

Incidence and Risk Factors of Emergence Delirium after General and Regional Anesthesia in Elective Non-Cardiac Surgery Patients

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Objective: To evaluate the incidence and risk factors of emergence delirium (ED) after general and regional anesthesia in elective non-cardiac surgery.

Materials and Methods: A prospective observational study was conducted among 454 patients aged over 18 years. The incidence of ED was assessed. Perioperative and intraoperative factors were also assessed using the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method (CAM) Thai version. Univariable analysis was performed followed by multivariable logistic regression.

Results: Sixty-five (14.32%) patients developed ED, of whom 9.25% presented hypoactive delirium and 5.07% presented hyperactive delirium. In multivariable analysis, patients older than 60 years [$p=0.003$; adjusted odds ratio (adjusted OR) 2.50], having underlying chronic kidney disease ($p=0.016$; adjusted OR 2.56), and anesthetic induction with etomidate ($p=0.017$; adjusted OR 9.60), cisatracurium ($p=0.006$; adjusted OR 0.35), sevoflurane ($p=0.003$; adjusted OR 2.52), and postoperative pain score ≤ 3 ($p=0.010$; adjusted OR 3.63) were significantly more likely to experience ED.

Conclusion: Patients aged more than 60 years, with underlying chronic kidney disease, mild pain score, and anesthetized with etomidate, cisatracurium, and sevoflurane had increased risk factors for ED. Therefore, to treat underlying disease and anesthetic medication, health providers should have essential knowledge to minimize the incidence of ED.

Keywords: Complication, Delirium, General anesthesia, Regional anesthesia, Recovery, Postoperative surgery

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Delirium is a common complication among medical inpatients and is associated with increased morbidity, mortality, length of hospital stay, and institutionalization⁽¹⁻³⁾. Short- and long-term outcomes are worse in subjects who develop postoperative delirium⁽³⁾. The prevalence of delirium on admission is 10% to 30% and new incidence is 3% to 29% while occurrence rate varied between 11% and 42% per admission⁽¹⁾. Early epidemiologic studies demonstrated many factors were related to this condition such as elderly status⁽³⁾, preexisting comorbidities⁽⁴⁾, type of surgery, and anesthetic agents⁽⁵⁾.

Emergence delirium (ED) in the post anesthesia care unit (PACU) is inadequately investigated. This could suddenly become dangerous, leading to serious consequences such as injury to the patient, increased

pain, hemorrhage, and displacement of catheters and self-extubation requiring physical or medical restraints⁽⁶⁾.

However, the risk factors and the mechanism of delirium have not been elucidated. The objective of the present prospective study was to determine the incidence and risk factors associated with ED to be better understood and to prevent these complications.

Materials and Methods

The present protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Ethics Committee at Phramongkutkdao Hospital to study between December 2016 and June 2017. All participants provided informed consents. A prospective observational study was conducted among 454 patients in the American Society of Anesthesiologist (ASA) status grade I, II, and III, aged over 18 years, undergoing elective non-cardiac surgery in either general anesthesia or regional anesthesia

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for various operative procedures. Exclusion criteria included a past medical history of neurological or psychiatric illness, a history of drug abuse, language barrier, pregnancy, and unable to extubate.

Participants were informed that they had the right to withdraw from the study at any time, without prejudice to their anesthetic treatment, and were not obliged to state any reason. Demographic data and cognitive function were assessed before undergoing operation. The anesthetic technique depended on the judgment of an anesthesiologist and was not influenced or intentionally altered as a result of participation in the study. All anesthetic data and types of surgery were recorded by the attending anesthesiologists during the intra-operative period. All participants were assessed by a blinded anesthetist nurse in the PACU using a brief delirium assessment based on the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method (CAM) Thai version⁽⁷⁾, which regarded from +1 to +4 of RASS and positive CAM for hyperactive delirium or -3 to 0 of RASS with positive CAM for hypoactive delirium.

The sample size was calculated based on the prevalence of delirium in the PACU 4.7%⁽⁶⁾. For a confidence level of 95% and absolute precision of 2%, a sample size of 431 would be required. Statistical analysis was performed using SPSS version 15 statistical software (IBM, Armonk, NY). Categorical data were presented as percentage and continuous data were presented using mean and standard deviation. Univariable analysis was performed with two-sample

t-test for numerical and Chi-squared test or Fisher's exact test (count less than 5) for hypothesized factor to correlate with ED. Multivariable analysis was performed using a backward binary stepwise logistic regression to examine and determine risk factors of delirium. All data were analyzed with the Statistical Package for Social Science (SPSS) version 15.0 for Windows. Results were expressed as odds ratio (OR) with 95% confidence interval (CI). A *p*-value of less than 0.05 was considered statistically significant.

Results

Four hundred fifty-four patients were enrolled into the present study over 11-month period. All of them were assessed, 65 patients had ED in PACU. The demographics and characteristics of the subjects were shown in Table 1. The mean age of the study subjects was 56.1±18 (range 18 to 90) years. The percentage of male totaled 52.42% (n = 454). Most patients (56.61%) were in the ASA physical status II and 8.59% were taking benzodiazepine as the premedication. Average duration of anesthesia was 2.57±1 hours. Patients who presented as hypertension, diabetes, chronic kidney disease (CKD), cardiovascular disease, various cancers, and liver disease totaled 46.04%, 28.63%, 10.57%, 10.13%, 7.93%, and 0.88%, respectively. The percentage of smoking totaled 16.3% and alcoholic drinking was 13.8%. The incidence of ED was found at 14.32% in the present study (9.25% for hypoactive delirium, and 5.07% for hyperactive delirium).

Univariate analysis showed significantly risk

Table 1. Demographic and characteristic data of the subjects

Variables	Delirium (n = 65), n (%)	Non-delirium (n = 389, n (%)	Total (n = 454), n (%)	<i>p</i> -value
Age over 60 years	43 (66.15)	157 (40.36)	200 (44.05)	<0.001*
Sex: male	43 (66.15)	195 (50.13)	238 (52.42)	0.017*
Disease				
Hypertension	43 (66.15)	166 (42.67)	209 (46.04)	<0.001*
Diabetes mellitus	21 (32.32)	109 (28.02)	130 (28.63)	0.479
Chronic kidney disease	15 (23.08)	33 (8.48)	48 (10.57)	<0.001*
Cardiovascular disease	12 (18.46)	34 (8.74)	46 (10.13)	0.016*
Various cancer	7 (10.77)	29 (7.46)	36 (7.93)	0.360
Liver disease	1 (1.54)	3 (0.77)	4 (0.88)	0.462
Smoking	10 (15.38)	64 (16.45)	74 (16.30)	0.829
Alcoholic drinking	9 (13.85)	54 (13.88)	63 (13.88)	0.994
Benzodiazepine premedication	1 (1.54)	38 (9.77)	39 (8.59)	0.107
Operative time >2 hours	31 (47.69)	206 (52.96)	237 (52.20)	0.432
ASA classifications				<0.001*
I	9 (7.50)	111 (28.53)	120 (26.43)	
II	33 (50.77)	224 (57.58)	257 (56.61)	
III	23 (35.73)	54 (13.88)	77 (16.96)	

ASA classification = American Society of Anesthesiologists Physical Status Classification System

* Statistical significance

factors were associated with ED among patients aged more than 60 years, complicated ASA classification, male, hypertension, CKD and cardiovascular disease as shown in Table 1. General anesthesia exhibited a significant trend toward possible ED compared with regional anesthesia and combined anesthesia [GA versus RA versus GA combined with RA: 43 (16.10%) versus 20 (15.38%) versus 2 (3.51%), respectively; $p=0.044$], but there was no significant difference in multivariate model. In addition, shivering was not a significant risk factor of ED ($p=0.110$), while pain score of 3 or less (11.64% of hypoactive type, 6.27% of hyperactive type) showed a significant possible factor

toward risk of ED ($p<0.001$) (Table 2).

Moreover, the present study showed risk factors of ED included being anesthetized by etomidate ($p<0.001$), cisatracurium ($p=0.03$), morphine ($p=0.028$), sevoflurane ($p=0.042$), desflurane ($p=0.014$), and glycopyrrorate ($p=0.001$) (Table 3). However, type of surgery was not significantly associated with ED (Table 4).

Multivariate analysis by backward binary stepwise logistic regression revealed that patients older than 60 years had 2.5 times the risk of developing ED [$p=0.003$; adjusted odds ratio (adjusted OR) 2.50, 95% confident interval (CI) 1.36 to 4.62], as well as patients having

Table 2. Summary of anesthetic techniques, shivering and postoperative pain score among patients with and without delirium and after anesthesia

Variables	Delirium, n (%)	Non-delirium, n (%)	Total, n (%)	<i>p</i> -value
Number of patients	65 (14.32)	389 (85.68)	454 (100)	
Choice of anesthesia				0.044*
General anesthesia (GA)	43 (16.10)	224 (83.90)	267 (58.81)	
Regional anesthesia (RA)	20 (15.38)	110 (84.62)	130 (28.63)	
GA combined with RA	2 (3.51)	55 (96.49)	57 (12.56)	
Shivering				0.110
No shivering	57 (87.69)	365 (93.83)	422 (92.95)	
Shivering	8 (12.31)	24 (6.17)	32 (7.05)	
Pain score				<0.001*
0 to 3	60 (17.91)	275 (82.09)	335 (73.79)	
4 to 10	5 (4.20)	114 (95.80)	119 (26.21)	

* Statistical significance

Table 3. Summary of anesthetic drugs among patients with and without delirium

Variables	Delirium, n (%)	Non-delirium, n (%)	Total, n (%)	<i>p</i> -value
Number of patients	65 (14.32)	389 (85.68)	454 (100)	
Induction				
Propofol	35 (53.85)	231 (59.38)	266 (58.59)	0.402
Thiopental	4 (6.15)	42 (10.80)	46 (10.13)	0.258
Midazolam	0 (0.00)	1 (0.26)	1 (0.22)	1.000*
Etomidate	6 (9.23)	2 (0.51)	8 (1.76)	<0.001*
NMB agent				
Cisatracurium	14 (21.54)	138 (35.48)	152 (33.48)	0.030*
Atracurium	19 (29.23)	87 (22.37)	106 (23.35)	0.228
Succinylcholine	12 (18.46)	43 (11.05)	55 (12.11)	0.090
Maintenance				
Sevoflurane	38 (58.46)	174 (44.73)	212 (46.70)	0.042*
Desflurane	7 (10.77)	98 (25.19)	105 (23.13)	0.014*
Intravenous propofol	0 (0.00)	3 (0.77)	3 (0.66)	1.000
Opioids				
Morphine	16 (24.62)	151 (38.82)	167 (36.78)	0.028*
Fentanyl	45 (69.23)	221 (56.81)	266 (58.59)	0.060
Meperidine	0 (0.00)	12 (3.08)	12 (2.64)	0.230
Reverse				
Neostigmine	43 (66.15)	259 (66.58)	302 (66.52)	0.946
Glycopyrrolate	15 (23.08)	37 (9.51)	52 (11.45)	0.001*

NMB agent = neuromuscular blocking agent

* Statistical significance

Table 4. Type of surgery

Operation	Delirium (n = 65) n (%)	Total (n = 454) n (%)	p-value
Abdominal surgery	27 (16.77)	161 (35.46)	0.269
Urological surgery	10 (15.87)	63 (13.87)	0.704
Orthopedic surgery	11 (10.28)	107 (23.57)	0.173
Neurological surgery	1 (08.33)	12 (2.64)	1.000
Vascular surgery	7 (29.17)	24 (5.86)	0.064
Eye/ear nose throat surgery	4 (8.33)	48 (10.57)	0.211
Colonoscopy	3 (25.0)	12 (2.64)	0.392
Gynecological surgery	2 (7.41)	27 (5.95)	0.402

Table 5. Multivariable analysis using multiple logistic regression

Factors	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Age >60	2.89 (1.66 to 5.02)	2.50 (1.35 to 4.60)	0.003*
CKD	3.24 (1.64 to 6.38)	2.56 (1.19 to 5.53)	0.016*
Etomidate	19.68 (3.88 to 99.79)	9.60 (1.49 to 61.88)	0.017*
Cisatracurium	0.50 (0.27 to 0.93)	0.35 (0.17 to 0.74)	0.006*
Sevoflurane	1.74 (1.02 to 2.96)	2.52 (1.36 to 4.68)	0.003*
Pain score ≤3	4.98 (1.95 to 12.71)	3.60 (1.35 to 9.75)	0.010*

CKD = chronic kidney disease; OR = odds ratio; CI = confidence interval

* Statistical significance

underlying CKD ($p=0.016$; adjusted OR 2.56, 95% CI 1.19 to 5.53). In addition, anesthetic medications included etomidate ($p=0.017$; adjusted OR 9.6, 95% CI 1.49 to 61.88) and cisatracurium ($p=0.006$; adjusted OR 0.35, 95% CI 0.17 to 0.74). Therefore, with sevoflurane ($p=0.003$; adjusted OR 2.52, 95% CI 1.36 to 4.68), patients who had postoperative pain score of 3 or less ($p=0.010$; adjusted OR 3.63, 95% CI 1.35 to 9.75) were significantly more likely to experience ED (Table 5).

Discussion

Several related studies investigated the incidence and risk factors of ED. The overall incidence of ED varied from 3%⁽⁸⁾ to 44%⁽³⁾. However, the present study revealed 14%, which was consistent with a related study that reported the incidences ranging from 5% to 15% among the elderly⁽⁸⁾.

General anesthesia showed a trend toward probable ED compared to regional anesthesia and combined anesthesia in univariate analysis. A proposed explanation for this is that some anesthetic drugs used in general anesthesia, especially anticholinergic usage, has been recognized as a usual risk factor for ED. Anticholinergics work by blocking the actions of acetylcholine in the substantia nigra. It is assumed that acetylcholine is neurotransmitters that may be

participated in the pathogenesis of ED⁽⁹⁾.

Although administration of many medications can be restricted from regional anesthetic techniques and expectedly reduced the risk of ED, the results are incongruity and pathophysiology is not fully understood. It appears that many patients had metabolic and neurochemical substances that disturb neuronal function⁽¹⁰⁾.

However, a relationship between type of anesthesia was not significantly linked to ED in multivariate analysis in prior studies^(11,12).

Some variables such as old age may predict the occurrence of ED^(3,5,8,13-15), which is in accordance with the present study that found that patients older than 60 years was a predictor of developing ED. Hypothetical mechanisms include disordered neurotransmission, inflammation, stress⁽¹⁵⁾, and the aging brain. Those demonstrate both quantitative and qualitative alterations in neuronal activity^(16,17). Conversely, a research study by Card et al⁽¹⁸⁾ showed no relationship between old age and ED. The present study found that CKD was a significant risk factor of ED, and assumed that electrolyte and fluid abnormality were precipitating factors⁽¹⁹⁾.

One common variable factor associated with ED is anesthetic agent. The present study found that inhaling anesthesia with sevoflurane showed a significant risk of ED, consistent with related studies demonstrating that sevoflurane continued to present a higher ED incidence among children⁽²⁰⁻²²⁾, but contrast to reports that sevoflurane did not pose any risk of ED^(6,23). In addition, the present study found that desflurane presented an increased risk for ED using univariate analysis, in accordance the related study reporting desflurane presented an increased risk for ED relative to both halothane and sevoflurane, based on the belief that the low blood gas solubility promotes rapid arousing that mutually increases sensitivity to ED⁽²⁴⁾. However, the present study found desflurane lacked any association by using multivariate analysis in accordance with the related study⁽⁶⁾.

In addition, one study reported that etomidate showed a significant risk of emergence agitation that was echoed in the study by Radtke et al⁽⁵⁾. The mechanism is believed to result from activity either in the brainstem or in the deep cerebral structures⁽²⁵⁾ and associated with frequent myoclonic movement⁽²⁶⁾.

Another interesting result was that the patients who received cisatracurium were at higher risk of ED compared with patients receiving atracurium or succinylcholine. Vijayakumar et al⁽²⁷⁾ found that

hypoxemia resulting from residual effects of non-depolarizing muscle relaxants following general anesthesia increased the risk of developing ED. In the present study, cisatracurium had a significant association when compared with the others, possibly due to prolonged duration. The residual neuromuscular agent can be observed in the PACU. However, monitoring neuromuscular action during surgery should reduce the risk of a residual neuromuscular agent⁽⁶⁾.

The present study found that type of operation did not influence ED. This finding is in contrast to related studies⁽⁵⁾. The study of Lepouse et al⁽⁶⁾ reported intra-abdominal surgery increased the risk for ED by three times. The operation is known to be very painful and of longer duration. In contrast to related studies^(5,7,27,28), the present study showed a pain score of 3 or less was significantly more likely to result in ED and associated with high incidence of hypoactive delirium.

The present study had several limitations. Firstly, neurosurgery was not addressed because most neurosurgical patients usually remain intubated after surgery and reside in a postoperative intensive care unit (ICU), making it difficult to assess. However, the term ICU delirium or ICU psychosis was appropriate in postoperative ICU⁽⁸⁾. Secondly, the patient might have underestimated the short-term period especially in PACU; patients develop the classic fluctuating mental status after the PACU period, usually between postoperative days 1 and 3⁽⁹⁾. Therefore, long term follow-up is recommended. Thirdly, other treatment modalities were not controlled such as analgesic medication and psychotherapy, meaning there might be confounding factors regarding the results.

Conclusion

ED has been a significant problem for healthcare providers in PACU. The findings demonstrate that certain demographic and clinical variables were associated with ED in particular age older than 60 years, coexisting disease like CKD, and postoperative pain score of 3 or less. Anesthesia induction with etomidate, using cisatracurium neuromuscular blocking agent and sevoflurane inhalation, indicated a risk factor for ED. Recognizing patients who are at high risk for delirium will help either treatment or prevention strategies to reduce the severity and preventing the incidence of delirium.

What is already known on this topic?

Previous studies summarized that risk factors of emergence agitation are multifactorial such as

preoperative benzodiazepines, breast and abdominal surgery, long duration of surgery⁽⁶⁾, and old age⁽¹³⁻¹⁶⁾. However, the risk factor and mechanism of delirium has not been elucidated.

What this study adds?

This study is a large study seeking to identify characteristics associated with ED specific in non-cardiac surgery. Firstly, the most surprising find from this study is that lower pain score is a significant risk of ED in hypoactive type. This result had never been reported before. Secondly, the incidences of emergence agitation in sevoflurane are not only in pediatrics⁽²⁹⁾ but also in adult. Thirdly, long active neuromuscular blocking agent increased risk of developing ED.

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Potential conflicts of interest

The authors declare no conflict of interest.

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