Original Article

Predisposing Factors of Emergence Agitation in Pediatric Anesthesia

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Objective: To identify pre-operative and intra-operative predictors of emergence agitation or delirium in pediatric patients after general anesthesia.

Materials and Methods: After IRB approval, the present study conducted a single-center, prospective, observational cohort study that included 607 patients, between the age of 2 and 21 years, undergoing elective ambulatory surgery between August 2013 and May 2014. The collected data was pre-operative demographics, anesthetic techniques, surgical procedures, and post anesthesia outcomes (including pain and agitation or delirium). The agitation or delirium was defined by the Pediatric Anesthesia Emergence Delirium (PAED) scale score of 10 or more lasting longer than 10 minutes in the post anesthesia care unit (PACU). A multivariable binary logistic regression model was generated, and the performance of the multivariable model was evaluated by the c statistic.

Results: Among the 429 patients with agitation data, 170 (39.6%) had high agitation score (scores of 10 or more) (95% confidence interval 35% to 44%). Univariate logistic regression model showed that age, weight of less than 20 kg and tonsillectomy and adenoidectomy (TandA) surgery were predictors of agitation. The utilization of intra-operative propofol, dexmedetomidine, or midazolam decreased agitation. Applying multivariate logistic regression modeling revealed that age between two and six years and TandA surgery were independent predictors of agitation.

Conclusion: The present prospective observation trial found that age and surgery type were independent predictors of agitation or delirium during recovery in children after surgery. Further study needs to focus on how to prevent post-operative agitation or delirium in the high-risk population.

Keywords: Emergence agitation, Pediatric anesthesia

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High quality outcomes in the post anesthesia care unit (PACU) have always been a goal of peri-operative care. A considerable number of metrics can be used to measure quality of outcomes in the PACU such as the incidence and degree of post-operative pain, emergence agitation or delirium, and post-operative vomiting. In the present study, the authors evaluated predictors of one aspect of poor post-anesthetic outcomes, the presence of emergence agitation or delirium. Many possible causes for delirium have been suggested by previous investigators, including pain, pre-operative anxiety, type of surgical procedures, and type of anesthetics(1).

There is conflicting evidence for many of the factors that have been associated with emergence agitation or delirium. Though pain has been suspected as a cause, emergence agitation or delirium has also been described after non-painful radiologic imaging procedures. Similarly, although the sevoflurane is highly suspected as a cause of emergence agitation or delirium, the reports are variable and there remains no definitive explanation why some children develop agitation when emerging from sevoflurane anesthesia, while others do not. Furthermore, multiple pharmacologic agents, including dexmedetomidine, propofol, and midazolam, have been tested for

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Table 1. Type of Surgery

Urology Department	Otolaryngology Department	Orthopedics Department	Plastic Surgery Department
• Circumcision	• Tonsillectomy	• Hip Arthroscopies	• Alveolar cleft repair
• Orchidoplexy	• Adenoidectomy	• Knee Arthroscopies	
• Hypospadias repair	• Tympanostomy	• Hardware removal	
• Hernia repair	• Tympanoplasty	• Tendon lengthening	
• Cystoscopy	• Mastoidectomy		
• Pyeloplasty			
• Ureteral reimplants			
• Ureteral stents			

prevention of emergence agitation or delirium in the pediatric populations, but there have been limited reports evaluating the effect of these anesthetic agents (particularly in combination) among patient undergoing ambulatory surgery.

The authors conducted a prospective observational study to identify peri-operative factors predictive of post-anesthesia agitation in children. The aim of the present study was to evaluate the incidence of emergence agitation in the PACU at Boston Children's Hospital (BCH) and to identify pre-operative demographic factors, intra-operative, and anesthetic predictors associated with this PACU outcome. The authors hypothesized that younger age and inhalation-only anesthesia would be associated with an increased incidence of emergence agitation or delirium.

Materials and Methods

After Institutional Review Board (IRB) approval, the present study was conducted as a single-center prospective observational cohort study in 607 patients between August 2013 and May 2014. The enrolled patients were aged 2 to 21 years undergoing qualifying surgeries (Table 1).

The authors followed patients on the day of surgery from arrival to the Day Surgery Unit or Pre-operative Holding Unit, into surgery, and through their recovery in the PACU.

The enrolled patients aged 2 to 21 years were scheduled for elective ambulatory surgeries including urology, otolaryngology, orthopedic, and plastic surgery (Table 1) at Boston Children Hospital between August 2013 and May 2014. The exclusion criteria were 1) surgery was cancelled, 2) patient needed to be hospitalized after surgery, and 3) parent or legal guardian withdrew permission prior to completing the study.

Data collection

Pre-operative (Day of Surgery-Demographics): Demographic data on each patient were collected including age, weight, diagnosis, history of previous surgery, and developmental status. These data were obtained from the electronic medical record after enrollment in the present study on the day of surgery.

Intra-operative: Data on the intra-operative care of each patient were collected through the Automated Information Management System (AIMS) at Boston Children's Hospital. The information included type of anesthetic agent such as inhalation agents, midazolam pre-medication, propofol (both as sole anesthetic agent and as adjunct to general anesthesia), and dexmedetomidine (bolus or infusion) as an adjunct to anesthesia.

Post-operative (in the PACU): Recovery data on each patient include 1) pain behavior information using the FLACC scale or Wong-Baker Faces Scale for patients seven years old and younger and patients that were too sedated to provide subjective assessment. A visual analog scale (VAS) or numerical pain scale (NPS) were used for developmentally appropriate older patients. An adapted Numerical Rating Scale used in the PACU to characterize pain in developmental delayed or decisional impaired patients were used for these participants. 2) Emergence agitation categorization through use of the Pediatric Anesthesia Emergence Delirium (PAED) scale.

These measures were recorded by reporting the highest level of pain or agitation that occurred for every 15 minutes interval.

Ethics statement

The present study obtained appropriate approval from the IRB of Boston Children's Hospital (IRB No. P00008050). The study protocol was registered at the ClinicalTrial.gov (ClinicalTrials.gov Identifier:

Table 2. Demographic information (n=605)

	Number of patients n (%)
Age(years)	
2 to 6	273 (45.1)
7 to 21	332 (54.9)
Developmental delayed	72 (11.9)
Sex	
Female	240 (39.7)
Male	365 (60.3)
ASA classification	
1 or 2	569 (94.0)
3-4	36 (6.0)
Propofol	93 (15.4)
Dexmedetomidine	83 (13.7)
Midazolam	246 (40.7)
Tonsillectomy/adenoidectomy	245 (40.5)
Tympanostomy	71 (11.7)
Urology procedure	94 (15.5)
Orthopedic procedure	183 (30.3)
Other	12 (2.0)

ASA=American Society of Anesthesiologists

NCT02189642). Written informed consents were obtained from all of the participants guardians.

Statistical analysis

Continuous data are represented as median and interquartile range (IQR). Patients were classified into low emergence agitation (PAED of less than 10) and high emergence agitation (PAED 10 to 20) groups where univariate analysis was first performed to identify candidate predictors of PAED 10 to 20 using the Mann-Whitney U test to compare continuous data and chi-square test for categorical variables. Using the univariate results as an initial screen, multivariable logistic regression was then applied to identify significant factors that independently differentiate between the two groups. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were determined for significant multivariable predictors of high emergence agitation (PAED 10 to 20) with the c-index used to judge predictive accuracy of the final model. Statistical analysis was conducted using IBM SPSS Statistcs version 24.0 (IBM Corporation, Armonk, NY). Two-tailed values of p-value less than 0.05 were considered statistically significant.

Results

Six hundred seven patients were enrolled in the present study. All patients were assessed for eligibility for the study between August 2013 and May 2014. Two patients were excluded because their surgeries were cancelled. The remaining 605 patients were enrolled in the present study. Among these patients, data for 176 patients were not analyzed due to lack of PAED score (Table 2). The median [IQR] age was 7.0 [4 to 13] years (range 2 to 21 years). The median [IQR] weight was 29.2 [17.1 to 56.2] kilograms (range 9.4 to 175.6 kilograms). The demographic data are shown in Table 2.

Information about post-operative pain score and PAED score are given in Figure 1 and 2. While 592 out of 605 patients had pain score data, only 492 out of 605 patients had PAED score in recovery period. The median [IQR] pain score was 5 [2 to 7]. The median [IQR] PAED score was 7 [3 to 14]. The number of patients considered as having displayed agitation, defined as PAED 10 to 20, was 197 of 492 (40%). The median [IQR] length of stay was 96 [70 to 136] minutes (range 22 to 534 minutes).

Only the 429 patients that had both post-operative pain score and PAED score were included in the univariate and multivariable logistic regression. Among patients with PAED score less than 10 (or not having emergence agitation or delirium), the median age was nine years old and the median weight was 34 kilograms. In patients with PAED score of 10 to 20 (or qualifying as emergence agitation or delirium) the median age was four years old and weight was 17.8 kilograms.

The authors performed the univariate analysis to identify the factors that associate strongly with emergence agitation (PAED score of 10 to 20) and should be included in the multivariable logistic regression model. The univariate variables are shown in Table 3. The incidence of emergence agitation or delirium was significantly lower in cases where propofol ($p=0.003$), dexmedetomidine ($p=0.003$), or midazolam was used ($p<0.001$). The incidence of emergence agitation or delirium was significantly higher in the age group between two and six years ($p<0.001$) and in lower weight group ($p<0.001$) as well as those who underwent tonsillectomy or adenoidectomy ($p<0.001$). No statistically significant differences were found between high and low PAED groups with respect to gender ($p=0.115$), hospital length of stay ($p=0.379$), ASA classification ($p=0.409$), and developmental delay ($p=0.213$).

The present study identified six important factors

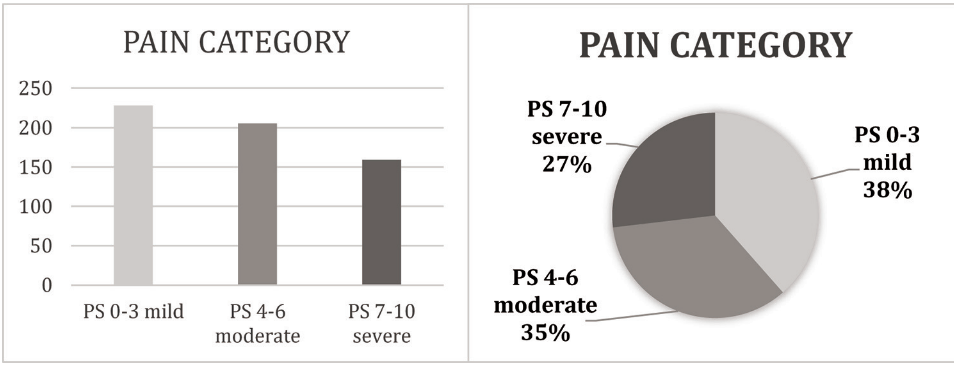

Figure 1. Pain category.

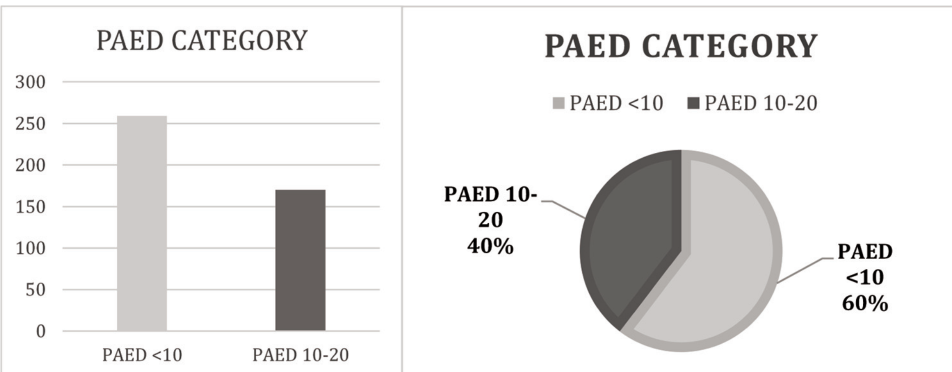

Figure 2. PAED category.

associated with a higher incidence of emergence agitation. The authors then performed multivariable logistic regression using all of the six factors displayed in Table 4. Among these factors (age two to six years, weight of less than 20 kilograms, ASA classification 3 or 4, gender, developmental delayed, lack of propofol use, lack of dexmedetomidine use, lack of midazolam use, and type of surgery), the results revealed two predictors for emergence agitation, age between two and six years and tonsillectomy procedure. Age between two and six years had likelihood ratio test of 17.88 ($p<0.001$) and adjusted OR of 2.8 (95% CI 1.7 to 4.4), tonsillectomy or adenoidectomy procedure had likelihood ratio test of 24.12 ($p<0.001$) and adjusted OR of 3.2 (95% CI 2.0 to 5.1).

The authors evaluated the predictive accuracy of the multivariable model as judged by the c-index and found very good accuracy based on these two significant predictors (c-index 0.731, 95% CI 0.671 to 0.790, $p<0.001$).

Discussion

In the present study the authors present a detailed evaluation of emergence agitation in a population of pediatric patients undergoing surgeries as a quaternary care children's hospital. After considering many possible contributing factors, the authors' findings confirm previous investigations that determined that age and surgery type are associated with increased rates of emergence agitation or delirium. The authors also found a relationship with the type of anesthetic used although this did not persist with multivariable analysis.

Emergence agitation or delirium is a challenging phenomenon and its origin remains unknown. The reported prevalence of emergence agitation or delirium varies greatly in the literature, ranging from 10% to 80%, depending on the definition and criteria of emergence agitation or delirium. There is no strong data supporting an exact mechanism of this phenomenon. Emergence agitation or delirium can be defined as a "dissociated state of consciousness in which the child is irritable, uncompromising, uncooperative, incoherent and inconsolably crying, moaning, kicking, or thrashing"[1]. When children wake up from general anesthesia crying in the

Table 3. Univariate regression comparing the association between potential risk factors and emergence agitation (PAED 10 to 20)

	PAED <10	PAED 10 to 20	p-value
Age group			<0.001*
2 to 6 years	35%	73%	
7 to 21 years	65%	27%	
Weight (kg), Median (IQR)	34 (19.1 to 62.3)	17.8 (15 to 29.5)	<0.001*
Length of stay (minutes), Median (IQR)	96 (69 to 132)	95.5 (70 to 148)	0.379
Sex			0.115
Female	40%	34%	
Male	60%	66%	
ASA classification			0.409
1 and 2	96%	94%	
3 and 4	4%	6%	
Developmental delayed	10%	14%	0.213
Medications			
Propofol	16%	7%	0.003*
Dexmedetomidine	11%	22%	0.003*
Midazolam	46%	18%	<0.001*
Type of surgery			<0.001*
Adenoidectomy and/or tonsillectomy	28%	69%	
Tympanostomy		8.2%	
Urology		13.5%	
Orthopedic		8.8%	
Other		0.6%	

PAED=Pediatric Anesthesia Emergence Delirium; ASA=American Society of Anesthesiologists; IQR=interquartile range

* Significant association by univariate analysis

Table 4. Multivariate logistic regression comparing the association between important risk factors and emergence agitation (PAED 10 to 20)

	LRT	p-value	Adjusted OR	95% CI
Age 2 to 6 years	17.88	<0.001*	2.8	1.7 to 4.4
Weight <20 kg	1.32	0.251		
ASA classification 3 or 4	0.08	0.785		
Sex	2.14	0.143		
Developmental delayed	0.13	0.722		
Propofol	0.37	0.545		
Dexmedetomidine	0.12	0.726		
Midazolam	2.68	0.102		
TandA vs. other surgeries	24.12	<0.001*	3.2	2.0 to 5.1

LRT=likelihood ratio test from logistic regression model; OR=odds ratio; CI=confidence interval; ASA=American Society of Anesthesiologists; TandA=tonsillectomy and adenoidectomy

* Significant independent multivariable predictor of high emergence agitation

recovery room after the operation, it can be difficult to differentiate if the child having post-operative pain or emergence agitation because of the similarity in their presentations. In an effort to standardize the classification of agitation or delirium and differentiate from other issues such pain, Sikich and Lerman developed the PAED scale, which incorporated cognitive-related assessment items in addition to agitation behaviors, and were able to provide more reliability and validity than other scores. The PAED scale is the recognized standard for the diagnosis of emergence delirium. The scores for each of the five listed behaviors are added to achieve a total score (maximum score of 20). A score of 10 or more displays 64% sensitivity and 86% specificity, and a score greater than 12 yields 100% sensitivity and 94.5% specificity for the diagnosis of emergence delirium(2). In the present study, the authors defined agitation or delirium as the PAED scale score of 10 or more lasting longer than 10 minutes in PACU. Utilizing these triggers, the authors strongly believe the data consistently identified patients who had adverse emergence phenomenon.

The most consistent predictor of emergence agitation or delirium reported in the literature is the use of volatile anesthesia. While most recent reports focus on the use of sevoflurane, emergence delirium has been reported with all inhalational agents. There does not seem to be a relationship between depth and the duration of anesthesia and emergence delirium(3). In the present hospital, the authors consistently used inhalation induction and maintenance with sevoflurane for ambulatory surgery in young pediatric patients. This may be responsible for the high incidence of emergence agitation or delirium (40%) in the present study. The initial data analysis confirmed that delirium was more common in the present study's patients who received only inhaled agents but did not hold up after multivariable analysis.

While emergence agitation can be seen in any age group, its peak incidence is in younger children (two to six years of age)(2). One hypothesis for emergence agitation or delirium involves the difference of clearance of volatile agents from the central nervous system, leading to differential recovery rate from anesthesia of brain functions(4,5). The psychological immaturity of children and their lack of adaptation to the peri-operative anxiety during the peri-operative period might also participate in the genesis of emergence delirium. This hypothesis is supported by the recent studies using functional imaging, which compares the pattern of brain area activation involved in the cognitive control between children and adults(6). The present study revealed similar findings. The statistical analysis showed that patients with emergence agitation are younger (age four versus nine years) and smaller (weight 17.8 versus 34 kilograms).

Because many studies had pointed to the influence of inhalation agents on central nervous system as a possible of emergence delirium or agitation after general anesthesia, patients with delayed development may have different brain physiology when compared with patients at the same age with normal development. The authors suspected that inhalation anesthetic might produce distinctive effects upon central nervous tissue in this group, which can subsequently increase the risk of developing emergence delirium or agitation. In the present study, 82 patients (13.5%) had a diagnosis of developmental delayed. The authors did not find the association between history of developmental delayed and the incidence of emergence delirium or agitation. It is possible that the differences in underlying brain pathology among the 82 patients influenced the response to inhaled anesthetic agents. Furthermore, developmental delay may be caused by genetic factors, problems with pregnancy, premature birth, or other unknown reasons, therefore, the heterogeneity of this population may have hidden the effect that any particular cause for developmental delay may have on the occurrence of emergence agitation or delirium.

Utilizing univariate logistic regression, the authors identified six important factors that were associated with a higher incidence of emergence agitation including absence of propofol as part of the anesthetic maintenance, absence of dexmedetomidine in the anesthetic, absence of midazolam, age group two to six years, smaller patients, and those who underwent tonsillectomy or adenoidectomy. These findings are consistent with most published data that have found that propofol, dexmedetomidine, or midazolam can be used to decrease the incidence of this post-operative event. Bryan described risk factors for emergence agitation or delirium after anesthesia in children as 1) preschool children, 2) male gender, 3) sevoflurane or desflurane anesthesia, 4) ear, nose, and throat surgery, and 5) pre-operative anxiety(7). Lee et al studied the clinical usefulness of a single dose of propofol (1 mg/kg) at the end of adenotonsillectomy for reducing the incidence and severity of emergence agitation or delirium after sevoflurane anesthesia but found no effect(8). The present study multivariate logistic regression analysis showed comparable results. The authors identified age between two and six years and tonsillectomy or adenoidectomy procedures as distinct predictors of emergence agitation. Contrary to previous investigators, the authors did not find the use of medications such as propofol, dexmedetomidine, or midazolam helped prevent agitation after multivariable regression analysis. This finding might be a result of the present study design, which was an observational study. Adjunctive medications such as propofol, dexmedetomidine, or midazolam, which are known to reduce the incidence of agitation, may well have been intentionally employed in patients if their anesthesia provider predicted an increased risk of developing post-operative agitation during pre-operative evaluation. This possible bias could have masked the effect of propofol, dexmedetomidine, or midazolam on reducing the incidence of post-operative delirium or agitation in the present study.

The authors were also limited to data available in the electronic medical records and recorded by nurses during routine care. The emergence agitation data (PAED score) was recorded for 492 out of 605 patients. A possible bias could have been introduced by the fact that patients without recorded PAED scores during the recovery period might have been more or less likely to have emergence agitation or delirium. Patients with emergence agitation or delirium require significant attention from PACU staff to manage their condition and this could conceivably distract the staff from charting PAED score. While the present study methods included multivariate analysis to attempt to account for potential bias, future studies with appropriate randomization and blinding would be needed to determine the overall impact of the anesthetics used.

The authors present a detailed evaluation of emergence agitation in a population of pediatric patients undergoing surgeries as a quaternary care children's hospital. After considering many possible contributing factors, the present findings confirm previous investigations that determined age and surgery type are associated with increased rates of emergence agitation or delirium. The authors also found a relationship with the type of anesthetic used, although this did not persist with multivariable analysis.

Emergence agitation or delirium is a challenging phenomenon and its origin remains unknown. The reported prevalence of emergence agitation or delirium varies greatly in the literature, ranging from 10% to 80%, depending on the definition and criteria of emergence agitation or delirium. There are no strong data supporting an exact mechanism of this phenomenon. Previous investigators have hypothesized that this phenomenon, is due to post-operative pain and/or the pharmacokinetics and pharmacodynamics of anesthetic agents employed[9].

Conclusion

Although the emergence agitation was reported widely as a complication after general anesthesia in children and many trials have focused on this issue, the underlying etiology is still not fully understood. Additionally, despite numerous efforts to identify peri-operative risk factors for this condition, the authors do not have practice guidelines aimed at preventing this common problem. The authors found that age between two and six years and tonsillectomy or adenoidectomy procedure as distinct predictors of emergence agitation or delirium. Further studies are needed to find strategies and develop guidelines that help prevent emergence agitation or delirium in the pediatric population after general anesthesia.

What is already known on this topic?

Pediatric patients are at risk of developing emergence agitation after general anesthesia. The highest risk groups consist of young patients who have had painful procedure, and, in particular, ear, nose, or throat surgery. Previous studies have shown that the use of a sedative (such as dexmedetomidine) as an adjunct to general anesthesia with inhalation agents can help decrease the incidence of emergence agitation.

What this study adds?

The use of a sedative such as propofol, dexmedetomidine, or midazolam did not decrease the incidence of agitation in this study. The overall incidence of agitation was 40%, which is relatively high but consistent with previous reports of high-risk groups. This data suggests that to maximize family satisfaction, more effort to find ways to prevent emergence agitation, especially in the high-risk populations, is indicated.

Conflicts of interest

The authors declare no conflict of interest.

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