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Risk factors of inadequate emergence following general anesthesia with an emphasis on patients with substance dependence history

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Background: This study aims to define the incidence and risk factors of both emergence agitation and hypoactive emergence in adult patients and substance-dependent patients following general anesthesia to elaborate on the risk factors and precise management of them.

Methods: The study recruited 1,136 adult patients who received elective surgeries under general anesthesia for this prospective observational study. Inadequate emergence was determined according to the Richmond Agitation-Sedation Scale (RASS). Emergence agitation was defined as a RASS ≥ +1 point, and hypoactive emergence was defined as a RASS ≤ −2 points. Subgroup analyses were then conducted on patients with substance dependence.

Results: Inadequate emergence in the post-anesthesia care unit (PACU) occurred in 20.3% of patients, including 13.9% with emergence agitation and 6.4% with hypoactive emergence. Ninety-five patients had a history of substance dependence. Compared to divorced patients, never-married and presently married patients, who underwent gynecological and thoracic surgeries, had a lower risk of agitation. Neurologic disorders, intraoperative blood loss, intraoperative morphine, and PACU analgesic drug administration were associated with increased agitation risk. Hypertension and psychological disorders, intraoperative opioids, and PACU Foley catheter fixation were associated with increased hypoactive emergence risk. Substance-dependent patients had higher risk for agitation (21.1%, P = 0.019) and hypoactive emergence (10.5%, P = 0.044).

Conclusions: Inadequate emergence in PACU following general anesthesia is a significant problem correlated with several perioperative factors. Patients with a history of substance dependence appear to be more at risk of inadequate emergence than the general population.

Keywords: Elective surgery; Emergence agitation; General anesthesia; Hypoactive emergence; Post anesthesia care unit; Substance dependence.

Introduction

Emergence is defined as the transition from the sleep state to full consciousness [1]. Emergence from general anesthesia is usually smooth and uneventful. Inadequate emergence is characterized by a disturbance of activity level in the immediate postoperative period and is classified into two subtypes—emergence agitation and hypoactive emergence. Emergence agitation may consist of hallucinations, delusions, and confusion that

manifests as restlessness, moaning, involuntary physical activity, and thrashing [2], while a delayed recovery characterizes hypoactive emergence after anesthesia. However, there are no clear diagnostic criteria defining emergence agitation or hypoactive emergence [3]. The term 'emergence delirium' is often misused in the literature as a reference to emergence agitation, whereas agitation and delirium have distinctive descriptions in the Diagnostic and Statistical Manual of Mental Disorders (DSM) Fifth Edition [4]. Problems of post-anesthesia emergence have been shown to occur in 5–10% of general surgery patients of all ages. Its incidence is even higher after the preoperative use of benzodiazepines, breast surgery, abdominal surgery, musculoskeletal surgery, long operation durations, induction of anesthesia with etomidate, a pain numeric rating scale (NRS) of 6 to 10 in the post-anesthesia care unit (PACU), as well as at both extremes of patient age [5–7]. The clinical importance of inadequate emergence in either form has not been thoroughly investigated. It is shown that patients with emergence agitation are at an increased risk of injury, hemorrhage, extended PACU stay, morbidity, mortality, and resource utilization [5,8,9]. However, hypoactive emergence has rarely been studied. Radtke et al. [6] found 60 of 1,868 patients presented hypoactive emergence in their study (3.2%), which was more common for younger age, longer duration of surgery, and intra-abdominal surgery.

This prospective observational study aimed to define the incidence and risk factors of inadequate emergence (both emergence agitation and hypoactive emergence) that was resolved by the time of PACU discharge in adult patients after general anesthesia for elective surgery. It was shown earlier that psychological problems such as depression and anxiety, as well as alterations in organ functions, were significantly higher in substance-dependent patients [10,11]. Furthermore, clinical findings indicate that baseline psychological disorders such as anxiety and depression can be associated with postoperative delirium emergence [12]. Moreover, due to the progressively high frequency of substance dependence in the general population [13,14], we focused our study on substance dependence and its relationship with inadequate emergence.

Materials and Methods

This research was done per the Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2018). After institutional ethics committee approval with IRB number 86100059 , patients classified with an American Society of Anesthesiologists I–III physical status and undergoing elective general anesthesia during the six months period from March to September 2018 were enrolled in this prospective observational study with their informed consent. The study excluded patients under 18 years old, with a history of dementia, cerebral insult, intracranial surgery, or those under neuraxial and regional anesthesia. Anesthesia was induced according to standard protocols in our department—(1) preoxygenation and intravenous induction using a short-acting narcotic, ketamine, sodium thiopental, or propofol and neuromuscular blockade using succinylcholine or atracurium, (2) maintenance of anesthesia using volatile anesthetics or total intravenous anesthesia, short-acting or long-acting narcotics, and ketamine, (3) reversal of neuromuscular blockade using neostigmine and atropine, and (4) awake extubation and transportation to the PACU. In the PACU, all patients received oxygen if their oxygen saturation was below 95% in room air. Postoperative pain management included optional non-opioid analgesics for mild postoperative pain (NRS 3–4) or opioid analgesics for moderate to severe pain (NRS ≥ 5). Patients were assessed at 10 minutes after admission to the PACU by experienced anesthesia nurses who were blinded to the patient care. The NRS pain score was recorded, and the presence of inadequate emergence and its severity was determined according to the Richmond Agitation-Sedation Scale (RASS, Table 1). Emergence agitation was defined as RASS ≥ +1, normal emergence was defined as RASS between 0 and –1, and hypoactive emergence was defined as RASS ≤ –2 [6].

Table 1. Richmond Agitation-Sedation Scale

+4	Combative	Overtly combative or violent; immediate danger to staff
3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
2	Agitated	Frequent non-purposeful movement or patient–ventilator desynchrony
1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
–1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
–2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation

The following variables for each patient were recorded—age, gender, body mass index; pre-existing medical conditions, psychological disorders, history of substance dependency (alcohol, opium, stimulants, psychedelics; according to DSM IV criteria), type of surgery, smoking, intraoperative estimated blood loss, intravenous fluid administration, transfusion, type and dosage of intraoperative analgesics, having a urinary catheter in the PACU, type and dosage of postoperative analgesics, and postoperative pain score (NRS).

Statistical analysis

This study was conducted as a prospective observational study. Three emergence groups were defined as agitated, normal, and hypoactive. Demographic and descriptive data analyses were done for the study population and the three groups above. Frequencies were expressed as counts (percentage) and continuous variables as mean with standard deviation (SD). After testing the normality with the Kolmogorov-Smirnov test, we used the Student's t-test and the chi-squared test for univariate analysis. We performed multivariate analyses using a backward binary stepwise logistic regression to examine and determine the odds ratios (OR) of the risk factors for inadequate emergence, with 95% confidence for the CI. Furthermore, the statistical analyses (both univariate and multivariate) were also conducted in the subgroup of patients with a history of substance dependence. We made no adjustments for multiple testing in all these exploratory data analyses. SPSS ver. 22.0 software (IBM Corp., USA) was used for analyses, and the study considered $P < 0.05$ (two-sided) as significant.

Results

In this study, 1,136 patients were enrolled, including 770 female patients (68%). The mean age was 39 years (range 18–99 yr). Inadequate emergence in the PACU occurred in 231 patients (20.3%), out of which, 158 patients (13.9%) had emergence agitation, and 73 patients (6.4%) had hypoactive emergence. Substance dependence was reported in 95 patients (8%) of whom, 62.1% abused opium, and 37.9% abused stimulants. All patients regained a normal cognitive status before discharge from the PACU. The mean ± SD of stay time in PACU was 47 ± 13 minutes, which was not significantly different in subgroups comparison: substance-dependent vs. normal patients ($P = 0.654$) as well as patients with vs. without inadequate emergence ($P = 0.321$).

Univariate analysis

The incidence of inadequate emergence differed significantly between genders ($P = 0.002$; Table 2), it was more frequent in men (94 of all the male patients included in the study, 25.7%). Inadequate emergence was also seen more in patients over 50 years old compared to younger patients (29.1% vs. 17.9%, respectively, $P = 0.001$).

In married patients, the incidence of emergence agitation was less than the total of single and divorced patients (12.8% vs. 17.5%, $P = 0.009$). Hypoactive emergence is more frequent in married patients (7.4% vs. 3.1%). In patients with emergence agitation, 36.36% had a history of neurologic diseases versus 14.23% with other pre-existing illnesses ($P = 0.012$) (Table 2).

A history of substance dependence was significantly associated with a higher incidence of inadequate emergence ($P = 0.001$). Emergence agitation was more common in patients with substance dependence than in patients without substance dependence (21.1% vs. 13.3%, $P = 0.019$). Hypoactive emergence was also more common in patients with substance dependence than in patients without substance dependence (10.5% vs. 6.1%, $P = 0.044$).

Emergence agitation was significantly less common in patients undergoing gynecological (7.1%) and thoracic surgeries (4.9%) than in patients with other surgeries (19.8%, $P < 0.001$ and $P = 0.034$, respectively). Hypoactive emergence was also more frequent in thoracic surgery (25% of all patients with hypoactive emergence, $P < 0.001$). Conversely, intra-abdominal and laparoscopic surgeries were associated with higher incidences of emergence agitation (28.2% of patients under intra-abdominal surgery vs. 13.1% of other patients, $P < 0.001$ and 28.6% of patients under laparoscopic surgery vs. 13.0% of other patients, $P < 0.001$).

The intraoperative consumption of morphine in patients with emergence agitation and hypoactive emergence (mean ± SD dose, 5.52 ± 1.78 mg, and 7.41 ± 2.90 mg, respectively) was significantly higher than in patients with normal emergence (4.70 ± 1.12 mg, $P < 0.001$). Our results also showed that the intraoperative bleeding administered fluids in patients with emergence agitation and hypoactive emergence was significantly higher than in patients with normal emergence ($P < 0.001$) (Table 2).

Foley catheter fixation in the PACU correlates with a higher incidence of hypoactive emergence. Of all patients with Foley catheter fixation, 12.8% suffered hypoactive emergence vs. 2.4% in patients without Foley catheter fixation ($P < 0.001$).

Analgesic drug administration in the PACU seems to be correlated with a higher incidence of emergence agitation (28% vs. 12.9% in patients without analgesic drugs consumption, $P = 0.009$).

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Table 2. Risk Factors of Inadequate Emergence in PACU after General Anesthesia for Elective Surgery

	NE	EA	P value	HE	P value
	(n = 905)	(n = 158)	EA vs. NE	(n = 73)	HE vs. NE
> Age 50 yr	728 (82.1)	116 (13.1)	0.043	43 (4.8)	< 0.001
< Age 50 yr	177 (70.9)	42 (17.0)		30 (12.1)	
Sex (M/F)	272/633	59/99	0.067	35/38	0.001
BMI (kg/m^2)	28.4 (23.4)	28.2 (27.3)	0.928	26.1 (5.5)	0.402
Single	195 (80.6)	40 (16.5)	0.298	7 (2.9)	0.015
Married	702 (79.8)	113 (12.8)	0.097	65 (7.4)	0.021
Divorced	8 (57.1)	5 (35.7)	0.016	1 (7.1)	0.675
≤ Diploma	729 (78.6)	132 (14.2)	0.376	66 (7.1)	0.037
Bachelor	153 (84)	23 (12.6)	0.827	6 (3.2)	0.010
> Bachelor	23 (85.2)	3 (11.1)	0.629	1 (3.7)	0.533
*Hypertension	49 (75.4)	8 (12.3)	0.771	8 (12.3)	0.026
*Diabetes mellitus	13 (59.1)	5 (22.7)	0.156	4 (18.2)	0.005
*TD	47 (87)	4 (7.4)	0.139	3 (5.6)	0.931
*ND	6 (54.5)	4 (36.4)	0.034	1 (9.1)	0.390
*Others	151 (81.6)	20 (10.8)	0.315	14 (7.6)	0.208
Pre-existing PD	32 (66.7)	10 (20.8)	0.096	6 (12.5)	0.046
Alcohol	79 (73.8)	18 (16.8)	0.283	10 (9.3)	0.155
Smoking	94 (71.8)	24 (18.3)	0.076	13 (9.9)	0.051
Substance abuse	65 (68.4)	20 (21.1)	0.019	10 (10.5)	0.044
†Gynecological	329 (89.4)	26 (7.1)	< 0.001	13 (3.53)	0.001
†Head & neck	311 (77.8)	63 (15.8)	0.180	26 (6.5)	0.828
†Thoracic	63 (76.8)	4 (4.9)	0.034	15 (18.3)	< 0.001
†Intraabdominal	48 (67.6)	20 (28.2)	0.001	3 (4.2)	0.064
†Laparoscopic	52 (67.5)	22 (28.6)	0.001	3 (3.9)	0.044
†Musculoskeletal	36 (73.5)	13 (25.4)	0.031	0 (0)	-
IBV (ml)	155 ± 9	210 ± 16	< 0.001	417.9 ± 77.1	< 0.001
IV fluid (ml)	1539 ± 43	1818 ± 99	< 0.001	2832.1 ± 247.0	< 0.001
§0 units	888 (80.2)	153 (13.8)	0.294	66 (6)	0.001
§1–2 units	15 (68.2)	5 (22.7)	0.199	2 (9.1)	0.437
§≥ 3 units	2 (28.6)	0 (0)	-	5 (71.4)	-
‡Fentanyl (μg)	178.6 ± 83.6	200.0 ± 7.5	0.154	223.5 ± 84.5	0.038
‡Morphine (mg)	5.5 ± 1.8	4.7 ± 1.1	< 0.001	7.4 ± 2.9	< 0.001
‡Pethidine (mg)	20.3 ± 7.6	21.7 ± 2.9	0.022	0	< 0.001
‡Remifentanil (μg)	1321.8 ± 642	1142.9 ± 475.6	0.001	1500.0 ± 912.9	0.028
‡Alfentanil (μg)	26.4 ± 42.5	69.0 ± 14.9	0.003	15.9 ± 28.7	< 0.001
‡Sufentanil (μg)	4.0 ± 2.5	1.0 ± 0	< 0.001	4.4 ± 2.5	0.029
PACU analgesics	54 (72.0)	21 (28.0)	0.001	0 (0)	-
Foley catheters	315 (71.9)	67 (15.3)	0.066	56 (12.8)	< 0.001
||NRS < 5	875 (79.8)	150 (13.7)	0.274	71 (6.5)	0.070
||NRS ≥ 5	30 (72.2)	8 (22.2)		2 (5.6)	

Values are presented as number (%) or mean ± SD. PACU: postanesthesia care unit, NE: normal emergence, EA: emergence agitation, HE: hypoactive emergence, BMI: body mass index, TD: thyroid dysfunction, ND: neurologic disorders, PD: psychological disorders, IBV: intraoperative bleeding volume, IV: intravenous, NRS: numeric rating scale. *Pre-existing medical illness, †Site of surgery, ‡Intraoperative opioids, §Packed cell transfusion, ||Postoperative pain.

Table 3. Risk Factors of Emergence Agitation in the PACU

Variable	Odds ratio	95% CI	P value
Single vs. divorced	0.158	0.039–0.637	0.009
Married vs. divorced	0.161	0.042–0.615	0.008
Pre-existing ND	6.779	1.359–33.804	0.020
Gynecological surgery	0.292	0.120–0.712	0.007
Thoracic surgery	0.230	0.066–0.800	0.021
IO bleeding	1.001	1.000–1.002	0.047
IO morphine administration	1.145	1.027–1.278	0.015
Analgesic drugs in PACU	2.989	1.559–5.730	0.001

ND: neurologic disorders, IO: intraoperative, PACU: post-anesthesia care unit, P value: backward binary stepwise logistic regression, significant to include or exclude equal to 0.05.

Table 4. Risk Factors of Hypoactive Emergence in the PACU

Variable	Odds Ratio	95% CI	P value
Pre-existing hypertension	5.382	1.528–18.960	0.009
Pre-existing psychological disorders	3.897	1.152–13.180	0.007
Intraoperative alfentanil administration	2.338	1.521–3.593	< 0.001
Intraoperative morphine administration	1.364	1.208–1.539	< 0.001
Intraoperative sufentanil administration	1.024	1.013–1.035	< 0.001
Foley catheter insertion in PACU	9.680	4.531–20.679	< 0.001

PACU: post-anesthesia care unit, P value: backward binary stepwise logistic regression, significant to include or exclude equal to 0.05.

Multivariate analysis

The univariate analysis between both groups (normal emergence vs. emergence agitation) showed that the incidence of emergence agitation was significantly related to 10 variables (age ≥ 50 yr, marital status [divorced patients], pre-existing neurologic disorders, substance dependence, site of surgery, intraoperative bleeding volume, intravenous [IV] fluid administration, intraoperative opioids, and analgesic drug administration in the PACU).

Hypoactive emergence was significantly related to 14 variables (age ≥ 50 yr, male gender, marital status [married patients], education level [less than a bachelor degree], pre-existing hypertension, diabetes mellitus, pre-existing psychological disorders, substance dependence, site of surgery, intraoperative bleeding volume, IV fluid administration, packed cell transfusion, intraoperative opioids, and Foley catheter fixation).

Multivariate analysis by backward binary stepwise logistic regression has shown that out the 10 variables used in our model, seven were significant to the onset of emergence agitation in the PACU (Table 3).

The risk of emergence agitation among single and married patients is reduced by an order about 0.15 times comparing with divorced patients (OR = 0.158, 95% CI [0.039–0.637], P = 0.009; OR = 0.161, 95% CI [0.042–0.615], P = 0.008, respectively). Pre-existing neurologic disease increased the frequency of agitation about 7 times (OR = 6.779, 95% CI [1.359–33.804], P = 0.020) and patients with gynecological and thoracic surgeries had lower risk of emergence agitation compared to other patients (OR = 0.292, 95% CI [0.120–0.712], P = 0.007; OR = 0.230, 95% CI [0.066–0.800], P = 0.021, respectively). Intraoperative bleeding volume and intraoperative morphine administration slightly increased the risk of emergence agitation (OR = 1.001, 95% CI [1.000–1.002], P = 0.047; OR = 1.145, 95% CI [1.027–1.278], P = 0.015, respectively). An interesting observation was that analgesic drug administration in the PACU also increased the risk of agitation about 3 times (OR = 2.989, 95% CI [1.559–5.730], P = 0.001).

For hypoactive emergence, we found six factors which increased the risk of hypoactive emergence (Table 4). Pre-existing hypertension increased the risk about 5 times (OR = 5.382, 95% CI [1.528–18.960], P = 0.009) and history of psychological disorders increased the risk about 4 times (OR = 3.897, 95% CI [1.152–13.180], P = 0.029). Intraoperative alfentanil administration significantly increased the risk of hypoactive emergence (OR = 2.338, 95% CI [1.521–3.593], P < 0.001). Sufentanil and higher doses of morphine administration during operation also increased the risk of hypoactive emergence slightly (OR = 1.024, 95% CI [1.013–1.035], P < 0.001; OR = 1.364, 95% CI [1.208–1.539], P < 0.001, respectively). Surprisingly, Foley catheter fixation significantly correlated to the

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Table 5. Risk Factors of Inadequate Emergence in the PACU after General Anesthesia in Elective Surgery Patients with a History of Substance Dependence

	NE	EA	P value	HE	P value
	(n = 65)	(n = 20)	EA vs. NE	(n = 10)	HE vs. NE
> Age 50 yr	47 (69.11)	17 (25)	0.289	4 (5.9)	0.033
< Age 50 yr	17 (65.4)	3 (11.5)		6 (23.1)	
Sex (M/F)	54/11	16/4	0.752	10/0	-
BMI (kg/m^2)	24.93 (4.2)	25.6 (4.7)	0.520	25.2 (3.8)	0.875
Single	22 (78.6)	5 (17.9)	0.457	1 (3.6)	0.127
Married	41 (64.1)	14 (21.9)	0.571	9 (14.1)	0.092
Divorced	2 (66.7)	1 (33.3)	-	0 (0)	-
≤ Diploma	51 (65.4)	18 (23.1)	0.248	9 (11.5)	0.395
Bachelor	13 (86.7)	2 (13.3)	0.304	0 (0)	-
> Bachelor	1 (50)	0 (0)	-	1 (50)	-
Alcohol	53 (63.8)	16 (21.1)	0.877	7 (9.2)	0.395
Smoking	41 (73.2)	9 (16.1)	0.150	6 (10.7)	0.851
Abuse opium	37 (64.4)	12 (20.3)	0.902	9 (15.3)	0.045
Abuse stimulants	28 (75.7)	8 (22.2)		1 (2.8)	
IBV (ml)	180 ± 62	174 ± 18	0.962	559 ± 73	0.082
IV fluid (ml)	1488 ± 1128	1930 ± 1091	0.126	3667 ± 2194	< 0.001
*Fentanyl (μg)	187.1 ± 81.2	219.4 ± 105.9	0.172	225.0 ± 59.8	0.179
*Morphine (mg)	6.5 ± 2.7	5.6 ± 1.0	0.154	8.8 ± 4.8	0.032
*Pethidine (mg)	32.5 ± 10.6	0 (0)	-	0 (0)	-
*Remifentanil (μg)	1177.8 ± 772.6	-	-		-
*Sufentanil (μg)	6.0 ± 5.7		-		-
PACU analgesics	5 (41.7)	7 (58.3)	0.002	0 (0)	-
Foley catheters	15 (53.6)	5 (17.9)	0.859	8 (28.8)	< 0.001
†NRS < 5	63 (69.2)	18 (19.8)	0.201	10 (11.0)	-
†NRS ≥ 5	2 (50)	2 (50)		0	-

Values are presented as number (%) or mean ± SD. NE: normal emergence, EA: emergence agitation, HE: hypoactive emergence, BMI: body mass index, IBV: intraoperative bleeding volume, IV: Intravenous, PACU: postanesthesia care unit, NRS: numeric rating scale. *Intraoperative opioids, †Postoperative pain.

incidence of hypoactive emergence in the PACU (OR = 9.680, 95% CI [4.531–20.679], P < 0.001).

Univariate analysis in patients with substance dependence

The current study showed that the incidence of hypoactive emergence in patients older than 50 years was significantly more than younger patients (23.1% and 5.9%, respectively, P = 0.033). It is also more common in opium dependence rather than stimulants (15.3% vs. 2.8%, P = 0.045) (Table 5).

Higher amounts of IV fluid administered during surgery were related to more frequency of hypoactive emergence in the PACU. Morphine administration, as an analgesic drug, also had the same effect on the development of hypoactive emergence. Our results showed that analgesic drug administration in the PACU was positively correlated to the occurrence of emergence agitation (58.3% of patients with substance dependence who received analgesic drugs in the PACU vs. 15% of patients without receiving analgesics in the PACU, P < 0.001) (Table 5).

Foley catheter fixation in the PACU also correlated with a higher incidence of hypoactive emergence (80% of all substance-dependent patients with Foley catheter vs. 20% in patients without Foley catheter, P < 0.001) (Table 5).

Multivariate analysis in patients with substance dependence

In patients with substance dependence, analgesic drug administration in the PACU increased the risk of emergence agitation (OR = 86.059, CI [2.175–3405.894], P = 0.018) and history of smoking decreased the risk of emergence agitation (OR = 0.075, CI [0.008–0.708], P = 0.024).

Discussion

Inadequate emergence in adult patients has rarely been examined. Thus, there are only a few recommendations regarding treatment, except for pediatric anesthesia. Caution is warranted for patients at increased risk. Based on pediatric anesthesia, it may be helpful to keep patients away from stressful stimuli by providing a quiet, darkened recovery room. If necessary, it is appropriate to administer additional analgesics and a sedative [15]. IV propofol (0.5 mg/kg) or IV midazolam (0.02 mg/kg) have both been used successfully in treating emergence agitation in children [16,17]. One in every five patients in our study experienced inadequate emergence. It is a significant issue that deserves more attention [5,6,18]. Despite the scarcity of studies with reports on hypoactive emergence [6], emergence agitation has been evaluated more extensively. In children, emergence agitation is frequently a complication, with described incidences up to 60% [19,20]. However, the incidence of emergence agitation in adults has been about 5% in most studies [5,6], which is lower than our observation. There are different scales of agitation assessment, such as the Richmond Agitation-Sedation Scale (RASS), Riker Sedation-Agitation Scale (SAS), Motor Activity Assessment Scale, and the New Sheffield Sedation Scale. They are more precise in the evaluation of agitation than the Ramsay sedation scale, which rates sedation. Studies have demonstrated that both RASS and SAS have excellent inter-rater reliability [21–23]. These scales have been used for adults in intensive care units and are not well-established in the PACU. However, these scales are useful, especially in emergencies.

Emergence agitation

It is crucial to identify patients at risk of emergence agitation to be prepared to prevent emergence delirium. Lepousé et al found that breast and abdominal surgeries extended duration of surgical procedures, intraoperative bleeding, and premedication by benzodiazepines are risk factors for postoperative delirium. Pre-existing neurologic disorders were also correlated with emergence agitation. On the other hand, a known history of illness, long-term treatment by antidepressants, gynecological surgeries, and thoracic surgeries are associated with a lower risk of emergence agitation [5].

We found that age does not influence the occurrence of emergence agitation. Nevertheless, other studies have reported a higher incidence of agitation in younger patients [5]. Radtke and colleagues found that both younger (less than 40 years old) and older patients (greater than 64 years old) showed a higher incidence of emergence agitation than middle-aged patients [6].

In our study, a history of substance dependence was significantly associated with a higher incidence of inadequate emergence ($P = 0.001$). Patients with opium or stimulant dependence had a higher risk of agitated emergence (20.3% and 22.2%) compared to other patients (13.3%). We could not find any similar study in literature with which to compare our results, so this may be the first study reporting the incidence of inadequate emergence in the PACU in patients with a history of substance dependence.

Although postoperative pain has been identified as a potential risk factor for emergence agitation in other studies [5,6,24], we did not find a significant association between postoperative pain in the PACU (NRS $\geq$ 5 vs. NRS $<$ 5) with emergence agitation ($P = 0.274$), notwithstanding the hurdle of assessing the pain accurately during emergence agitation. Nevertheless, we observed an increased rate of emergence agitation with higher doses of intraoperative opioid administration.

Managing emergence agitation demands more staff and financial resources. Restraining an agitated patient may require six or more healthcare people with a risk of injury to the staff. It may cause anxiety for other concurrent patients, especially if they feel neglected. Emergence agitation may increase anesthesia morbidities such as self-extubation, removal of catheters, aspiration pneumonia, or emergency surgery. Emergence agitation also adds to the cost of medical and surgical treatments and may prolong the length of a PACU stay. Therefore, routine monitoring for emergence agitation in the PACU is essential.

Hypoactive emergence

Hypoactive emergence is more common in patients with dependence on opium rather than stimulants (15.3% vs. 2.8%, $P = 0.045$). Hypoactive emergence has been associated with a history of hypertension, pre-existing psychological disorders, and intraoperative opioid administration (morphine, sufentanil, and alfentanil). Lower doses of alfentanil (1.0 ± 0 mg) were associated with agitation while higher doses (4.4 ± 2.5 mg) was associated with hypoactive emergence. Low-dose sufentanil (15.9 ± 28.7 μg), however, was associated with hypoactive emergence.

Card and colleagues found that total opioid administration (fentanyl equivalents) are associated with postoperative delirium. In their cohort study, patients receiving opioids equivalent to 383 μg fentanyl were six times more likely to develop delirium in the PACU than those receiving 50 μg fentanyl (odds ratio [OR] 6.2, 95% CI [1.7, 22.1]). Higher doses of opioids bore a similar risk of developing postoperative delirium, which could either reflect a ceiling effect of the role of opioids in contributing to postoperative delirium or be merely due to the fewer number of patients receiving such large doses [18].

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Foley catheter fixation in the PACU significantly correlates with a higher incidence of hypoactive emergence, which is contrary to an earlier study in which urinary catheterization related to higher rates of emergence agitation [25].

Specific factors in substance-dependent patients

In patients with substance dependence, analgesic drug administration in the PACU related to an increased risk of emergence agitation. Interestingly, smoking history in patients with substance dependence decreased the risk of emergence agitation, potentially because of the nicotinic acetylcholine receptors that modulate aggression [26].

Limitation of the study

The present study did not assess the patients for delirium after discharge from the PACU, especially during their postoperative course in the hospital or long-term outcomes. Moreover, we did not differentiate between chronic substance-dependent patients and acute dependency, or those who abuse substances causally. Another limitation of our study was that we did not consider the effects of different drugs, used as anesthetics during induction and maintenance of general anesthesia, on producing inadequate emergence during the postoperative period. In patients with a history of substance dependence, the incidence of inadequate emergence following general anesthesia appears to be higher than in the general population. While analgesic drug administration in the PACU is a risk factor for emergence agitation, smoking history can decrease its risk in these patients.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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References

1. Burns S. Delirium during emergence from anesthesia: a case study. Crit Care Nurse 2003; 23: 66-9.
2. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology 2004; 100: 1138-45.
3. O'Keefe S, Chonchubhair A. Postoperative delirium in the elderly. Br J Anaesth 1994; 73: 673-87.
4. European Delirium Association; American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014; 12: 141.
5. Lepousé C, Lautner C, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. Br J Anaesth 2006; 96: 747-53.
6. Radtke F, Franck M, Hagemann L, Seeling M, Wernecke KD, Spies CD. Risk factors for inadequate emergence after anesthesia: emergence delirium and hypoactive emergence. Minerva Anestesiol 2010; 76: 349-403.
7. Sharma PT, Sieber FE, Zakriya KJ, Pauldine RW, Gerold KB, Hang J, et al. Recovery room delirium predicts postoperative delirium after hip-fracture repair. Anesth Analg 2005; 101: 1215-20.

8. Olin K, Eriksdotter-Jonhagen M, Jansson A, Herrington MK, Kristiansson M, Permert J. Postoperative delirium in elderly patients after major abdominal surgery. Br J Surg 2005; 92: 1559-64.
9. Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK. Premature death associated with delirium at 1-year follow-up. Arch Intern Med 2005; 165: 1657-62.
10. Bala N, Kaur G, Attri JP, Singh M, Thakur M, Jain P. Psychiatric and anesthetic implications of substance dependence: present scenario. Anesth Essays Res 2015; 9: 304-9.
11. Hernandez M, Birnbach DJ, Van Zundert AA. Anesthetic management of the illicit-substance-using patient. Curr Opin Anaesthesiol 2005; 18: 315-24.
12. McGuire JM. The incidence of and risk factors for emergence delirium in U.S. military combat veterans. J Perianesth Nurs 2012; 27: 236-45.
13. Mokri A. Brief overview of the status of drug abuse in Iran. Arch Iranian Med 2002; 5: 184-90.
14. Alam-mehrjerdi Z, Noori R, Dolan K. Opioid use, treatment and harm reduction services: the first report from the Persian Gulf region. J Subst Use 2016; 21: 217-23.
15. Manworren RC, Paulos CL, Pop R. Treating children for acute agitation in the PACU: differentiating pain and emergence delirium. J Perianesth Nurs 2004; 19: 183-93.
16. Voepel-Lewis T, Malviya S, Tait A. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg 2003; 96: 1625-30.
17. Gary MS, Jeffrey IG. Emergence delirium: a re-emerging interest. Semin Anesth Perioper Med Pain 2006; 25: 100-4.
18. Card E, Pandharipande P, Tomes C, Lee C, Woo J. Emergence from general anaesthesia and evolution of delirium signs in the post-anaesthesia care unit. Br J Anaesth 2015; 115: 411-17.
19. Silva LM, Braz LG, Módolo NS. Emergence agitation in pediatric anesthesia: current features. J Pediatr 2008; 84: 107-13.
20. Son JS, Jang E, Oh MW, Lee JH, Han YJ, Ko S. A comparison of postoperative emergence agitation between sevoflurane and thiopental anesthesia induction in pediatric patients. Korean J Anesthesiol 2015; 68: 373-8.
21. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166: 1338-44.
22. Riker R, Fraser GL, Simmons LE, Wilkins ML. Validating the sedation-agitation scale with the bispectral index and visual analog scale in adult ICU patients after cardiac surgery. Intensive Care Med 2001; 27: 853-8.
23. Brandl K, Langley K, Riker R, Dork L, Quails C. Confirming the reliability of the sedation-agitation scale administered by ICU nurses without experience in its use. Pharmacotherapy 2001; 21: 431-6.
24. Mei W, Seeling M, Franck M, Radtke F, Brantner B, Wernecke KD, et al. Independent risk factors for postoperative pain in need of intervention early after awakening from general anaesthesia. Eur J Pain 2010; 14: 149.e1-7.
25. Yu D, Chai W, Sun X, Yao L. Emergence agitation in adults: risk factors in 2,000 patients. Can J Anaesth 2010; 57: 843-8.
26. Picciotto MR, Lewis AS, van Schalkwyk GI, Mineur YS. Mood and anxiety regulation by nicotinic acetylcholine receptors: A potential pathway to modulate aggression and related behavioral states. Neuropharmacology 2015; 96: 235-43.

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