

Risk factors of emergence agitation after general anesthesia in adult patients

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Background: Emergence agitation (EA) is one of the most common complications after general anesthesia. The goal of this retrospective study was to determine the risk factors of EA in adult patients who underwent general anesthesia.

Methods: We retrospectively investigated the medical records of 5,358 adult patients who stayed in the postanesthesia care unit (PACU) of our hospital after general anesthesia during the 1-year period from January 2014 to December 2014. Psychological and behavioral status in the PACU was determined by the Aono four-point scale. Grade of 3 or 4 were considered as manifestations of EA. Multiple variables assessed EA risk factors.

Results: Two-hundred-forty-five patients (4.6%) developed EA. In multivariate analysis, male gender (OR = 1.626, $P = 0.001$), older age (OR = 1.010, $P = 0.035$), abdominal surgery (OR = 1.633, $P = 0.002$), spine surgery (OR = 1.777, $P = 0.015$), longer duration of anesthesia (OR = 1.002, $P < 0.001$), postoperative nausea and vomiting (OR = 20.164, $P < 0.001$) and postoperative pain (OR = 3.614, $P < 0.001$) were risk factors of EA.

Conclusions: Male gender and older patients were risk factors of EA after general anesthesia in adult patients. Careful attention is needed for patients who receive abdominal or spine surgery, and who receive prolonged anesthesia. Adequate postoperative analgesia and antiemetic therapy should be provided to reduce the incidence of EA. (*Anesth Pain Med* 2016; 11: 410-416)

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INTRODUCTION

Emergence agitation (EA) comprises agitation, confusion, disorientation or violent behavior in the early phase of recovery from general anesthesia [1]. EA is one of the most common complications after general anesthesia [2]. Premedication with benzodiazepines, longer duration of surgery, breast surgery and abdominal surgery are important risk factors [3-5]. Postoperative pain was identified as a risk factor of EA [6]. However, the influence of postoperative pain on EA has yet to be determined [3].

EA is a common complication that develops in the postanesthesia care unit (PACU), but it can easily be underestimated. It can cause serious consequences including injury, increased pain, hemorrhage, self-extubation and removal of catheters, and may even necessitate physical or chemical restraint [6]. Furthermore, it may lead to injury of medical staff and increase of hospital costs [7]. Identifying of risk factors of EA to prevent these aforementioned problems is important for the anesthesiologist.

Nonetheless, EA in adult patients has not been fully studied. In addition, different scales for estimating EA has been used in some previous studies, resulting in various incidence of EA after general anesthesia from 3% to 21.3% depending on the study [3,4,6,8]. EA risk factors have been inconsistent in the studies.

To clarify the issue, we performed this retrospective study to determine the incidence and the risk factors of EA after general anesthesia in adult patients in the PACU.

MATERIALS AND METHODS

This retrospective study approved by the Institutional Review Board of our hospital investigated the medical records of patients who underwent general anesthesia for surgery from

January 2014 to December 2014 at our hospital. Patients with no PACU data owing to intensive care unit (ICU) admission and those < 18 years of age were excluded. Assuming that that stimulation of central nervous system can affect EA, patients who underwent neurosurgery other than spinal cord surgery were also excluded.

We recorded the physical factors of patients including age, gender, body mass index (BMI, < 25 kg/m² vs. ≥ 25 kg/m²) and American Society of Anesthesiologist (ASA) physical status (1 vs. ≥ 2) before induction of anesthesia. We also checked the site of surgery and type of surgery (elective or emergent). In the patients who underwent abdominal surgery, the type of surgery (open or laparoscopic) was investigated. The data of patient health status including drinking history, smoking history and coexisting diseases were collected. Patients who smoked everyday were regarded as a current smoker. Habitual drinker was defined as an individual who drank at least one or more times a week. The use of glycopyrrolate or diazepam for preanesthetic medication was checked. We investigated the agent used for induction of general anesthesia. Maintenance of anesthesia selected between total intravenous anesthesia (TIVA) and inhalation anesthesia using one of either desflurane, isoflurane or sevoflurane was also investigated. We recorded the type of neuromuscular blockers (NMBs) used. The use of opioid analgesics or nitrous oxide (N₂O) during anesthesia was also recorded. In addition, we investigated the length of anesthesia.

In the PACU, the degree of postoperative pain and presence of postoperative nausea and vomiting (PONV) were checked by nursing staff. Postoperative pain was assessed immediately after the patient was transferred to the PACU and reassessed every 15 minutes by using a numerical rating scale (NRS). Patients with NRS ≥ 6 in the PACU were considered to have postoperative pain.

In our hospital, the status of emotion and behavior during emergence from general anesthesia is evaluated and recorded routinely by nursing staff using an established Aono four-point scale: 1 = calm; 2 = not calm but could be easily calmed; 3 = not easily calmed, moderately agitated or restless; and 4 = combative, excited, or disoriented [9]. Patients with a score of 3 or 4 in the PACU were considered to have experienced EA.

Statistical analyses were performed using the Statistical Package for Social Sciences Version 19.0 software (SPSS Inc., USA). In univariate analysis, categorical variables were analyzed by the chi-square test. The t-test was used for normally distributed variables and the Mann-Whitney U test for

non-normally distributed variables in comparison of the continuous data. The variables that were significant at $P < 0.05$ were selected, and backward stepwise multivariate logistic regression analysis was conducted to determine the risk factors of EA. All independent variables were expressed as odds ratio (OR) with 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

RESULTS

The total number of the patients was 7,602. Of these, 2,244 patients were eliminated due to an inadequate PACU data, age < 18 years and history of neurosurgery (Fig. 1). Finally, 5,358 patients were enrolled in the analysis; 3,142 (58.6%) had Aono score of 1, 1,971 (36.8%) had Aono score of 2, 240 (4.5%) had Aono score of 3, and 5 (0.1%) had Aono score of 4. EA was evident as a score of 3 or 4 in 245 patients (4.6%).

Results of univariate analysis of the incidence of EA and risk factors between non-agitated patients and agitated patients are presented in Table 1. Male gender was associated with a higher incidence of EA ($P = 0.003$). Average age of agitated patients (55.2 ± 17.4 years) was significantly higher compared with that of non-agitated patients (51.6 ± 16.4 years) ($P = 0.001$). Among the coexisting diseases, only neuropsychiatric disease was significantly correlated with the incidence of EA ($P = 0.030$). Patients who underwent abdominal surgery ($P < 0.001$) and spine surgery ($P = 0.016$) were significantly more often agitated, whereas head surgery and neck surgery ($P < 0.001$) were less frequent in agitated patients. In addition, there

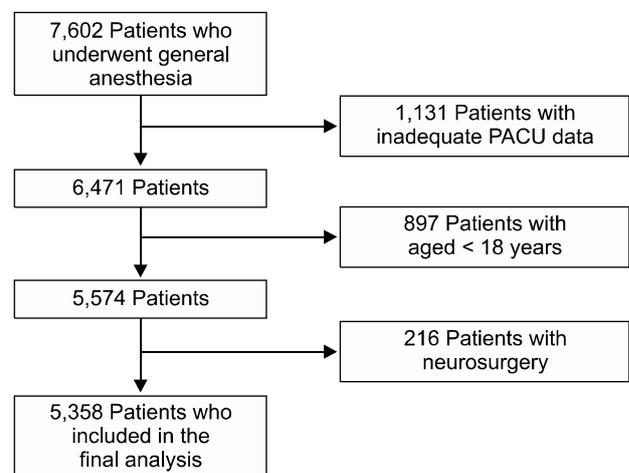


Fig. 1. Flowchart of study population.

Table 1. Incidence of Emergence Agitation Relative to Perioperative Factors in Adult Patients

	Total (n = 5,358)	Non-agitated (n = 5,113)	Agitated (n = 245)	P value
Male gender	2,764 (52%)	2,615 (51%)	149 (61%)	0.003
Age (yr)	51.7 ± 16.5	51.6 ± 16.4	55.2 ± 17.4	< 0.001
BMI (≥ 25 kg/m ²)	1,736 (32%)	1,652 (32%)	84 (34%)	0.530
ASA (≥ 2)	4,104 (77%)	3,905 (76%)	199 (81%)	0.089
Coexisting disease				
Cardiovascular	1,475 (28%)	1,397 (27%)	78 (32%)	0.125
Respiratory	267 (5%)	255 (5%)	12 (5%)	1.000
Gastrointestinal	284 (5%)	268 (5%)	16 (7%)	0.379
Renal	143 (3%)	136 (3%)	7 (3%)	0.838
Musculoskeletal	63 (1%)	61 (1%)	2 (1%)	1.000
Neuropsychiatric	338 (6%)	314 (6%)	24 (10%)	0.030
Endocrine	906 (17%)	862 (17%)	44 (18%)	0.663
Current smoker	953 (18%)	901 (18%)	52 (21%)	0.147
Habitual drinker	1,472 (27%)	1,408 (28%)	64 (26%)	0.661
Preanesthetic glycopyrrolate	4,609 (86%)	4,402 (86%)	207 (85%)	0.452
Preanesthetic benzodiazepine	3,722 (69%)	3,564 (70%)	158 (65%)	0.088
Emergency surgery	827 (15%)	784 (15%)	43 (18%)	0.365
Site of surgery				
Head	1,271 (24%)	1,240 (24%)	31 (13%)	< 0.001
Neck	482 (9%)	472 (9%)	10 (4%)	0.004
Breast	202 (4%)	197 (4%)	5 (2%)	0.170
Thoracic	113 (2%)	107 (2%)	6 (2%)	0.647
Abdomen	1,697 (32%)	1,587 (31%)	110 (45%)	< 0.001
Urology	313 (6%)	297 (6%)	16 (7%)	0.579
Spine	440 (8%)	409 (8%)	31 (13%)	0.016
Extremities	707 (13%)	675 (13%)	32 (13%)	1.000
Others	125 (2%)	122 (2%)	3 (1%)	0.381
Induction agents				0.640
Barbiturate	82 (2%)	80 (2%)	2 (1%)	
Etomidate	39 (1%)	37 (1%)	2 (1%)	
Propofol	5,237 (97%)	4,996 (98%)	241 (98%)	
TIVA	284 (5%)	259 (5%)	25 (10%)	0.002
Use of N ₂ O	3,115 (58%)	2,995 (59%)	120 (49%)	0.003
Inhalation agents				0.242
Desflurane	2,421 (45%)	2,328 (48%)	93 (42%)	
Isoflurane	2 (0%)	2 (0%)	0 (0%)	
Sevoflurane	2,651 (49%)	2,524 (52%)	127 (58%)	
The type of NMBs				0.052
Rocuronium	1,150 (22%)	1,098 (22%)	52 (21%)	
Cisatracurium	109 (2%)	99 (2%)	10 (4%)	
Succinylcholine	89 (2%)	88 (2%)	1 (0%)	
Vecuronium	4,010 (75%)	3,828 (75%)	182 (74%)	
Use of opioid analgesics	1,506 (28%)	1,442 (28%)	64 (26%)	0.513
Duration of anesthesia (min)	146.6 ± 93.4	145.2 ± 92.5	175.8 ± 106.5	< 0.001
PONV	284 (5%)	200 (4%)	84 (34%)	< 0.001
Postoperative pain (NRS ≥ 6)	851 (16%)	768 (15%)	83 (34%)	< 0.001

Values are number (%) or mean ± SD. BMI: body mass index, ASA: American Society of Anesthesiologist physical status, TIVA: total intravenous anesthesia, NMBs: neuromuscular blockers, PONV: postoperative nausea and vomiting, NRS: numerical rating scale.

was no significant difference on the occurrence of EA between laparoscopic abdominal surgery and open abdominal surgery (laparoscopic group; 5.9%, open group; 8.1%, $P = 0.102$). Total intravenous anesthesia TIVA ($P = 0.002$) and use of N_2O ($P = 0.003$) were significantly associated with higher incidence of EA. The mean of duration of anesthesia in agitated patients (175.8 ± 106.5 min) was also significantly higher than that of non-agitated patients (145.2 ± 92.5 min; $P < 0.001$). PONV ($P < 0.001$) and postoperative pain ($P < 0.001$) significantly correlated with the higher incidence of EA. However, $BMI \geq 25$ kg/m² ($P = 0.530$) and ASA physical status ≥ 2 ($P = 0.089$) were not associated with the incidence of EA. EA was not correlated with premedication with glycopyrrolate ($P = 0.452$) or benzodiazepine ($P = 0.088$), types of induction agents ($P = 0.640$), inhalation agents ($P = 0.242$), NMBs ($P = 0.052$) and emergency surgery ($P = 0.365$). No difference in the incidence of EA was found in patients who received opioid analgesics ($P = 0.513$) during anesthesia. In addition, no difference was found in the incidence of EA in the patients who currently smoked ($P = 0.147$) and habitually drank ($P = 0.661$).

Univariate analysis revealed a significant association between the incidence of EA and 12 variables (male gender, older age, neuropsychiatric disease, abdominal surgery, spine surgery, head surgery, neck surgery, TIVA, use of N_2O , longer duration of anesthesia, PONV and postoperative pain). Multivariate analysis of these 12 variables using logistic regression showed that male gender, older age, abdominal surgery, spine surgery, longer duration of anesthesia, PONV and postoperative pain

Table 2. Multivariate Analysis of Factors Predictive of Emergence Agitation in Adult Patients

Factors	Odds ratio	95% CI	P value
Male gender	1.626	1.220-2.167	0.001
Age	1.010	1.001-1.019	0.035
Neuropsychiatric ds.	1.574	0.970-2.553	0.066
Head surgery	0.735	0.454-1.189	0.210
Neck surgery	0.487	0.236-1.008	0.052
Abdominal surgery	1.633	1.195-2.232	0.002
Spine surgery	1.777	1.120-2.819	0.015
TIVA	1.103	0.650-1.873	0.716
Use of N_2O	0.769	0.576-1.026	0.074
Duration of anesthesia (min)	1.002	1.001-1.003	< 0.001
PONV	20.164	14.420-28.197	< 0.001
Postoperative pain (NRS ≥ 6)	3.614	2.652-4.924	< 0.001

CI: confidence interval, TIVA: total intravenous anesthesia, PONV: postoperative nausea and vomiting, NRS: numerical rating scale.

were independent risk factors of EA (Table 2).

Among the risk factors associated with EA, male gender, abdominal surgery, spine surgery and longer duration of anesthesia were significantly associated with postoperative pain (NRS ≥ 6) (Table 3).

DISCUSSION

Although EA is a common problem in the PACU, its incidence and etiology in adults are unclear [3]. Recent studies reported a 3% to 21% the incidence of EA after general anesthesia in adults [3,4,6,8]. In this study, the overall incidence of EA was 4.6%. This is comparable to a prior study [6]. Seven independent risk factors including male gender, older age, abdominal surgery, spine surgery, longer duration of surgery, PONV and postoperative pain were identified in the multivariate analysis.

Patient age was examined as a continuous variable. The incidence of EA was significantly higher in older patients. Radtke et al. [3] classified three age groups (18 to 39, 40 to 64, and ≥ 65 years) and showed that younger and older patients were at a higher risk for EA compared to middle aged patients. In comparison, some studies demonstrated that EA occurred more frequently in younger patients [5,10,11]. Unlike these studies, others failed to prove the significant relationship between the incidence of EA and age [4,6]. Considering the disagreement of the aforementioned studies, an additional prospective randomized controlled study to clarify the correlation between age and the incidence of EA is needed.

Patients with EA also had significant longer duration of anesthesia in this study. Lepoussé et al. [6] described that duration of surgery was also statistically significant for incidence of EA. Over 50 years ago, Smessaert et al. [10] speculated that the longer duration of surgery may be relayed

Table 3. Relationship between the Postoperative Pain and the Risk Factors of Emergence Agitation

Factors	Odds ratio	95% confidence interval	P value
Male gender	1.231	1.059-1.429	0.007
Age	0.998	0.993-1.002	0.353
Abdominal surgery	2.310	1.969-2.709	< 0.001
Spine surgery	2.035	1.568-2.640	< 0.001
Duration of anesthesia (min)	1.001	1.000-1.002	0.032

to the incidence of EA by increasing subsequent postoperative pain unrelated to the surgery itself. Similar with a prior study [3], the duration of anesthesia increased significantly with the degree of postoperative pain in the present study.

Postoperative pain has been identified as a risk factor for EA [3,5,6]. Presently, postoperative pain markedly increased the odds of EA; the risk for EA in the patients who had postoperative pain was increased nearly five-fold. We hypothesized that use of opioid analgesics during anesthesia may lower the incidence of EA. However, no difference was observed ($P = 0.513$). Sixteen percent of patients were estimated to have stronger postoperative pain ($\text{NRS} \geq 6$) in the PACU. Similarly, in another study 28.5% of patients were reported to have suffered from the postoperative pain ($\text{NRS} \geq 5$) in the recovery room [12]. These figures suggest that adequate control of postoperative pain has not been fully achieved despite the significance of the postoperative pain on the occurrence of EA. More aggressive postoperative pain control are needed to lower the incidence of EA.

Lepou   et al. [6] reported that abdominal surgery increased the risk for EA by three-fold. They correlated the invasive surgery with a higher pain level. Identically, we were able to show that abdominal surgery was associated with a higher incidence of EA in the multivariate analysis. There was a significant correlation between abdominal surgery and postoperative pain ($\text{NRS} \geq 6$). In addition, we compared the laparoscopic abdominal surgery to open abdominal surgery on the basis of assumption that less invasiveness of laparoscopic abdominal surgery may lower the incidence of EA. However, there was no significant difference in the occurrence of EA between the laparoscopic group (5.9%) and the open group (8.1%) ($P = 0.102$). Tolver et al. [13] stated that visceral pain is by far the dominating pain component compared with incisional and shoulder pain. Accordingly, there is a possibility of little relationship between postoperative pain and the size of the incision. In our study, spine surgery was also associated with a higher incidence of EA. Conventional spinal surgery often involves extensive dissection of subcutaneous tissues, bones and ligaments, resulting in considerable postoperative pain [14]. In this study, a significant association between spinal surgery and postoperative pain ($\text{NRS} \geq 6$) was also identified. Furthermore, the majority of patients had suffered from preexisting chronic pain that was treated with analgesics or narcotics. Altered pain perception in these patients may complicate pain management, increasing the incidence of EA. We suggest that more powerful analgesics during the

perioperative period will be required after abdominal and spine surgery [12].

Some recent epidemiologic studies indicated that women are at significantly greater risk for many clinical pain conditions. Women were tended to report more severe pain at lower thresholds than men in experimental pain paradigms [15]. The prevalence of common forms of pain is reportedly higher in women than men, and women report greater pain after invasive procedures than men [16]. When considering the relationship between the postoperative pain and EA as stated above, the incidence of EA in females is expected to be higher than in males. However, to the contrary, the incidence of EA in males was significantly higher than in females in the present study. Lower pain tolerance in males may contribute to this result [4]. Previous studies also have mentioned that men complain of more pain and consume more patient-controlled analgesia than women [17,18]. Similarly, there was a significant relationship between male gender and postoperative pain ($\text{NRS} \geq 6$) in this study. In addition, male gender was a reported risk factor in a prior [19]. Contrarily, there were no significant relationships between the gender and incidence of EA in other studies [3,6,11].

Presently, PONV was the main cause of EA. Kim et al. [11] reported no significant difference between patients with PONV and patients without in terms of the incidence of EA. PONV is one of the most common causes of patient dissatisfaction after anesthesia with a reported incidence as high as 63% after laparoscopic cholecystectomy [20,21]. PONV can contribute to anxiety, dehydration, metabolic abnormality, wound disruption, delayed recovery and other issues, and eventually may lead to susceptibility to EA [22]. Thus, appropriate antiemetic therapy should be considered.

In some studies, premedication of benzodiazepine was reported as a risk factor of EA [3,6]. Conversely, benzodiazepine lowered the incidence of EA in elderly hospitalized patients in another study [23]. No relationship between preanesthetic benzodiazepine and EA was presently evident. Although premedication of benzodiazepine is conducted to reduce preoperative anxiety, subsequently reduce incidence of EA, the effect on incidence of EA is disputable.

Some studies reported that ENT surgery is related with a higher incidence of EA in adults and children [4,5,24]. In contrast, we observed that head and neck surgery tended to lower the incidence of EA in univariate analysis, although multivariate analysis failed to show any significant difference. Relatively less incision and invasiveness of surgery might have

influenced.

Radtke et al. reported that induction with etomidate is independent risk factor of EA, citing that etomidate may cause frequent myoclonic movement [3,25]. In our study, however, no difference was observed among the induction agent.

Patients who received TIVA were reportedly less frequently agitated than who anesthetized with inhalation agents [26]. In our study, similar to the findings of Lepou   et al. [6], no significant difference between two anesthetic maintenance methods was found in multivariate analysis. Also, there were no differences among the inhalation agents.

There are some limitations to the present study. First, patients admitted to the ICU were not recruited. In our institute, patients who need intensive monitoring or airway maintenance with endotracheal intubation are directly transferred to the ICU without PACU stay after surgery. The exclusion of these patients who may be prone to EA may have influenced the results. Second, we did not evaluate hypoactive delirium (HD). Various scales, including the Richmond agitation and sedation scale, Riker sedation-agitated scale and the Aono four-point scale were used to evaluate the degree of EA in other studies [3,6,9]. The latter four-point scale has been used routinely in our hospital because of its relative simplicity. It cannot be used to evaluate the degree of HD. Park et al. [27] stated that incidence of EA can be underestimated by residual sedation, thus the degree of sedation should be assessed in all patients during evaluation of EA. Other studies proposed that HD is more frequent than EA in younger patients after general anesthesia, suggesting longer duration of surgery and intra-abdominal surgery as risk factors [3,28]. HD may often be unrecognized, misdiagnosed as dementia or simply attributed to old age [29]. Considering that HD may lengthen the hospitalization time, although does not require human resources, additional study to investigate the incidence and risk factors of HD will be needed. Third, this observational study was conducted retrospectively. The calculation of the power and sample size was not performed. Thus, insufficient size of sample may have not yield statistical significance in the result that achieved no significance in this study.

In conclusion, EA after general anesthesia is a relatively common complication in adult patients. The overall incidence of EA was 4.6%. Male gender, older age, abdominal surgery, spine surgery, longer duration of surgery, PONV and post-operative pain were identified as the independent risk factors. To promote the prevention of EA, sufficient postoperative pain management and adequate antiemetic therapy should be done.

In addition, special attention should be paid to patients with the presently identified risk factors.

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