors of POD include age more than 65 years, history of mental and medical disease (eg, cerebrovascular accident (CVA), renal disease), complexity of surgery, emergency surgery, low hematocrit, acute infection, low cardiac output, prolonged cardiopulmonary bypass, atrial fibrillation, and massive blood transfusions.^[5,16] In addition, the effect of POD on patient outcomes in ICU and hospital is still unknown. However, it is assumed that POD is associated with prolonged LOS in ICU and hospital.^[16] The potential inhibition of proinflammatory response by corticosteroids might improve outcomes, such as improvement of myocardial function, reduction of extubation time, shortening of ICU and hospital LOS.^[17,18]

The beneficial effect of dexamethasone on neurologic sequelae has been shown previously, but its value in the context of cardiac surgery still remains controversial.^[19,20] Despite the high incidence of neurologic deficits and importance of immediate postoperative period, there are a few studies in the literature that have been found evaluating the postoperative period.^[21] To our knowledge, there is a little knowledge about the effects of dexamethasone on the outcomes of cardiac surgeries. The aim of our study was to assess the predictors and subsequently, the outcomes of POD in CABG patients who received dexamethasone.

MATERIALS AND METHODS

Study design

After obtaining the approval from the ethics committee of Isfahan University of Medical Sciences, the study was registered in official website of Iranian registry of clinical Trials (IRCT ID: IRCT201202229108N1). The total number of 196 patients who were undergoing CABG in Chamran Heart Center Hospital and fulfilled an informed consent, participated in our study. This study is part of a randomized clinical trial with the aim to evaluate the effect of dexamethasone on POD after CABG surgery. This study was conducted from January 2009 to September 2011 at Chamran Heart Center Hospital. Exclusion criteria were longer duration of CPB (more than 3 h), age more than 80 years, instability of hemodynamic status, and emergency operation.

The participants' cognitive status was assessed on the first postoperative day via mini-mental status examination (MMSE) as a screening method for diagnosing probable cognitive impairment. The MMSE screening questionnaire, including 11 items with a maximum score of 30 and requiring up to 10 min to fulfill.^[22] A total score of ≤ 23 was considered as a possible indicator for cognitive impairment. Hence, to diagnose POD, interviews were performed based on DSM-IV criteria in any patient who obtained a score of 23 or lesser.

Surgical method

After performing routine care and cardiorespiratory monitoring for all subjects, they received a constant anesthesia. Patients received 8 mg of dexamethasone intravenously before induction of anesthesia and followed by 8 mg of dexamethasone every 8 h for 2 days in cardiac surgery intensive care unit (CSICU). Surgery was performed by CPB and moderate hypothermia (28°C–30°C) approaches. After cannulation of right atrium and aorta, potassium cardioplegia administered, and aorta was cross-clamped. Flow rate was kept at 2.5 L/min/M² and radial arterial pressure maintained in range of 60–80 mmHg. After anastomosing grafts and repairing impaired valves (if it was indicated), cross clamp was removed and patient's body was warmed up. Moreover, after transferring patients to ICU, all of them were profited from standardized

managements, such as mechanical ventilation, fast-tracking, administrating low-dose nitrates and dopamine/dobutamine, and antibiotic therapy.

Data analysis

All analysis was performed by using SPSS (version 16, SPSS Inc.). Continuous variables of study described by mean and standard deviation (SD) values that in this study shown by mean \pm SD. Additionally, frequency and percent of categorical variables are indicating as frequency (%) and determined by means of descriptive statistic. After verifying normality of continuous variables by using one-sample Kolmogorov–Smirnov test. Analysis of continuous data was performed by using independent sample *t* test. However, we analyzed categoric statistics by univariate logistic regression for testing of POD predictors. We entered pre- and perioperative variables of study into backward stepwise logistic regression analysis. Because many variables entered into the model, only significant variables of final step were reported. Also, we used Chi-square test or Fisher (as appropriate) analysis for comparison of categoric data between groups. In all of the tests, a *P* value < 0.05 was considered as significant.

RESULTS

Totally, a number of 196 patients who underwent CABG operation participated in the study. They were divided into 2 groups: delirious (N = 34) and nondelirious (N = 162). A delirium prevalence of 17.34% was seen among the groups. Pre- and postoperative medical characteristics of these groups are summarized in Table 1. Univariate analyses results are represented in Table 2 and revealed that 8 of all the variables were statistically significant. We categorized these predictors into predisposing predictors (preoperative factors) and precipitating predictors (perioperative factors). Patients with a prior history of chronic renal failure (CRF) were significantly associated with 7.3-fold higher risk for development of POD (OR: 7.350, CI 95%: 1.991– 27.132; *P* value = 0.003). Chronic obstructive pulmonary disease (COPD) was the strongest independent predictor and associated with about 13-fold increase in the risk for POD after cardiac surgery (OR: 13.006, CI 95%: 1.291– 131.005; *P* value = 0.029). Another factor which predisposes patients to

Table 1: Medical characteristics

Characteristics	Total no. of patients (N = 196)	
	Delirious (N = 34) N (%) or Mean \pm SD	Nondelirious (N = 162) N (%) or Mean \pm SD
Preoperative		
Age (years)	60.13 \pm 11	62.20 \pm 12
LVEF (%)	51.42 \pm 4.17	51.54 \pm 5.02
Male gender	80 (88.2)	153 (96.3)
CVA	9 (26.5)	19 (11.7)
CRF	9 (26.5)	25 (15.4)
DM	2 (5.9)	14 (8.6)
Hypertension	13 (38.2)	15 (9.3)
COPD	2 (5.9)	4 (2.5)
Addiction	13 (38.2)	15 (9.3)
Carotid Bruit	6 (17.6)	12 (7.4)
Recent MI	8 (23.5)	11 (6.8)
Intraoperative		
IABP	10 (29.4)	11 (6.8)
CABG	34 (100)	140 (86.4)
CABG + valve surgery	0 (0)	22 (13.6)
Grafts	3.00 \pm 0.49	3.19 \pm 0.70
Cross-clamp time	85 \pm 14	83 \pm 11
Pump time	110 \pm 14	108 \pm 19
Hemoglobin (mg/dL)	8.47 \pm 1.05	8.44 \pm 11.6
Temperature ($^{\circ}$ C)	28.64 \pm 0.69	28.60 \pm 0.53
Dexamethasone	15 (16.1)	19 (18.4)
Postoperative		
FFP > 4 U	13 (38.4)	48 (29.6)
PC > 4 U	13 (38.2)	34 (21)
pCO ₂ > 60	8 (23.5)	12 (7.4)
pO ₂ < 50	5 (14.7)	14 (8.6)
Arrest	1 (2.9)	0
AVB	0	10 (6.2)
AF	9 (26.5)	23 (14.2)

LVEF, Left ventricular rejection fraction; CVA, Cerebrovascular accidents; CRF, Chronic renal failure; DM, Debates mellitus; COPD, Chronic obstructive pulmonary disease; MI, Myocardial infarction; IABP, Intra-aortic balloon pump; CABG, Coronary arteries bypass graft; PC, Packed cell; FFP, Fresh frozen plasma.

POD is a history of smoking (OR: 8.358, CI 95%: 1.855– 37.870; *P* value = 0.008). Finally, opioid addiction was identified as an additional predisposing predictor for development of POD (OR: 8.897, CI 95%: 2.309–34.281; *P* value = 0.001). Two recent predictors were associated with

Table 2: Predictors of postoperative delirium

Univariate analysis of potential risk predictors (N = 196)			
	Odds ratio	CI (95%)	P value
Predisposing factors			
CRF	7.350	1.991, 27.132	0.003
COPD	13.006	1.291, 131.005	0.029
Smoking	8.358	1.855, 37.870	0.008
Addiction	8.897	2.309, 34.281	0.001
Precipitating factors			
IABP	4.914	1.232, 19.603	0.024
PC > 4 U	4.626	1.354, 15.799	0.015
AF	4.519	1.041, 19.610	0.044
Dexamethasone	0.890	0.20, 0.394	0.002

CRF, Chronic renal failure, DM, Debates Mellitus, COPD, Chronic obstructive pulmonary disease, IABP, Intraaortic balloon pump, P.C, Packed cell

Table 3: Comparison of hospital outcomes between the groups

Outcome	Total no. of patients (N = 196)		P value
	Delirious (N = 34)	Nondelirious (N = 162)	
	Mean ± SD	Mean ± SD	
Extubation time (min)	11.52 ± 4.16	9.44 ± 2.02	<0.01
Inotrope use (days)	2.20 ± 0.41	2.08 ± 0.28	0.04
ICU LOS (days)	4.14 ± 1.01	3.61 ± 1.39	0.04
Hospital LOS (days)	13.35 ± 2.30	13.41 ± 1.28	0.84

ICU, Intensive care unit; LOS, Length of stay.

about 8-fold increase for occurrence of POD after a CABG operation.

As an identified precipitating predictor, intra-aortic balloon pump (IABP) is significantly associated with a higher risk of POD (OR: 4.914, CI 95%: 1.232–19.603; *P* value = 0.024). Additionally, our results indicated that transfusion of packed cell (PC) more than 4 U significantly correlated with an incident of POD after bypass surgery (OR: 4.626, CI 95%: 1.354–15.799; *P* value = 0.015). Correspondingly, with previous precipitating factors, atrial fibrillation (AF) rhythm was associated with about 4-fold higher risk for

developing POD among patients (OR: 4.519, CI 95%: 1.041–19.610; *P* value = 0.044). Remarkably, POD in the patients who did not receive dexamethasone was 1.2-fold higher than who received (OR: 0.890, CI 95%: 0.20–0.394; *P* value = 0.002).

Comparison of hospital outcomes between the groups represented in Table 3. These results indicated that delirious patients significantly had longer extubation time (11.52 ± 4.16 vs 9.44 ± 2.02 ; *P* value < 0.01). Moreover, the mean of days which patients received inotrope in ICU, was significantly longer in delirious patients (2.20 ± 0.41 vs 2.08 ± 0.28 ; *P* value = 0.04). Our results showed that delirious patients had a more LOS in ICU rather than nondelirious patients (4.14 ± 1.01 vs 3.61 ± 1.39 , respectively; *P* value = 0.04).

DISCUSSION

POD is one of the most common postoperative complications in patients who had undergone cardiac surgery and is associated with increased mortality, morbidity, and longer LOS in ICU and hospital. Therefore, a good understanding of POD predictors and its related outcomes has a significant importance. In this way, we analyzed some of the possible predictors of 196 patients after CABG. Analyses revealed that the incidence of postoperative delirium was 17.34%, which is in range of the previous reported incidence of POD (8%–50%).^[7]

Several factors were known as predictors of POD in hospitalized patients in CSICU. Previous identified predictors included age more than 65 years, history of mental and medical disease (eg, CVA, renal disease), complexity of surgery, emergency surgery, low hematocrit, acute infection, low cardiac output, atrial fibrillation, and massive blood transfusion.^[5] In our study, POD correlated with history of prior CRF (*P* value = 0.003). This association between CRF and POD might be resulted by the accumulation of metabolic endproducts during ischemic time.^[23,24] Because of CPB insertion, anaerobic metabolism of free fatty acids led to the increase of excessive levels of toxic metabolic endproducts during surgery.^[24,25] On the other hand, excessive levels of urea, uric acid, creatinine, and other toxins that cannot be eliminated by the dysfunctional kidneys

led to greater risk of cognitive decline in patients undergoing CABG.^[23]

Also, another predictor was history of COPD, which significantly associated with POD (OR: 13; *P* value = 0.029). Previously, restrictive pulmonary diseases were known as a predictor for delirium, but this finding was not frequently reported.^[16,26,27] Delirium is commonly diagnosed among patients suffering from COPD and acute respiratory failure. It is known that chronic hypoxia–hypercapnia is associated with development of delirium.^[28,29] The most possible explanation is the fact that hypercapnia leads to acidosis, and carbon dioxide narcosis, which might represent delirium.^[30,31] In addition, mild retention of carbon dioxide in COPD patients by dysregulation of cerebral arteries tonicity can weaken the cerebral perfusion and oxygenation.^[27,30]

Furthermore, patients with history of smoking and opioid addiction were more likely to be delirious in our study (*P* value = 0.008, 0.001, respectively). Findings of a higher incidence of postoperative delirium in smokers or addict patients have not been widely reported. Dubois and colleagues^[32] were reported that delirium occurred in smoker patients with higher rates. They were referred to imbalances of acetyl cholinergic and dopaminergic transmitters after smoking cessation, which link to delirium pathogenesis, as a hypothetical mechanism for the development of POD. Additionally, they mentioned higher rate of COPD in heavy smokers as another possible way for the development of POD in smokers. In any way, our results can verify their report. Moreover, the higher prevalence of smoking habit in addict patients could serve as another reason for this finding.^[33,34]

Obviously, addict patients have some degree of narcotic tolerance and they need higher doses of opioids for analgesia and/or avoiding withdrawal syndrome. Morphine, meperidine, and fentanyl are commonly used for analgesia and sedation in our CSICU. However, narcotics usage is strongly associated with delirium because of their anticholinergic properties.^[32,35] Deficiency of cholinergic reserve in elderly patients aggravates risk of development of POD.^[26] Consequently, administration of higher doses of opiates in addict patients can be a reason for this result. On other hand, sometimes addict patients receive

fewer opiates and it results in more agitation and withdrawal syndrome, which demonstrates as POD or may interact with its diagnosis.

A relationship between IABP and POD after cardiac surgery previously has been reported.^[7] This finding supported our results, which indicated that patients with IABP are at higher risk for development of POD (OR: 4.91; *P* value = 0.024). The results of thousands of brain autopsies revealed that dislodged microemboli played an important role in the development of POD after cardiac surgery. Theoretically, manipulation of atherosclerotic aorta can increase the risk of aortic emboli, which upon reaching the brain leads to cerebral ischemia and further leads to POD.^[5,26] Although it is not certain how IABP contributes to the development of POD, it is assumed that thrombosis or dislodgment of aortic plaque trapping into cerebral circulation leads to cognitive dysfunction and delirium.^[27] Practically, the IABP is frequently used in hypoperfusion and low cardiac output conditions and this condition can reduce cerebral perfusion, resulting in POD.^[27]

Recent studies confirm the existence of correlation between transfusion of PCs and POD after cardiac surgery.^[5] The results of our study also indicated that patients who had more transfusion of PCs (more than 4 U) are more prone to experience POD after cardiac surgery (OR: 4.62; *P* value = 0.015). It is common knowledge that transfusion of PCs routinely performed in the management of anemic patients. This is implying that more transfusion of PC meant more anemic conditions. On the other hand, anemia can induce hypoxia, brain ischemia, and POD after cardiac surgery.^[27,36]

Our results revealed that AF significantly associated with POD after cardiac surgery (OR: 4.51; *P* value = 0.044). Previous studies which evaluated predictors of delirium after cardiac surgery confirm our results.^[7,36] AF can cause POD by development of emboli and reduction of cerebral perfusion after decrease of cardiac output.^[7,32] However, there is no evidence indicating that restoration of arrhythmia to normal sinus rhythm could reduce the risk of development of delirium.^[7]

Our results show that the administration of dexamethasone significantly reduces the risk for POD (OR: 0.890; *P* value = 0.002). Speculatively, ischemia-reperfusion damage

during cardiopulmonary bypass leads to the activation of inflammatory cytokines, oxidative stress, and production of reactive oxygen species, which increases the blood–brain barrier (BBB) permeability.^[37,38] Breakdown of BBB integrity facilitates destruction of the brain parenchyma.^[39] Finally, infiltration of inflammatory cells into the damaged cerebral tissue causes extension of water inflow into brain, which leads to brain edema and cell dysfunction.^[13,39,40] In summary, overload of proinflammatory cytokines inflow into the brain can cause dysfunction of the nervous and neuroendocrine systems that may result in delirium.^[41] Consequently, dexamethasone with its modulatory effect on inflammatory mediators (tissue plasminogen activator, IL-6, IL8, and TNF- α) and disruption of the above processes might have a positive effect on reduction of delirium after utilization of CPB.^[42]

CONCLUSION

In our study, delirium was significantly correlated with adverse outcomes including longer extubation time, and inotrope use. The results of this study indicated that the delirious patients were intubated for a longer time. This finding is important because longer intubation time is related to more complications (eg, ventilator-associated pneumonia). Furthermore, we conclude that delirium is associated with prolonged intubation time because of the hypnotic/sedative agents that are administered for delirium management.^[43] The full consciousness and obedience of patients are two necessities for extubation, but administration of hypnotic/sedative medications for management of POD can decrease consciousness of patients.

It is previously known that delirium after cardiac surgery associated with prolonged ICU and hospital LOS.^[16,27,43] In any way, our results indicated that POD significantly increases LOS in ICU (P value = 0.04) but had no meaningful effect on hospital LOS (P value = 0.84). The potential explanation for this prolongation in ICU stay is a circumstance that POD is associated with more complications after cardiac surgery.^[16] Another potential explanation is the fact that management of delirium naturally required more ICU LOS.^[44] Pharmacologic agents commonly used for controlling of patient agitation, such as benzodiazepines, opiates, propofol, and

haloperidol, can extend ICU LOS. In addition, these pharmacologic agents may present a paradoxical agitation and new complications to delirious patients, which these complications might prolong ICU stay patients more than before.^[44,45]

Because of the relationship between POD in patients and hospital outcomes, recognition of its predictors plays an important role in the management of patients who undergo CABG. Early and accurate diagnosis of POD can protect patients from further complications. In addition, improvement of patient outcome leads to decrease in the LOS in ICU and subsequently hospital costs. Our study addresses predictors of POD, which patients might challenge them in CSICU. Verification of predictors of POD potentially leads to identification of patients at higher risk of POD. High-risk patients need intensive followup and aggressive treatment for the prevention of further complications. Additionally, some of the POD predictors are modifiable. Hence, prevention of modifiable predictors of POD, such as AF arrhythmia, might improve cognitive outcomes of cardiac surgeries easier.

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