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RESEARCH ARTICLE

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Perioperative variables associated with emergence delirium in children following strabismus surgery: A five-year retrospective single-center cohort study

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ABSTRACT

Background: Emergence Delirium (ED) is common among children. Several factors have been linked to ED related to patient characteristics, anesthesia, or the type of surgery. Strabismus surgery has been associated with the development of ED. The aim of this study was to determine the perioperative variables associated with ED after strabismus surgery in children.

Methodology: A retrospective cohort study of children who underwent strabismus surgery from January 2018 to December 2022 was conducted. Data on factors leading to ED, including patient characteristics, preoperative anxiety, postoperative pain, surgery-related characteristics anesthesia-related characteristics, were analyzed. Emergence delirium was assessed using the Pediatric Anesthesia Emergence Delirium (PAED) scale.

Results: Three-hundred-and-thirty-six children were included in the analysis. Fourteen percent of patients developed ED. Predictors of ED were age, multiple muscle surgery, binocular surgery. Midazolam premedication, intraoperative dexmedetomidine and fentanyl were associated with lower incidence of ED. On multivariable analysis, younger age (Odds Ratio (OR) = 1.05; $p = 0.039$), multiple muscle correction (OR = 1.91; $p = 0.041$), binocular surgery (OR = 1.85; $p = 0.021$) midazolam premedication (OR = 2.02; $p = 0.007$), intraoperative fentanyl administration (OR = 1.88; $p = 0.031$), and intraoperative dexmedetomidine administration (OR = 1.32; $p <$ 0.001), were independent predictors of ED.

Conclusion: In this study, younger age, multiple muscle surgery, and binocular surgery were the main non-modifiable factors associated with ED in children following strabismus surgery. Administration of midazolam, dexmedetomidine, or fentanyl were associated with lower incidence of ED. Patients at higher risk for ED could be selected for prophylaxis against ED using these medications to prevent ED after strabismus correction surgery in children.

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1. Background

Emergence agitation, emergence excitation, and emergence delirium are all terms utilized to describe the state of behavioral dysregulation that can happen during emergence from general anesthesia. The condition was described by Eckenhoff *et al*. as “neurologic excitement” with the patients exhibiting a dissociated state of consciousness [1]. Although the terms “Emergence Agitation” (EA) and “Emergence Delirium” (ED) are commonly used interchangeably, they describe two distinct conditions with emergence delirium being described in the anesthesia literature as “a state of mental confusion, agitation, and dis-inhibition marked by some degree of hyper-excitability during recovery from general anesthesia.” [2]

Emergence Delirium (ED) is common among pediatric patients in particular, with an incidence of up to 80%, which causes concern for parents as well as healthcare providers [3]. During episodes of ED, children can potentially injure themselves or their caregivers. Removal of intravenous lines and drains, bleeding from operative site, and exacerbation of pain are among the complications that may arise due to ED. This often requires closer nursing supervision, which can increase the burden on nursing resources [4]. Several factors have been linked to postoperative ED related either to patient characteristics or to the type of surgery. Risk of ED is higher among younger aged children with the incidence increasing as age decreases [5]. The child’s preoperative psychological condition was also reported to affect the incidence of ED, with a higher incidence among children exhibiting preoperative anxiety as well as among those who were surrounded by parental anxiety [6].

Other factors contributing to ED in children are related to anesthesia and surgery. Several studies

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have shown an association between inhalational anesthetics particularly sevoflurane and desflurane and ED [5]. Additionally, the type of surgical procedure has also been linked to ED with the highest incidence among children undergoing otorhinolaryngeal or ophthalmic surgery [7]. Surgical correction of strabismus is a common procedure in ophthalmic practice and the most common procedure in pediatric ophthalmic surgery. Several studies have shown an association between ED and strabismus surgery [7].

Although ED is a self-limited condition lasting most commonly from 5 to 15 min it can lead to several complications. Moreover, children with ED have been shown to have longer recovery periods [8], which is particularly undesirable in the ambulatory setting. Several prophylactic strategies have been used to prevent ED including perioperative behavioral management, perioperative analgesia, and various prophylactic adjuvant medications such as midazolam, propofol, ketamine, tramadol, and dexmedetomidine, with varying degrees of success. These drugs, however, have side effects; thus, their use should be carefully considered in the ambulatory care setting, especially since ED is a self-limited disorder [9]. This warrants a careful selection of patients who will receive prophylaxis against ED based on the presence of risk factors. Our hospital is an ambulatory center for ophthalmic surgery with patients discharged within hours of undergoing the surgical procedure. We therefore conducted a retrospective analysis of the prevalence of ED and the perioperative variables associated with ED after ambulatory strabismus surgery under general anesthesia in pediatric patients.

2. Methodology

The study was designed as a retrospective cohort study. The study took place at Magrabi Eye Center in Saudi Arabia a specialist, Joint Commission International – accredited, eye hospital. The post-anesthesia care unit (PACU) has a capacity of four beds and is staffed with two qualified nurses. Approval for the study was obtained from the hospital ethical committee. No informed patient consent was required, as the study was based on medical records review and the patients' identities were not revealed. Two PACU nurses screened the electronic medical records between January 2018 and December 2022 and retrieved the relevant data which were subsequently validated by the study investigators. Children under 14 years of age who were admitted to the PACU after strabismus surgery were included in the study. Patients were all anesthetized by one of two anesthetists and all children were operated upon by the same surgeon sevoflurane was used for induction of anesthesia in all patients.

3. Measurements

The collected data included patients' characteristics: age, sex, American Society of Anesthesiologist (ASA) physical status, and body mass index (BMI). Surgery-related characteristics included the type of surgery and its duration. Anesthesia-related characteristics included medication given preoperatively and intraoperatively, duration of anesthesia, airway management technique, and time to recovery which was defined as time from admission to the PACU until reaching an Aldrete score of ≥9.

The "Modified Yale Preoperative Anxiety Scale – short version" (m-YPAS-sf) [10] was collected by a nurse at the preoperative holding area to assess children's anxiety level. It consists of four domains that assess the "levels of activity": scale 1 to 4, "vocalizations": scale 1 to 6, "emotional expressivity": scale 1 to 4, and "state of apparent arousal": scale 1 to 4. The rating for each item is divided by the highest rating possible for the item (6 for "vocalizations", 4 for all other items), then all resulting values are added and divided by 4, then multiplied by 100. Children with m-YPAS-sf scores higher than 40 were considered to be anxious [10].

The intensity of postoperative pain was monitored using the FLACC scale "Face, Legs, Activity, Cry, and Consolability" [11]. Each item on the score is given a score of 0 to 2, the maximum score is 10. The FLACC score in the PACU was assessed once the patient was able to move purposefully. A dose of 15 mg/kg paracetamol was given for pain relief for all children.

The primary outcome was the occurrence of Emergence Delirium. Emergence was defined as the interval between discontinuing the administration of inhalation anesthetic and 5 min after extubation [12]. ED was assessed by the recovery nurse using the "Pediatric Anesthesia Emergence Delirium" (PAED) scale [12], which consists of five items. Items 1, 2, 3 are scored as follows: 4 = "not at all", 3 = "just a little", 2 = "quite a bit", 1 = "very much", 0 = "extremely". Items 4 and 5 are scored as follows: 0 = "not at all', 1 = "just a little", 2 = "quite a bit", 3 = "very much", 4 = "extremely". The degree of ED is directly proportional to the total score (Table 1).

Table 1. Pediatric anesthesia emergence delirium scale [12].

1*	"Child makes eye contact with the care giver"
2*	"Child's actions are purposeful"
3*	"Child is aware of his/her surroundings"
4	"Child is restless"
5	"Child is inconsolable"

*Items "1", "2" and "3" are reverse scored.

4. Statistical analysis

The primary outcome was the incidence of ED, which was 19.3% in a previous study on children [5]. The sample size of 336 cases in our study could meet the tolerance error of 0.03 when the level of significance was set to 5% (two-sided). Data entry and analysis was done using statistical software R version 3.4.1 (R Foundation, Vienna, Austria). Continuous variables were expressed as mean and standard deviation (SD), while categorical variables were expressed as frequency and percentage. Univariable analysis was performed to identify which perioperative variables would be included in multivariate analysis for emergence delirium. Chi-square test or Fisher's exact test were used to evaluate categorical variables (sex, ASA physical status, preoperative anxiety, invasiveness of surgery, length of surgery, preoperative and intraoperative drugs, and airway management technique). Student t-test and Wilcoxon rank sum test were used to evaluate continuous variables (age, BMI, recovery duration, duration of anesthesia, FLACC score) between ED and no ED groups. All covariates with P less than 0.05 in univariable analysis were entered into a multiple logistic model for ED. The final model was based on the "Akaike Information Criterion" (AIC), likelihood ratio test, and significance threshold with $p < 0.05$. Model-fitting of logistic models was evaluated using "Hosmer-Lemeshow" goodness-of-fit test.

5. Results

Four-hundred-and-three children aged ≤14 years were identified for potential inclusion in the study, and 67 of those were excluded due to incomplete data. Three-hundred-and-thirty-six children were included in the final analysis. Figure 1 shows the flow diagram based on the primary outcome measure (ED). Patients' baseline characteristics are displayed in Table 2. The mean age ± standard deviation of the cohort was 5.5 ± 2.3 years old and 55.6% were male. The mean BMI was 16.3 ± 1.1. The mean preoperative anxiety score was 50.2 ± 21.9. Forty-seven (14%) patients developed emergence delirium. The baseline characteristic that was identified as a predictor of emergence delirium by univariate analysis was age ($p = 0.005$), while sex, BMI, ASA physical status, and preoperative anxiety were not identified as predictors of emergence delirium (Table 3). The surgical variables identified as predictors of ED were multiple muscle surgery ($p < 0.001$) and binocular surgery ($p < 0.001$) (Table 4). The anesthetic variables that were associated with lower incidence of ED were premedication with midazolam ($p < 0.0001$), intraoperative dexmedetomidine ($p = 0.0335$), and intraoperative fentanyl ($p = 0.0324$) (Table 5). On multivariable analysis, adjusting for other independent predictors of ED, younger age (Odds Ratio (OR) = 1.05 [95% Confidence Interval (CI) 1.01 to 1.11]; $p = 0.039$) for each year decrease in age, Multiple muscle correction (OR = 1.91 [95% CI 1.04 to 3.60]; $p = 0.041$) relative to single muscle correction, binocular surgery (OR = 1.85 [95% CI 1.11 to 3.08]; $p = 0.021$) relative to monocular surgery, midazolam premedication (OR = 2.02 [95% CI 1.22 to 3.29]; $p = 0.007$) relative to no midazolam premedication, intraoperative fentanyl administration (OR = 1.88 [95% CI 1.11,

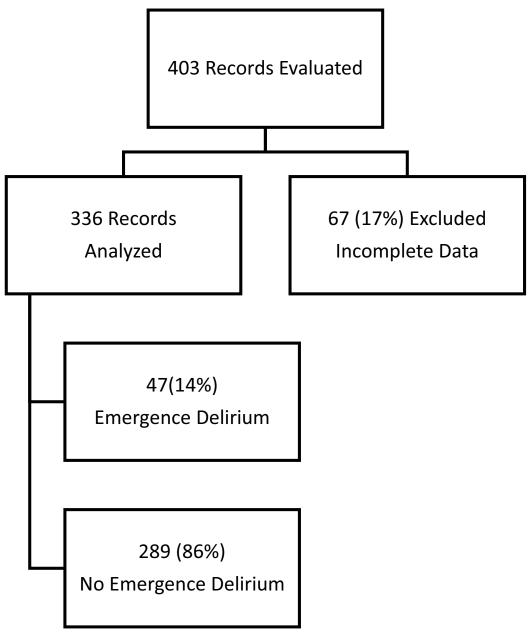

Figure 1. Flow diagram based on primary outcome (emergence delirium).

Table 2. The demographic data of the whole evaluated patients.

Variable	n=336
Age grouping	
1–3 years [N(%)].	60 (17.6%)
4–6 years [N(%)].	198 (58.4%)
>6 years [N(%)].	77 (23%)
Age mean (±SD)	5.5 (2.3)
Sex	
Male [N(%)].	187 (55.6%)
Female [N(%)].	149 (44.4%)
Body mass index (kg/m2)	
Underweight (<5th) [N(%)].	91(27.3%)
Normal weight (5-85th) [N(%)].	217 (64.5%)
Overweight (85th) [N(%)].	28 (8.2%)
Mean (±SD).	16.2 (1.0)
ASA physical status (ps)	
ASA ps class I [N(%)].	264 (78.6%)
ASA ps class II [N(%)].	72 (21.4%
Preoperative anxiety	
Low anxiety [N(%)].	154 (46%)
High anxiety [N(%)].	182 (54%)
Mean (±SD).	50.2 (21.9)
Recovery duration (min)	
Mean (±SD).	32.3 (6.1)
Emergence Delirium [N(%)]	
Yes	47 (14%)
No	289 (86%)

The data are presented by mean (±SD) and numbers (%).
N(%)= The number and the (percent) of patients in each variable.
Yes= Patients with Emergence Delirium. No= Patients without Emergence Delirium.
ASA= American Society of Anesthesiologists.

Table 3. The demographic data of the patients with emergence delirium.

		Emergence Delirium Status		
Variable	Whole evaluated patients (*n*= 366)	Yes (*N*= 47)	No (*N*=289)	P-value
Age (years):				
Mean (±SD)	5.5 (2.3)	3 (2.3)	6.6 (2.5)	0.005
Sex [N(%)]:				
Males.	187 (55.6)	25 (53.2)	162 (56.0)	
Females.	149	22 (46.8)	127 (44.0)	0.642
Body mass index (kg/m2):				
mean (±SD)	16.3 (1.1)	16.4 (1.5)	16.1(1.4)	0.840
ASA physical status (ps) [N(%)]:				
ASA ps class I	264 (78.6)	25 (53.2)	239 (82.7)	
ASA ps class II	72 (21.4)	22 (46.8)	50 (17.3)	0.701
Preoperative anxiety:				
Low anxiety[N(%)].	154 (46)	20 (42.5)	134 (46.4)	
High anxiety[N(%)].	182 (54)	27 (57.5)	155 (53.6)	0.080

The data are presented by mean (±SD) and numbers (%).
n= the total number of the analyzed patients.
N(%)= The number and the (percent) of patients in each variable.
ASA= American Society of Anesthesiologists.
m-YPAS-SF = Modified Yale Preoperative Anxiety Scale.
P<0.05 = Statistically significant.

Table 4. The correlation between each surgical variable and the incidence of emergence delirium (univariate analysis).

		Emergence Delirium Status		
Surgical variables	Whole evaluated patients (*n* = 336)	Yes (*N* = 47)	No (*N* = 289)	P-value
Invasiveness of surgery:				
Single muscle correction [N(%)].	101(30.1)	13 (27.6)	88 (30.4)	
Multiple muscle correction [N(%)].	235 (69.9)	34 (72.4)	201(69.6)	<0.001
Surgical eye:				
Monocular surgery [N(%)].	242 (72.0)	14 (29.8)	228 (78.9)	
Binocular surgery [N(%)].	94 (18.0)	33(70.2)	61(21.1)	<0.001
Duration of surgery:				
Less than 30 min [N(%)].	206 (61.3)	29(61.7)	177(61.2)	
More than 30 min [N(%)].	130 (38.7)	18(38.3)	112(38.8)	0.0613

The data are presented by numbers (%).
n= the total number of the analyzed patients.
Yes= Patients with Emergence Delirium.
No= Patients without Emergence Delirium.
N(%)= The number and the (percent) of patients in each variable.
P<0.05 = Statistically significant.

3.71]; $p = 0.031$) relative to no fentanyl, and intraoperative dexmedetomidine administration (OR = 1.32 [95% CI 1.14, 1.51]; $p < 0.001$) relative to no dexmedetomidine administration, were independent predictors of emergence delirium (Table 6).

6. Discussion

Emergence delirium is a problematic condition in children. The cause for higher prevalence of ED among children may be related to brain maturation. As pointed out by Martini [13], the pediatric brain can be viewed as: "a mirror image of a normal age-related regressive process with a consequent decline in norepinephrine, acetylcholine, dopamine, and γ-aminobutyric acid (GABA)". Accordingly, hippocampal and cholinergic function development may provide a possible explanation for the relatively higher affinity of younger children to delirium. There has also been an association between the occurrence of ED with strabismus surgery. This association has been explained by the presence of preoperative visual disturbances [14], in addition to the discomfort caused by application of ointment followed by a gauze patch or an eye shield [15].

The incidence of ED was 14% in this study. Reports about the incidence of ED in children have been found to vary widely (10–80%) according to the type of anesthesia and the surgical procedure [16]. The cause of this wide range is probably related to the variety of factors and difference in protocols. However, an incidence comparable to our findings was reported by Cho *et al.* [17] who reported an incidence of ED of 16.7% in 60 children undergoing strabismus surgery and receiving midazolam. Additionally, our study found no statistically significant association between the incidence of ED and sex, BMI, or ASA I/II. These findings are comparable to another study in Saudi Arabia in which the researchers conducted a retrospective analysis of 413 children undergoing elective surgery and found no correlation between these factors and the development of emergence delirium [18].

Table 5. The correlation between each anesthesia related variable and the incidence of emergence delirium (univariate analysis).

		Emergence Delirium Status		
Variable	Whole evaluated patients (*n* = 336)	Yes (*N* = 47)	No (*N* = 289)	P-value
Duration of anesthesia (min)				
Mean ±SD.	47(± 13)	48 ± 12	49± 13	0.531
Preoperative midazolam:				
Yes [N(%)].	231 (69%)	8(17.1)	223(77.2)	
No [N(%)].	105 (31%)	39(82.9)	66(22.8)	<0.0001
Sevoflurane induction:				
Yes [N(%)].	301(89%)	28(59.6)	273(94.5)	
No [N(%)].	35 (11%)	19(40.4)	16(5.5)	0.167
Propofol induction:				
Yes [N(%)].	35 (11%)	19(40.4)	16(5.5)	
No [N(%)].	301(89%)	28(59.6)	273(94.5)	0.167
Intraoperative paracetamol:				
Yes [N(%)].	247 (74%)	23(48.9)	224(77.5)	
No [N(%)].	89 (26%)	24(51.1)	65(22.5	0.840
Intraoperative fentanyl:				
Yes [N(%)].	154 (46%)	12(25.5)	221(76.5)	
No [N(%)].	182 (54%)	35(74.5)	68(23.5)	<0.0001
Intraoperative dexmedetomidine:				
Yes [N(%)].	54 (16%)	19(40.4)	35(12.1)	
No [N(%)].	282 (84%)	28(59.6)	254(87.9)	0.0335
Airway management technique				
Laryngeal mask [N(%)].	215 (64%)	20(42.5)	195(67.5)	
ETT [N(%)].	121 (36%)	27(57.5)	94(32.5)	
Recovery time (min):				
Mean ±SD	32.3 (6.1)	33.4(11.5)	30.5(10.3)	0.674
FLACC score: Median (interquartile range).	1 (0–3)	1(0–3)	1(1–3)	0.879

The data are presented by mean (±SD) and numbers (%).
n= the total number of the analyzed patients.
Yes= Patients with Emergence Delirium.
No= Patients without Emergence Delirium.
N(%)= The number and the (percent) of patients in each variable.
ETT: Endotracheal Tube.
FLACC: "Face, Legs, Activity, Cry, and Consolability".
P< 0.05 = Statistically significant.

Table 6. Predictors of emergence delirium by multivariable analysis.

	Emergence Delirium Status	
Variables	OR (95%CI)	P-value
Age	1.06 (1.01, 1.10)	0.039
Multiple muscle correction	1.91 (1.04, 3.60)	0.041
Binocular surgery	1.85 (1.11, 3.08)	0.021
Preoperative midazolam	2.02 (1.22, 3.29)	0.006
Intraoperative fentanyl	1.88 (1.11, 3.71)	0.031
Intraoperative dexmedetomidine	1.32 (1.14, 1.51)	<0.001

OR: "Odds ratio", CI: "Confidence Interval".

In the current study, younger age was associated with a higher incidence of ED. The mean age of children who experienced ED was 3 (2.3) while the mean age of those who did not develop ED was 6.6 (2.5). On multivariable analysis, this difference was statistically significant [OR (95% CI)1.06 (1.01, 1.10), $p = 0.039$]. Gooden *et al*. [5] found a similar association of age with the occurrence of ED in pediatric patients following outpatient surgery under sevoflurane anesthesia where 26% of children aged between 3 and 6 developed ED as opposed to 10% in the 7 to 10 year age group ($p = 0.01$). Similarly, a Thailand study reported an incidence of ED of 66.7% in the 2–5-year age group and 45.8% in the 6–9-year age group ($p = 0.002$) [19]. Other studies also support these findings [18,20]. Younger children are in general more prone to behavioral changes upon recovery from anesthesia, particularly the 2–5 age group. This may be due to the fact that they are more easily frightened and confused by unfamiliar experiences [21]. In addition to their psychological immaturity, waking up in a strange environment can also be a factor that contributes to the higher incidence of ED among preschool children [19].

Strong preoperative anxiety in both children and their parents has been associated with a higher incidence of agitation and delirium during anesthetic recovery. Kain *et al*. [22] conducted a retrospective analysis to investigate the relation between preoperative anxiety and postoperative maladaptive behaviors and emergence delirium. They reported that among 791 children receiving no premedication before surgery under sevoflurane anesthesia, the odds for developing intense emergence delirium were increased 10% for each 10-point incremental increase in m-YPAS scores. Contrastingly, our study found no significant relation between preoperative anxiety and emergence delirium. Twenty patients (42.5%) in the low anxiety group and 27 (57.5%) in the high anxiety group developed ED; this difference did not reach statistical significance. Other studies also failed to find an association between preoperative anxiety and ED; Faulk *et al*. [23] reported that preoperative anxiety did not significantly affect the PAED score of 400 patients aged 1–12 years undergoing outpatient dental procedures under general anesthesia. Similarly, Przybylo *et al*. [24] could not demonstrate a significant correlation between preanesthetic psychosocial factors and the occurrence of behavioral abnormalities in patients aged 2–9 years following strabismus repair under general anesthesia, although the use of a non-standardized self-developed observation tool and the small sample size (27 patients) limited the validity of their findings. In studying the effect of pre-operative anxiety on ED, it is better to focus on a similar age group; this may help explain why several studies could not demonstrate such a relationship. Preschool children are psychologically immature, they are thus more readily frightened and confused by unfamiliar experiences as compared to school-age children. Including both groups in the same study may result in reporting inexact relationships between preoperative anxiety and emergence delirium [15].

The current study demonstrated a correlation between the invasiveness of strabismus surgery and the occurrence of emergence delirium; patients who underwent surgery on both eyes, or those who had multiple muscle correction had a significantly higher rate of development of ED. Out of all children who developed ED, 72.4% had multiple muscle correction and 70.2% had binocular surgery. Correlation between invasiveness of surgery and occurrence of ED was confirmed by Joo et al. [15] who conducted a prospective observational study on 90 children aged between 3 and 5 undergoing strabismus surgery to determine the relation between the invasiveness of surgery and the occurrence of ED. The authors found that children who underwent multiple muscle correction had higher PAED scores and a higher incidence of emergence delirium, than those who underwent single muscle correction. Additionally, patients who underwent binocular strabismus correction surgery had higher maximum PAED scores than those who underwent monocular strabismus repair surgery, which is consistent with earlier research findings [14]. The higher degree of pain associated with more complicated surgical procedures and having both eyes covered after surgery may explain this finding.

In this study, anesthesia was induced using propofol in only 11% of patients while 89% received inhalational induction using sevoflurane, and all patients received sevoflurane for maintenance of anesthesia. As its administration was not optional in this study, sevoflurane was considered a homogenous variable making the preoperative and intraoperative medications given in addition to sevoflurane the most significant anesthesia-related variables to affect the incidence of ED. Inhalation anesthetics, particularly desflurane and sevoflurane, were confirmed to be triggers of ED in children [25]. One study reported a 60% incidence of ED in children who underwent surgery under sevoflurane induction and maintenance without receiving any premedication [26].

Our findings indicate that analgesic and sedative medications including dexmedetomidine, fentanyl, and midazolam have a prophylactic effect in preventing ED. In our study, dexmedetomidine lowered the incidence of ED ($p = 0.0335$). The anxiolytic, sympatholytic, and opioid-sparing effects of dexmedetomidine may help decrease the dose of hypnotic agents and opioids used during surgery. Undesirable side effects such as prolonged sedation, bradycardia, hypotension, bradycardia, and longer extubation time have been reported; they are, however, dose-dependent and usually do not present a major concern in pediatric patients. Several studies showed comparable results; A recent randomized control trial by Yao *et al*. [27] on 156 patients scheduled for strabismus surgery showed that premedication with 2 mg/kg of dexmedetomidine intranasally reduced the incidence of ED more than midazolam or placebo. Similarly, Elghamry *et al*. [28] performed a clinical trial in which 70 patients aged 3–7 years old undergoing strabismus correction surgeries under sevoflurane anesthesia were assigned to randomly receive dexmedetomidine 0.3 µg/kg or saline placebo intravenously. The researchers reported an incidence of ED of 17.6% in the group receiving dexmedetomidine compared to 57.6% in the control group. Several earlier studies have also confirmed these results [29–31]. On the other hand, Cao *et al*. [32] failed to demonstrate such results in their study of 60 children undergoing adenotonsillectomy. The authors concluded that dexmedetomidine had no significant effect on the reduction of ED. These conflicting results may be due to the different doses used and the difference in the type of surgery. It is worth mentioning that despite the positive effects of dexmedetomidine on emergence delirium, the fact that it may cause bradycardia and hypotension may limit its use in a day-surgery setting.

Reports on the use of fentanyl to prevent emergence delirium varied in literature. The current study showed a lower incidence of ED among children receiving 2 µg/kg fentanyl. Similar observations were reported by Baek *et al*. [33] in a randomized clinical trial on 90 children 2–8 years old undergoing strabismus correction surgery. Children who received 2 µg/kg fentanyl at induction exhibited lower incidences of emergence delirium, agitation, lower postoperative pain scores, and more favorable emergence characteristics. Similarly, Larsen *et al*. [4] conducted a randomized study of children 1–6 years old undergoing minor one-day surgeries. Doses of administered IV fentanyl ranged between 2 and 4 µg/kg. The researchers found that children receiving the highest dose of fentanyl (4 µg/kg) were the least agitated and the length of

PACU stay was not increased. Again, Cohen *et al*. [34] reported reduced incidence of emergence delirium in patients aged 2–7 years who received desflurane anesthesia and fentanyl for adenoidectomy, patients receiving fentanyl were, however, found to experience increased emergence time, extubation time, and remain for a longer time in the PACU. Conflicting results were reported by Sultana *et al*. [3] who recruited 120 children aged 2–8 years scheduled for different surgical procedures. Children received either fentanyl (1 µg/kg) or dexmedetomidine (0.15 µg/kg). The authors found that during early recovery, the incidence of ED was higher among patients receiving fentanyl compared to those receiving dexmedetomidine. These observations, together with the higher incidence of prolonging the awakening time and other opioid-related side effects, may favor other options than fentanyl for ED, especially in ambulatory settings.

Midazolam is often administered as premedication during pediatric anesthesia to decrease emotional distress due to its sedative and anxiolytic properties, additionally it was shown to reduce analgesic requirement and to prevent postoperative nausea and vomiting [18]. We observed that anxiolytic premedication with midazolam decreased the incidence of ED [OR (95% CI): 2.02 (1.22, 3.29), $p = 0.006$]. These findings support the results of Cho *et al*. [17] who undertook a randomized controlled trial on 90 patients aged 1–13 years old undergoing strabismus repair. Children were assigned randomly to either receive 0.03 mg/kg or 0.05 mg/kg midazolam or normal saline immediately before the surgery ended. Both groups receiving midazolam showed lower incidence of ED than the control group; however, patients who received a lower dose of midazolam had a longer emergence time.

Contrastingly, Cole *et al*. [35] reported a ninefold higher rate of ED in children receiving midazolam premedication before outpatient surgery with halothane or isoflurane compared to those who received no premedication. These findings may, however, be unreliable due to selection bias. These findings support the observations of Breschan *et al*. [36] who randomized 115 children scheduled for minor surgery to either receive 0.5 mg/kg or 1 mg/kg midazolam rectally. The researchers concluded that receiving a dose of 1 mg/kg of midazolam rectally resulted in better sedation at anesthetic induction; however, it did not decrease the incidence of emergence delirium. This may be explained by the fact that benzodiazepines are themselves associated with agitation or paradoxical reactions that are reversible by flumazenil [36]. Moreover, midazolam has anti-analgesic effects that may increase the perception of pain and lead to a form of nonspecific agitation resembling emergence delirium [36]. In fact, early studies reported paranoid delusions and severe agitation in pediatric patients 3–8 years old undergoing different procedures under sevoflurane anesthesia and midazolam premedication [21]. Furthermore, studies comparing dexmedetomidine and midazolam reported a significantly lower incidence of ED among children who received dexmedetomidine compared to those receiving midazolam or 0.9% saline and no significant difference in ED between patients receiving midazolam and those receiving 0.9% saline [27]. However, other studies showed that combining midazolam with small doses of diazepam may prolong the beneficial effects of midazolam to the recovery phase, which may decrease the incidence of emergence delirium [6].

Postoperative pain has been shown to cause agitation in children, and it is considered a potential confounder in all studies that investigate ED, however, during strabismus surgery pain is usually mild and easy to control (median pain score by FLACC = 1 in the current study). In this study, most of the children received IV paracetamol for pain relief (74%) and there was no significant association between the occurrence of emergence delirium and the administration of paracetamol. Contrastingly, a study conducted in Saudi Arabia on 413 children who underwent elective surgery revealed that when fentanyl was combined with paracetamol, the incidence of ED decreased [18]. Similarly, Rezaee *et al*. [37] performed a placebo-controlled randomized trial of 80 children aged 5–12 years in which children received either 5–10 mg/kg paracetamol or 0.9% saline. Their results showed that, in addition to the decrease in pain intensity, children receiving paracetamol had significantly lower PAED scores. It was however challenging to compare these findings with literature as the number of similar trials is small.

Few studies have compared the incidence of ED in children following different airway management techniques. Our results showed no association between the incidence of ED and the airway management technique used (endotracheal tube or laryngeal mask airway). Interestingly, Keles and Kocaturk [38] conducted a clinical trial on 70 children who were scheduled for treatment of dental decay under general anesthesia. Children were assigned to either the endotracheal intubation (ETT) group or the laryngeal mask airway (LMA) group. In the PACU, ED scores were significantly less in the LMA group compared to the ETT group ($p = 0.00$). This may be related to the increased laryngeal pain in the ETT group, however more research needs to be conducted in this area.

Due to the retrospective nature of this study, certain limitations were encountered. Some potential confounding factors were not evaluated, such as previous surgery, sleep deprivation, and psychosocial condition; these factors may be associated with ED and may have affected the findings of this study. Although these limitations may affect the generalizability of our findings, the fact that our data was found to be consistent with previous randomized controlled trials lends validity to our results.

7. Conclusion

In this study, younger age, multiple muscle surgery, and binocular surgery were the main non-modifiable factors associated with ED in children following strabismus surgery. Administration of midazolam, dexmedetomidine, or fentanyl were associated with lower incidence of ED. Patients at higher risk for ED could be selected for prophylaxis against ED using these medications to prevent ED after strabismus correction surgery in children.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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