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Emergence agitation in adults: risk factors in 2,000 patients
Agitation au réveil chez l'adulte: facteurs de risque chez 2000 patients

Daihua Yu, MD · Wei Chai, MD · Xude Sun, MD · Linong Yao, MD

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Abstract

Purpose *The study was designed to determine the incidence of postoperative agitation following general anesthesia in 2,000 adult patients and to examine the associated risk factors.*

Methods *The study enrolled 2,000 adults who were scheduled for surgery under general anesthesia in a single institution during December 2007 to December 2008. The following risk factors were examined: age, gender, ASA physical status, type of surgery, anesthesia technique (inhalational or intravenous), administration of neostigmine or doxapram, adequate postoperative analgesia, pain, presence of a tracheal tube, and presence of a urinary catheter.*

Results *Agitation occurred in 426 patients (21.3%). It was more common in males (28.1%) than in females (16.1%) (P = 0.017) and more prevalent after inhalational (27.8%) than total intravenous (7.5%) anesthesia (P = 0.001). Agitation was more common after oral cavity and otolaryngological surgery than after other types of surgery. Multivariate analysis showed that use of doxapram (odds ratio [OR] = 9.2; 95% confidence interval [CI] = 6.2 - 15.4; P = 0.002) and pain (OR = 8.2; 95% CI = 4.5 - 16.9; P < 0.001) were the most important risk factors associated with emergence agitation. Other causes were the presence of a tracheal tube and/or a urinary catheter. Adequate postoperative analgesia was associated with less agitation (OR = 0.4; 95% CI = 0.1 - 0.4; P = 0.006).*

Conclusion *Doxapram administration, pain, and presence of a tracheal tube and/or a urinary catheter appear to be the most important causes of postoperative agitation. To avoid this complication, it is suggested, whenever possible, to use intravenous anesthesia, to remove endotracheal tubes and urinary catheters as early as possible, and to provide adequate postoperative analgesia.*

Résumé

Objectif *Cette étude a été conçue afin de déterminer l'incidence d'agitation postopératoire après une anesthésie générale chez 2000 patients adultes et d'examiner les facteurs de risque associés.*

Méthode *L'étude a recruté 2000 adultes devant subir une chirurgie sous anesthésie générale dans une seule institution entre décembre 2007 et décembre 2008. Les facteurs de risque suivants ont été examinés: l'âge, le sexe, le statut physique ASA, le type de chirurgie, la technique anesthésique (par inhalation ou intraveineuse), l'administration de néostigmine ou de doxapram, une analgésie postopératoire adaptée, la douleur, la présence d'une sonde endotrachéale et la présence d'un cathéter urinaire.*

Résultats *Au total, 426 patients ont montré des signes d'agitation (21,3 %). Elle était plus courante chez les hommes (28,1 %) que chez les femmes (16,1 %) (P = 0,017) et plus prévalente après une anesthésie par inhalation (27,8 %) qu'après une anesthésie réalisée exclusivement par intraveineuse (7,5 %) (P = 0,001). L'agitation était plus fréquente après une chirurgie otorhinolaryngologique ou de la cavité orale qu'après d'autres types de chirurgie. Une analyse multivariée a montré que l'utilisation de doxapram (rapport de cotes*

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D. Yu, MD (✉) · W. Chai, MD · X. Sun, MD · L. Yao, MD
Department of Anesthesiology, Tangdu Hospital, the Fourth Military Medical University, Xi'An city, Shanxi Provence 710038, China
e-mail: yudaihua@hotmail.com

[RC] = 9,2; intervalle de confiance [IC] 95 % = 6,2 – 15,4; P = 0,002) et la douleur (RC = 8,2; IC 95 % = 4,5 – 16,9; P < 0,001) étaient les plus importants facteurs de risque associés à l'agitation au réveil. Les autres causes étaient la présence d'une sonde trachéale et/ou d'un cathéter urinaire. Une analgésie postopératoire adéquate était associée à moins d'agitation (RC = 0,4; IC 95 % = 0,1 – 0,4; P = 0,006).

Conclusion *L'administration de doxapram, la douleur et la présence d'une sonde trachéale et/ou d'un cathéter urinaire semblent être les causes les plus importantes d'agitation postopératoire. Afin d'éviter cette complication, nous suggérons, dans la mesure du possible, d'utiliser une anesthésie intraveineuse, d'extuber et de retirer les cathéters urinaires aussi tôt que possible, et de procurer une analgésie postopératoire adaptée.*

Emergence agitation during the immediate postanesthetic period is common.[1] It may lead to serious consequences for the patient, such as injury, increased pain, hemorrhage, self-extubation, and removal of catheters, and it can necessitate physically or chemically restraining the patient.[2] Emergence agitation is also disturbing to anesthesiologists and recovery room staff and can lead to increased hospital costs.[3] The cause of postoperative agitation after general anesthesia remains unknown; however, many factors predispose a patient to agitation, which is initiated frequently by uncomfortable stimuli.[4]

Despite its common occurrence, unclear etiology, and serious sequelae, emergence agitation has rarely been studied in adults.[5,6] In this observational study, we analyzed the cases of postoperative agitation that occurred in Tangdu Hospital during the years 2007 and 2008. We also examined the possible factors associated with agitation during the immediate postanesthetic period, such as age, gender, American Society of Anesthesiologists (ASA) physical status, type of surgery, anesthesia technique (inhalational or intravenous), administration of neostigmine or doxapram, adequate postoperative analgesia, pain, presence of a tracheal tube, and presence of a urinary catheter.

Methods

This prospective observational study was conducted in the Tangdu Hospital from December 2007 to December 2008. Following approval of the Local Ethics Committee (Tangdu Hospital, the Fourth Military Medical University, No. 07/021) and after obtaining informed written consent, adult patients aged 16-70 yr, ASA physical status I or II, scheduled to receive general anesthesia with tracheal intubation for selective surgery (oral cavity, ear nose and throat [ENT], thyroid gland, breast, orthopedic, abdomen, and urology surgery) were included in the study. Patients were excluded if they had a neurological disease potentially associated with symptoms of agitation, a family history of malignant hyperthermia, or mental retardation.

All patients were given midazolam 0.1 $mg \cdot kg^{-1}$ and atropine 0.5 mg *im* 30 min before surgery. Routine monitors, including electrocardiogram (ECG), non-invasive blood pressure (NBP), pulse oxygen saturation (SpO_2), and end-tidal CO_2 ($ETCO_2$), were used throughout anesthesia. Anesthesia was induced with midazolam 0.05 $mg \cdot kg^{-1}$, propofol 2 $mg \cdot kg^{-1}$, and fentanyl 2 $\mu g \cdot kg^{-1}$. Tracheal intubation was facilitated by vecuronium 0.1 $mg \cdot kg^{-1}$, and the patients' lungs were ventilated using 30% oxygen in air to maintain the $ETCO_2$ from 35-45 mmHg. After tracheal intubation, urinary catheters were inserted in all patients. These catheters were removed in most patients as soon as possible after emergence from anesthesia, and usually no later than six hours after surgery, according to the patient's condition. The choice of the maintenance agents, i.e., either inhalational agents or total intravenous anesthesia, was left to the attending anesthesiologist. In the inhalational group, anesthesia was maintained with 1-2% isoflurane. In the intravenous group, anesthesia was maintained with propofol using a target infusion pump (Graseby 3500, UK), with the target blood concentration set at 3-4 $\mu g \cdot mL^{-1}$. In all patients, muscle relaxation was maintained by injecting vecuronium 0.05 $mg \cdot kg^{-1}$ at regular intervals, and analgesia was maintained by an infusion of remifentanil 0.05-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to surgical stimulation and patient response. Fentanyl 1-2 $\mu g \cdot kg^{-1}$ was injected intravenously before stopping remifentanil infusion at the end of the surgery.

Reversal agents, such as neostigmine or doxapram, were administered according to a given patient's requirements. The endotracheal tube was removed when tidal volume was > 5 $mL \cdot kg^{-1}$, respiratory rate was > 12 min^{-1}, the swallowing reflex and cough reflex were active, and SpO_2 was maintained at $> 95\%$ for five minutes on room air. If these criteria were not present, patients were transferred to the postanesthetic care unit (PACU) with their tracheae intubated. Postoperative analgesia was left to the preference of the attending anesthesiologist and as dictated by the type of surgery. Pain was assessed after tracheal extubation and reassessed every ten minutes by having each patient provide a number from 0 to 10 (either verbally or by pointing) on a numerical rating scale (NRS). Patients who complained of pain were given small doses of fentanyl 10 μg on the first request, and this was titrated to maintain NRS < 4. Patients having an NRS ≥ 4 were considered to have pain. Patients receiving any form of regional or

continuous analgesia (patient-controlled analgesia) at the conclusion of the procedure were deemed to have adequate postoperative analgesia. Monitoring in the PACU included ECG, NBP, SpO_2, and $ETCO_2$. The degree of agitation was assessed blindly on a three-point scale by a special PACU nurse.[7] Agitation, defined as combative behaviour, thrashing, and hyperactive motor behaviour, was graded as *mild* if it occurred in response to powerful stimulation, such as suctioning phlegm, but stopped as soon as the stimulus was removed; *moderate* if it was observed without stimulation, lasted for at least five minutes, but did not require intervention of the attending staff; and *severe* if it lasted for at least five minutes and had to be controlled by drugs and/or a physical restraint. For patients with agitation during the immediate postanesthetic period, their legs and arms were constrained to the bed to prevent tossing. The degree of agitation and the most probable cause were also noted. Patients were discharged from the PACU after at least one hour if they were pain free, hemodynamically stable for 30 min, and exhibiting no bleeding, nausea, or vomiting.

The following data were assessed and recorded in the recovery room by the a special PACU nurse: age, gender, ASA physical status, type of surgery, anesthesia technique (inhalational or intravenous), administration of neostigmine or doxapram, adequate postoperative analgesia, pain, presence of a tracheal tube, presence of a urinary catheter, and length of stay in the PACU. Although blinded to the study's objectives, the PACU nurse was given free access to the patients' data. Agitation was correlated with the following factors: 1) age; 2) gender; 3) ASA physical status; 4) type of surgery; 5) anesthetic technique (inhalational or total intravenous); 6) use of neostigmine; 7) use of doxapram; 8) adequate postoperative analgesia, defined as regional or continuous analgesia (patient-controlled analgesia) at the conclusion of the procedure; 9) pain, defined as NRS $\geq$ 4; 10) presence of a tracheal tube; and 11) presence of a urinary catheter.

Statistical analysis

This study was conducted as a prospective cohort study of the incidence of postoperative agitation in patients undergoing surgery. Two groups were defined by the occurrence of agitation, i.e., agitated patients and non-agitated patients. Statistical analyses were performed using SPSS® for Windows®, v.11.5 (SPSS Inc., Chicago, IL, USA). In the univariate analysis, tests used to compare groups were two-sample *t* test and Pearson Chi square. A multivariable analysis was performed using a backward binary stepwise logistic regression to examine and determine risk factors of agitation. All variables statistically linked to occurrence of agitation were included in the regression model, with agitation as the dependent variable. The independent variables were age, gender, ASA physical status, type of surgery, anesthetic technique, neostigmine, doxapram, adequate postoperative analgesia, pain, presence of a tracheal tube, and presence of a urinary catheter. $P < 0.05$ was considered to be statistically significant.

Results

Sixteen of the 2,016 patients who were approached and agreed to participate in the study had their procedure cancelled by the surgeons. The remaining 2,000 patients (865 males and 1,135 females) were eligible and completed the trial. The mean age was 42 (range 16-70) yr. Of the 2,000 patients, 426 (21.3%) developed different degrees of postoperative agitation. Of these 426 patients, 49.8% experienced mild agitation (n = 212), 41.8% moderate agitation (n = 178), and 8.4 % severe agitation (n = 36). Of these, 22 patients attempted self-extubation. Table 1 shows the risk factors of postoperative agitation using univariate analysis. Postoperative agitation was not correlated with age and ASA physical status, but it was more common in males, after ENT procedures, and after surgery of the oral cavity. Also, it was more common in patients who received general inhalational anesthesia than in patients who received total intravenous anesthesia. In addition, pain and presence of a tracheal tube and/or a urinary catheter also resulted in postoperative agitation. Agitated patients also stayed longer (105 [standard deviation (SD) 18.1] min) than non-agitated patients (72.6 [SD 13.3] min) in the PACU (P = 0.003).

Multivariable analysis by backward binary stepwise logistic regression performed on these variables confirmed that gender, type of surgery, anesthetic technique, doxapram, pain, presence of tracheal tubes and /or a urinary catheter were significant risk factors for emergence agitation during the postoperative period (Table 2). Use of doxapram was the highest risk factor (odds ratio [OR] = 9.2; 95% confidence interval [CI] = 6.2 - 15.4; P = 0.002). Operations on the oral cavity, ENT surgery, and inhalational anesthesia were additional risk factors. Adequate postoperative analgesia was an important factor in reducing postoperative agitation (OR = 0.4; 95% CI = 0.1 - 0.4; P = 0.006).

Discussion

This study shows that emergence agitation is a common occurrence in adults after general anesthesia. The incidence of postoperative agitation was 21.3%. Severe agitation necessitating medical or physical control was present in only 8.4% of those with agitation or 1.8% of all patients. This is similar to the 3% average of severe emergence

Table 1 Univariate analysis: risk factors of postoperative agitation in general anesthesia surgery patients

	Non-agitated (n = 1,574) (78.7%)	Agitated (n = 426) (21.3%)	Total (n = 2,000)	P value
Age	41 (16-70) yr ‡	44 (17-68) yr ‡	42 (16-70) yr ‡	0.953§
Gender				0.017*
Male	622 (71.9%)	243 (28.1 %)	865	
Female	952 (83.9%)	183 (16.1%)	1135	
ASA				0.805*
I	677 (79.1%)	179 (20.9%)	856	
II	897 (78.4%)	247 (21.6%)	1,144	
Type of surgery				0.018*
Oral cavity	16 (40%)	24 (60%)	40	
ENT	83 (44.6%)	103 (55.4%)	186	
Thyroid gland	177 (78.3%)	49 (21.7%)	226	
Breast	205 (93.6%)	14 (6.4%)	219	
Orthopedic	196 (73.2%)	72 (26.8%)	268	
Abdomen	910 (88.8%)	115 (11.2%)	1,025	
Urology	311 (86.4%)	49 (13.6%)	360	
Anesthetic technique				0.001*
Inhalational	983 (72.2%)	378 (27.8%)	1,361	
Total intravenous	591 (92.5%)	48 (7.5%)	639	
Neostigmine				0.629*
Yes	1,271 (79.3%)	333 (20.7%)	1,603	
No	303 (76.3%)	93 (23.7%)	397	
Doxapram				< 0.001*
Yes	13 (37.2%)	22 (62.8%)	35	
No	1,561 (79.4%)	404 (20.6%)	1,965	
Adequate postoperative analgesia				< 0.001*
Yes	1,060 (97.1%)	31 (2.9%)	1,091	
No	514 (56.5%)	395 (43.5%)	909	
Pain				< 0.001*
Yes	53 (19.8%)	215 (80.2%)	268	
No	1,521 (87.8%)	211 (12.2%)	1,732	
Presence of tracheal tube				0.015*
Yes	45 (28.3%)	114 (71.7%)	159	
No	1,529 (83.1%)	312 (16.9%)	1,841	
Presence of urinary catheter				0.022*
Yes	38 (36.5%)	66 (63.5%)	104	
No	1,536 (81%)	360 (19%)	1,896	

*Pearson Chi square; ‡Mean (range); §Two-sample *t* test. Adequate postoperative analgesia = regional or continuous analgesia (patient-controlled analgesia) at the conclusion of the procedure; Pain = score ≥ 4 on a numerical rating scale (NRS) (assessed after extubation of the tracheal tube); ASA = American Society of Anesthesiologists physical status; ENT = ear, nose, and throat

agitation reported in the literature.[8] In a recent study, Lepousé *et al.* recorded a 4.7% overall incidence of agitation, and more than 50% of these (2.4% of the total number of patients) were recorded as being dangerously agitated.[2] These differences in the incidence of emergence agitation may reflect the scarcity of studies addressing the problem and the absence of a specific scale for recording postoperative agitation.

Different scales for describing agitation exist, such as the Riker agitation–sedation scale, the Richmond sedation–agitation scale, the motor activity assessment scale, and the New Sheffield sedation scale. Although these scales were validated in the intensive care unit,[9-13] none of them was validated in the recovery room. Additionally, stimulating patients to assess the sedation component of these scales may initiate agitation in the postoperative setting. If agitation occurred in the present study, it was graded on a three-point scale according to whether it was observed only in response to patient stimulation, occurred spontaneously, or required intervention. In addition to its simplicity, this scale was shown to have excellent inter-rater agreement in a pilot study.

Table 2 Logistic regression: risk factors of postoperative agitation in general anesthesia surgery patients, based on risk adjusted and unadjusted data

Variable	Unadjusted		Adjusted	
	OR (95% CI)	*P** value	OR (95% CI)	*P** value
Gender		0.006		0.005
Male	5.6 (3.7-7.1)		5.7 (4.2-7.3)	
Female	1.0 (reference)		1.0 (reference)	
Type of surgery		0.023		0.012
Oral cavity	6.1 (4.6-8.2)		6.2 (4.8–8.5)	
ENT	8.5 (6.3-11.8)		8.0 (6.1–10.2)	
Thyroid gland	0.8 (0.6-1.6)		0.8 (0.6-1.7)	
Breast	1.3 (0.7-1.9)		1.3 (0.7-2.6)	
Orthopedic	1.6 (0.7-1.5)		1.6 (0.5-1.6)	
Abdomen	0.9 (0.5-1.8)		0.9 (0.5-2.0)	
Urology	1.0 (reference)		1.0 (reference)	
Anesthetic technique		0.001		0.001
Inhalational	1.3 (1.1-1.6)		1.2 (1.0–1.5)	
Total intravenous	1.0 (reference)		1.0 (reference)	
Neostigmine (Yes/No)	0.8 (0.6-1.2)	0.52	0.8 (0.7-1.2)	0.56
Doxapram (Yes/No)	10.3 (7.5-16.3)	0.002	9.2 (6.2–15.4)	0.002
Adequate postoperative analgesia (Yes/No)	0.3 (0.1-0.4)	< 0.001	0.4 (0.1–0.4)	0.006
Pain (Yes/No)	8.1 (4.6-16.3)	< 0.001	8.2 (4.5–16.9)	< 0.001
Presence of tracheal tube (Yes/No)	7.6 (5.4-11.2)	0.01	7.8 (5.1–11.3)	0.01
Presence of urinary catheter (Yes/No)	4.4 (2.2-8.7)	0.004	4.4 (2.6–8.9)	0.004

*P** denotes backward binary stepwise logistic regression, significant to include or exclude equal to 0.15. 95% CI = confidence interval of 95%; OR = odds ratio; ENT = ear, nose, and throat

The causes of postoperative agitation after general anesthesia remain unknown. Some recent studies have shown that general anesthetics cause non-uniform inhibition of the different parts of the central nervous system, thus they recover at different rates.[13,14] As patients emerge from the anesthetic, parts of the cerebral cortex and the reticular activating system remain inhibited. This situation can be expressed in different ways: most patients are quiet and drowsy, but some patients experience low-grade disorientation and vague cerebral function. These patients may develop emergence agitation due to uncomfortable stimuli. In order to find out what was linked to postoperative agitation, we analyzed some potential factors, including age, gender, ASA physical status, type of surgery, anesthesia technique (inhalational or total intravenous), administration of neostigmine or doxapram, adequate postoperative analgesia, pain, presence of a tracheal tube, and presence of a urinary catheter. Doxapram administration, pain, irritation caused by the endotracheal tube, and the overwhelming need to urinate despite the presence of an indwelling urinary catheter appeared to be the most important causes of agitation in our study.

Pain is also a main cause of postoperative agitation in our population; incidence of agitation was 80.2% in patients who had postoperative pain. Incidence of agitation in the patients without postoperative analgesia was 43.5%, higher than in those who received adequate postoperative analgesia (2.9%). Thus, we strongly recommend that pain should be anticipated and treated preventively, as early as during surgery itself, and that the proper postoperative analgesia be used after major operations, such as thoracic and abdominal surgeries.[2,15] The incidence of agitation in males was greater than in females. This may be due to the lower pain tolerance in males following surgery, as previous studies have reported that men report more pain and consume more patient-controlled analgesia than women.[16,17]

Operations on the oral cavity and ENT surgery were associated with a higher incidence of agitation in the present study. In a prospective cohort study, Voepel-Lewis *et al.*[18] found that ENT procedures were an independent risk factor for the development of emergence agitation in children. In 1961, Eckenhoff *et al.*[19] speculated that patients undergoing head and neck procedures may have a sense of suffocation during emergence from anesthesia, which may increase the incidence of emergence agitation.

Regarding the anesthetic technique, only one study in adults compared the incidence of emergence delirium between patients anesthetized with inhalational anesthetics and those anesthetized with total intravenous anesthesia.[11] The incidence of agitation in patients who received general inhalational anesthesia was higher than in those who received total intravenous anesthesia, probably because propofol and remifentanil were eliminated more rapidly and completely when given intravenously rather than via

inhalation. Sixty-three percent of patients who received doxapram (35 patients) developed postoperative agitation, probably because these patients emerged rapidly from anesthesia and struggled seriously against tubes and masks. This also may be related to the pharmacokinetic properties of doxapram.[20]

Emergence agitation is associated with many hazards.[2] Self-extubation and removal of catheters can lead to hypoxia, aspiration pneumonia, or emergency surgery. Self-injury and injury to the attending staff are additional risks. The main line of management of postoperative agitation is elimination of the cause. Before the causes are identified, it is very important to protect patients to avoid serious complications. Once the causes are identified, they should be eliminated immediately. Postoperative agitation can be reduced by providing continuous analgesia as soon as anesthesia is stopped and by removing the tracheal tube and urinary catheter early after surgery. For the occasional patient who remains agitated after elimination of the obvious causes, a rapidly acting sedative of short duration, such as propofol,[A] clonidine,[21] or midazolam,[22] can be administered. Doxapram should be used with caution; it is better to wait for patients to recover naturally without the use of doxapram. If doxapram must be used, it is better to use lower doses to avoid overexcitement and agitation and then repeat administration if necessary.

In conclusion, the causes of postoperative agitation are not yet clear. Since there are many factors that may lead to postoperative agitation, it is difficult to prevent completely. However, postoperative agitation can be reduced significantly if predisposing factors are avoided. Following are the main keys to a smooth recovery that is free of emergence agitation: choosing a suitable anesthetic technique, removing tracheal tubes and urinary catheters as early as possible after the operation, and providing adequate postoperative analgesia.

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