


Sugammadex affects emergence agitation in children undergoing strabismus surgery

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Abstract

Objective: Emergence agitation (EA) has a multifactorial origin, and the effect of sugammadex on EA has not been established. We investigated the effect of sugammadex on EA incidence and severity.

Methods: We performed a retrospective study of children aged 1 to 13 years who underwent strabismus surgery. Patients received sugammadex or conventional neuromuscular reversal agents. The primary outcome variables were EA incidence and severity. Secondary outcome variables were postoperative fentanyl use, postoperative nausea and vomiting, time from reversal agent administration to extubation, time from the end of surgery to arrival in the post-anesthesia care unit (PACU) and time spent in the PACU. We used propensity score matching to eliminate baseline imbalances.

Results: Age, sex, use of desflurane, and intraoperative fentanyl were significant predictors of agitation severity using a multivariable analysis. Sugammadex did not significantly affect EA in logistic regression and multiple regression analyses. In the propensity-matched analysis, patients in the sugammadex group showed rapid recovery, but there was no difference in the EA incidence or severity.

Conclusion: Sugammadex did not affect EA incidence or severity compared with conventional cholinesterase inhibitors, although it showed a favorable recovery profile in children undergoing strabismus surgery.

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Keywords

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Introduction

Emergence from anesthesia and surgery is often accompanied by several complications. In the pediatric population, emergence agitation (EA), also known as emergence delirium, is a common complication in the post-anesthesia care unit (PACU). EA features a variety of presentations including crying, excitement, agitation, and delirium occurring in the early stage of recovery from anesthesia. Although EA is different from persistent postoperative delirium, it increases self-injury risk and leads to the enhanced use of nursing resources in the PACU.¹ The type of surgery, including ophthalmology and otorhinolaryngology procedures, is a proposed contributor to EA. Voepel-Lewis et al.² reported a higher incidence (28%) of EA after ophthalmologic procedures. They did not clarify the mechanism, but they hypothesized that a “sense of suffocation” may contribute to EA.²

Postoperative pulmonary dysfunction and hypoxia have been associated with delirium.³ Sugammadex (Bridion®) reverses residual neuromuscular block (NMB) without cholinergic side effects and reduces the incidence of postoperative pulmonary complications and hypoxia compared to conventional reversal agents.⁴ Additionally, sugammadex resulted in a lower incidence of dizziness, dry mouth, and procedural hypotension compared with a combination of neostigmine and glycopyrrolate.⁵

We hypothesized that these advantages of sugammadex might relieve patient anxiety. Previous studies support the correlation between respiratory function and

anxiety.⁶⁻⁸ Patient anxiety is a likely contributor to EA,⁹ and improved pulmonary function with adequate oxygenation after reversing NMB using sugammadex may reduce the incidence of EA. However, the effect of sugammadex on EA has not been investigated.

A brief report from our center suggested that sugammadex-treated pediatric patients showed a lower tendency for EA compared with non-sugammadex-treated pediatric patients. In the current retrospective study, we assessed the effect of sugammadex on the incidence of EA in children after strabismus surgery, while considering other factors that may also contribute to this complication.

Methods

This study was approved by the institutional review board of the Korea University Ansan Hospital (IRB no. AS16051-001) and was registered at cris.nih.go.kr. In this retrospective study, we included children, aged 1 to 13 years and American Society of Anesthesiologists (ASA) class I–II, who underwent strabismus surgery between March 1, 2014 and March 31, 2016. We excluded patients with cognitive or developmental disabilities and a previous history of receiving sedative drugs or general anesthesia. We extracted all data from medical records. Age, sex, presence of preoperative anxiety, type of induction and volatile agents, intraoperative fentanyl use, and type of agent used to reverse NMB were considered to be variables that may correlate with EA. The primary outcome

variables were EA incidence and severity. The secondary outcome variables were postoperative fentanyl use, postoperative nausea and vomiting (PONV), time from reversal agent administration to extubation, the time interval between the end of surgery and arrival in the PACU, and the duration of time the patient remained in the PACU.

We divided patients into two groups by the type of agent used for to reverse the NMB. Sugammadex (2.0 mg/kg; MSD Korea Ltd., Korea) was administered to the sugammadex group while a combination of pyridostigmine (0.25 mg/kg; Myungmoon Pharm. Co. Ltd., Korea) and glycopyrrolate (0.01 mg/kg; Myungmoon Pharm. Co. Ltd., Korea) was administered to the control group. EA severity was assessed using the four-point EA scale (Watcha scale) during the preoperative period and in the post-anesthesia care unit.¹⁰ EA was assessed using the four-point scale as follows: 1, asleep or calm; 2, crying, can be consoled; 3, crying, cannot be consoled; and 4, agitated, thrashing around. For this analysis, we defined significant agitation as a Watcha score greater than 2.

Preoperative anxiety was assessed according to the pediatric anesthesia behavior score¹¹ (1, happy: calm and controlled, compliant with induction; 2, sad: tearful and/or withdrawn but compliant with induction; and 3, mad: loud vocal resistance (screaming or shouting) and/or physical resistance to induction requiring physical restraint by staff and/or parents). Anxiety was considered to be present before induction of anesthesia when the score was 3.

Anesthetic technique

Following premedication with intramuscular atropine (0.01 mg/kg; Diahon Pharm Co. Ltd., Korea), anesthesia was induced using intravenous thiopental sodium (5 mg/kg; JW Pharmaceutical, Korea), propofol (2 mg/kg; Fresenius Kabi, Korea),

midazolam (0.15 mg/kg; Bukwang Pharm Co. Ltd., Korea), or ketamine (1 mg/kg; Huons Co. Ltd., Korea). Following induction, 1 minimum alveolar concentration (MAC) of desflurane or sevoflurane was administered with oxygen (6 L/min) through a face mask, and rocuronium (0.6 mg/kg) was administered intravenously to facilitate tracheal intubation. Anesthesia was maintained with 1 to 1.3 MAC of desflurane or sevoflurane with a mixture of oxygen and nitrous oxide, each at a dose of 1.5 L/min. If there was a significant increase in blood pressure or heart rate during surgery (more than 20% of baseline) despite increasing the dose of the inhalational agent, fentanyl (0.5 µg/kg) was administered intravenously. Neuromuscular function was monitored using acceleromyography (TOF-Watch[®] SX; Mainline Medical Inc., Norcross, GA, USA). At the end of the surgery, the inhalational agent and nitrous oxide were stopped, and the oxygen flow was increased to 6 L/min. When the T4 response appeared on train-of-four (TOF) stimulation, muscle relaxation was reversed with either intravenous sugammadex (2 mg) or a combination of intravenous glycopyrrolate (0.01 mg/kg) and pyridostigmine (0.25 mg/kg). When the TOF ratio was 0.9, a normal respiratory pattern had returned, and the face was no longer flaccid, the endotracheal tube was removed. After extubation, the patient was transferred to the recovery room after the respiratory parameters returned to normal.

In the recovery room, the children were with their parents, and the level of the patients' postoperative discomfort was evaluated. In children who were unable to express themselves, the presence of nausea was identified by observing the child's behavior. The patients' attempt to vomit was considered nausea. Antiemetic agents were not routinely administered. When EA occurred in the PACU, fentanyl (0.5 µg/kg) was administered intravenously. Postoperative pain was assessed using the

Children's and Infants' Postoperative Pain Scale (CHIPPS).¹² The presence of other postoperative complications including nausea, vomiting, and shivering was noted. Children were transferred to the general ward when they recovered from anesthesia, on attaining a modified Aldrete score of >9.

Statistical methods

Data are expressed as the mean \pm standard deviation (SD), and were compared using independent *t*-tests or Mann–Whitney U tests. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Logistic regression analysis was performed to predict the incidence of EA. Multiple regression analysis was performed to predict EA severity using candidate variables, as described previously. Propensity score matching was performed to minimize the baseline imbalance of candidate variables between the two groups. Matching 1:1, discarding units beyond the common support in both groups, false replacement, and a caliper of 0.2 were the chosen options when conducting propensity score matching.

Statistical analyses and propensity score matching were performed using IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA) and R (version 2.15.2; <https://www.R-project.org>). Based on the postoperative agitation results obtained from the propensity score-matched data, we performed a power analysis to derive an appropriate sample size with a significance level of 5% to achieve a power of 80%. A *p*-value of <0.05 was considered significant.

Results

We reviewed the case records of 427 children who underwent strabismus surgery. Three hundred and ninety-seven children were included in the final analysis with 91 in the sugammadex group, and 306 in the

control group (Figure 1). No severe complications were encountered among the children studied.

Children in the sugammadex group were older than those in the control group. Intraoperative fentanyl use was more common in the sugammadex group, while thiopental and sevoflurane used was more often in the control group. The sex distribution and preoperative anxiety were not significantly different between the two groups (Table 1).

The raw data results showed a lower EA incidence, lower EA severity, and less postoperative fentanyl use in the sugammadex group compared with the control group. The incidence of PONV was not significantly different between the groups (Table 1).

Multiple regression analysis showed that age, sex, desflurane, and intraoperative fentanyl use were significant predictors of the severity of agitation (Table 2).

Binary logistic regression showed that older age and female sex showed a significant low odds ratio for predicting agitation (Table 3). Age was the only significant factor that predicted postoperative fentanyl use (Table 3).

Figure 2 shows the standardized differences before and after propensity score matching. After propensity matching, most standardized differences for each factor were less than 0.1. In 76 propensity-matched pairs in the sugammadex and control groups, demographic features including age and sex, use of induction, volatile agents, the incidence of preoperative anxiety, and intraoperative fentanyl use were not significantly different (Table 4). There was also no significant difference in the incidence and severity of agitation, postoperative fentanyl use, and PONV between the two groups (Table 4).

Based on propensity score-matched postoperative agitation, the effect size was 0.223. A power analysis suggested that a minimum sample size of 317 patients in

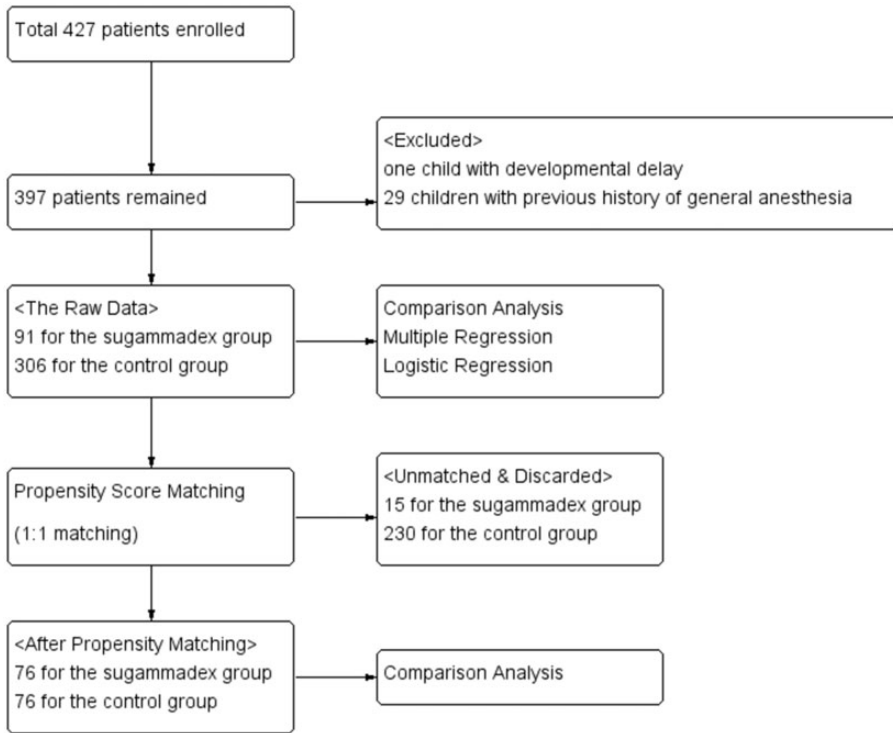


Figure 1. Flow diagram.

each group would be required at a significance level of 5% to achieve a power of 80%.

Discussion

Sugammadex is a selective binding agent for aminosteroidal non-depolarizing muscle relaxants. It is used to reverse the NMB that is induced during general anesthesia, and has been compared with acetylcholinesterase inhibitors; however, the mechanism of action is different.⁵ A previous study showed that sugammadex had favorable effects in recovery from residual postoperative paralysis compared to neostigmine.¹³ Postoperative residual NMB delays discharge from the recovery room,¹⁴ and thus, it is reasonable to assume that sugammadex may enable

early transfer to the wards.¹⁵ Additionally, sugammadex has many advantages including improvement of respiratory function⁴ and a lower incidence of dizziness, dry mouth, and procedural hypotension.⁵

Given its numerous favorable effects compared to acetylcholinesterase inhibitors, we hypothesized that sugammadex reduces the incidence of EA. The raw data seemed to show that there was a lower incidence of agitation and postoperative fentanyl use in the sugammadex group compared with the control group. However, there were several imbalances in the distribution of baseline covariates.

In the present study, a younger age was a significant factor that predicted both the incidence and severity of EA, which is consistent with previous reviews.^{9,16} Although previous studies did not show a sex difference for EA

Table 1. Demographic and clinical characteristics: raw data analysis

	Sugammadex (n=91)	Control (n=306)
Age (months) (≤ 6/> 6–12/12yr)	76.96 ± 33.68 (42/47/2)	67.67 ± 31.66* (0.016) (178/124/4)
Sex (M/F)	45/46	138/168
Induction drug		
Ketamine	33	25
Propofol	30	48
Thiopental	27	233*
Midazolam	1	0
Volatile agent		(<0.001)
Desflurane	66	51
Sevoflurane	25	255*
Preoperative anxiety		
Yes	44	134
No	47	172
Intraoperative fentanyl (Y/N)	77/14	205/101*
Postoperative agitation	1.70 ± 0.94	2.01 ± 1.06*
1	52	134
2	19	70
3	15	66
4	5	36
Presence of agitation (Y/N)	20/71	102/204*
Postoperative fentanyl (Y/N)	18/73	99/207*
PONV		
Y	4	3
N	87	303
Time from reversal agent administration to extubation (min)	3.68 ± 1.59	5.84 ± 3.15*
Time from end of surgery to arrival in PACU (min)	9.36 ± 2.17	12.99 ± 4.07*
Time from arrival to discharge from PACU (min)	35.71 ± 7.36	38.01 ± 8.76*

Values are presented as the mean ± SD or the number of patients. PACU, post anesthesia care unit; sugammadex group, 2.0 mg/kg of sugammadex was administered as an agent to reverse the neuromuscular blockade; control group, 0.25 mg/kg of pyridostigmine and 0.01 mg/kg of glycopyrrolate were administered as agents to reverse the neuromuscular blockade

incidence,¹⁶ female children in our study had a lower EA incidence and severity. We suggest that this discordance may be explained by a difference in the temperament regarding social and gender issues. Pre-existing behaviors are related to preoperative anxiety.^{9,17} The male gender showed a high reactivity temperament,¹⁸ which is a risk factor for pre-school behavior problems.¹⁹

Although a direct correlation between anxiety and EA was not found, preoperative anxiety is known to be correlated with EA.⁹ In a previous study that evaluated the level of anxiety in children using the modified Yale Preoperative Anxiety Scale (mYPAS), an increasing odds ratio for EA was observed with increasing anxiety scores, although no cause-effect relationship was

Table 2. Multiple regression analysis of factors related to postoperative agitation (4-point scale)

Independent variables	B	Beta	t	p	VIF
(Constant)	2.758		14.330*	< 0.001	
Sugammadex	-0.034	-0.014	-0.248	0.805	1.396
Age (month)	-0.007	-0.212	-3.530	< 0.001	1.602
Sex (female)	-0.244	-0.117	-2.457	0.014	1.008
Induction agent (ketamine)	-0.357	-0.121	-1.798	0.073	2.026
Volatile agent (Desflurane)	29.420	0.198	2.291*	0.023	1.946
Preoperative anxiety	0.171	0.082	1.299	0.195	1.757
Intraoperative fentanyl	-0.254	-0.111	-2.172*	0.030	1.160

Adjusted $R^2 = 0.112$; ANOVA for model, 8.151 ($p < 0.001$); Durbin-Watson, 2.163

Table 3. Logistic regression analysis

Independent variables	Prediction of postoperative agitation (Binary)			Prediction of postoperative fentanyl use		
	OR	95% CI of OR	P	OR	95% CI of OR	P
(Constant)	2.219		0.072	1.882		0.155
Sugammadex	1.110	0.568–2.171	0.760	0.974	0.494–1.922	0.939
Age (months)	0.985*	0.976–0.995	0.002	0.985*	0.976–0.995	0.002
Sex (female)	0.621*	0.395–0.977	0.039	0.674	0.428–1.062	0.089
Induction agent (ketamine)	0.427	0.155–1.177	0.100	0.478	0.172–1.329	0.157
Volatile agent (desflurane)	0.553	0.261–1.170	0.122	0.543	0.253–1.164	0.117
Preoperative anxiety	1.140	0.646–2.012	0.652	1.087	0.614–1.926	0.774
Intraoperative fentanyl use	0.742	0.450–1.224	0.243	0.854	0.515–1.415	0.540

For prediction of post-operative agitation (Binary): Adjusted R^2 , 0.138; Hosmer & Lemeshow test, $P = 0.224$; classification accuracy, 69.5%

For prediction of postoperative fentanyl use: Adjusted R^2 , 0.123; Hosmer & Lemeshow test, $P = 0.079$; classification accuracy, 70.8%

suggested.²⁰ In our study, we assessed anxiety using the pediatric anesthesia behavior score. Unlike previous studies, in the present study, preoperative anxiety was not a significant factor in the development of EA. This inconsistency may have occurred because the pediatric anesthesia behavior score may be too simplistic to assess childhood anxiety.

For induction drugs, ketamine was associated with less EA, but neither the incidence ($p = 0.100$) nor the severity ($p = 0.073$) was statistically significant

compared with other agents. The effect of induction agents on EA was controversial in several studies. Cohen et al.²¹ reported that midazolam or propofol do not reduce the incidence of EA. Jung et al.²² reported that thiopental sodium and ketamine used as anesthetic induction agents in children undergoing ophthalmic surgery showed a similar incidence of EA.²² However, other studies reported that ketamine premedication²³ or intraoperative use of ketamine²⁴ were effective in preventing EA.

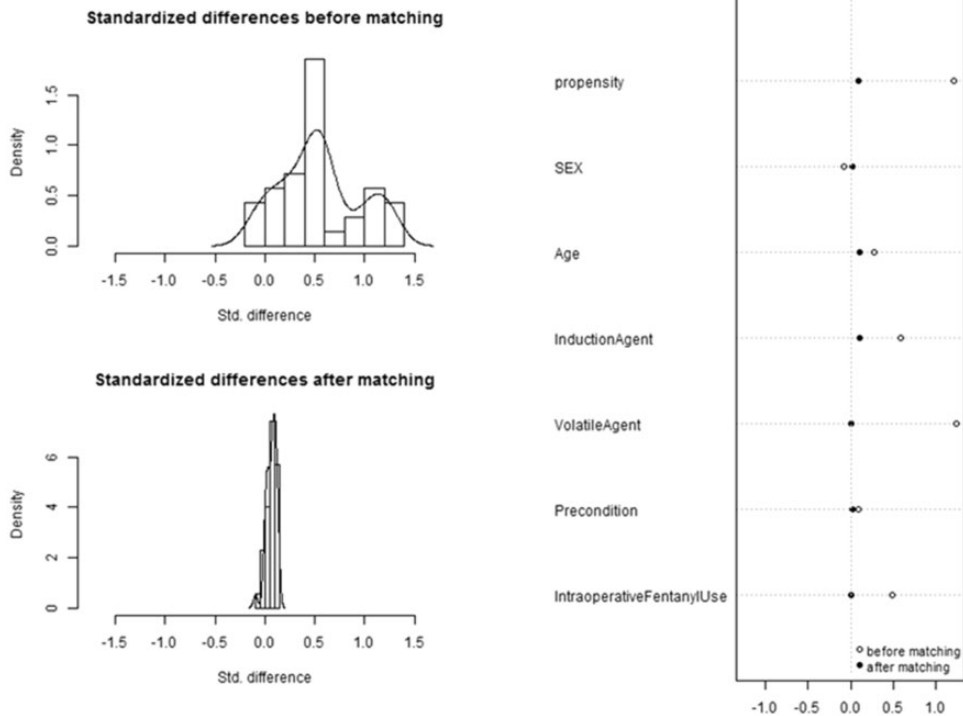


Figure 2. (A) Histogram of standardized differences, and (B) Dot plot of standardized mean differences before and after propensity score matching.

We used desflurane or sevoflurane for maintenance of anesthesia, and both these inhalational anesthetics are known to cause EA during recovery from general anesthesia.⁹ Welborn et al.²⁵ reported a higher incidence of EA in children following adenoidectomy with bilateral myringotomy with desflurane compared to sevoflurane. According to a recent systemic review, the emergence time was shorter for desflurane, but the incidence of EA was comparable with sevoflurane and desflurane.²⁶ In our study, desflurane increased the severity, but not the incidence of EA.

We also found that intraoperative fentanyl use reduced EA severity, but it did not reduce the EA incidence or postoperative fentanyl use. A recent systemic review supported the use of intraoperative fentanyl in

the prevention of EA.²⁷ They showed that fentanyl use at, or 10 to 20 minutes before, the completion of surgery was effective in reducing EA. They also showed that fentanyl administered at the end of surgery increased the incidence of PONV (to 5.12-times that of the relative risk). However, administration of fentanyl 10 to 20 minutes before the end of surgery did not increase the PONV risk in their meta-analysis. In our study, most patients received fentanyl during surgery, and not at the completion of surgery. We did not find any significant effect on the incidence of PONV using fentanyl or sugammadex.

Generally, observational study designs are used when randomized controlled trials (RCTs) are not feasible because of the cost involved, the long duration that

Table 4. Propensity matched analysis

	Sugammadex (n=76)	Control (n=76)
Age (months)	73.37 ± 32.56	69.88 ± 30.25 (0.495)
(≤ 6/> 6–12/12yr)	(38/37/1)	(42/32/2)
Sex (M/F)	37/39	38/38 (1.000)
Induction drug		(0.479)
Ketamine	27	23
Propofol	21	18
Thiopental	27	35
Midazolam	1	0
Volatile agent		(1.000)
Desflurane	25	25
Sevoflurane	51	51
Preoperative anxiety		(1.000)
Yes	38	37
No	38	39
Intraoperative fentanyl (Y/N)	62/14	62/14 (1.000)
Propensity Score	0.42 ± 0.23	0.40 ± 0.22 (0.570)
Postoperative agitation	1.66 ± 0.95	1.88 ± 1.02 (0.163)
1	47	36 (0.144)
2	12	21
3	13	11
4	4	8
Presence of agitation (Y/N)	17/59	19/57 (0.703)
Postoperative fentanyl (Y/N)	16/60	19/57 (0.563)
PONV		(0.681)
Y	4	2
N	72	74
Time from reversal agent administration to extubation (min)	3.68 ± 1.63	5.55 ± 2.43* (<0.001)
Time from end of surgery to arrival in the PACU (min)	9.30 ± 2.15	12.66 ± 4.12* (<0.001)
Time from arrival to discharge from PACU (min)	35.92 ± 7.43	38.95 ± 10.47* (0.042)

Values are presented as the mean ± SD or the number of patients. PACU, post anesthesia care unit; sugammadex group, 2.0 mg/kg of sugammadex was administered as an agent to reverse the neuromuscular blockade; control group, 0.25 mg/kg of pyridostigmine and 0.01 mg/kg of glycopyrrolate were administered as agents to reverse the neuromuscular blockade

such studies require, or ethical issues. With sugammadex, RCTs could not be performed for ethical reasons because of the lack of evidence for its use in the pediatric population. However, treatment selection is influenced by baseline characteristics of patients in observational studies. Considering the possible imbalance in patient characteristics at baseline, we

used a propensity score-matched analysis to assess the efficacy of sugammadex in the reduction of EA incidence and severity. Propensity score matching is used to reduce selection bias in observational studies.²⁸ Compared to unmatched analysis, in the propensity-matched model, sugammadex did not affect EA or the use of postoperative fentanyl.

There are several limitations to this study. First, the assessment tools for EA or preoperative anxiety may have overlooked some details. We used a 4-point scale to evaluate EA severity without using more specific methods such as the pediatric anesthesia emergence delirium scale (PAED scale). More elaborate tools including mYPAS and temperament assessment (emotionality, activity, sociability, and impulsivity; EASI) are required for accurate analysis. Unfortunately, in ophthalmic surgery, PAED evaluation is not feasible because the eyes are covered in the recovery room. In our previous study, we showed the efficacy of the Watcha scale for strabismus patients.²⁹ Bajwa et al.¹⁰ reported that the Watcha score was superior in the assessment of childhood delirium compared with other delirium scores.

Second, at the end of surgery, most children were extubated when a TOF ratio of 0.9 or higher was attained. Although residual block in the PACU cannot be ruled out, it is unlikely because we used a relatively low dose of rocuronium during anesthetic induction. In procedures that require high-dose muscle relaxants, sugammadex may have favorable effects on EA.

Our study has several strengths. There are few studies that have addressed the efficacy of sugammadex in reducing EA in children. The lack of evidence with the use of sugammadex in children is because of the ethical problems involved in the conduct of such a study. In the present study, we showed a significant reduction in recovery times and demonstrated the safety of sugammadex use without severe complications in pediatric patients. Additionally, we used the propensity model to compensate for the disadvantages of a retrospective observational study. We also provided an *a priori* sample size calculation. Based on our results, a RCT would require a sample size of over 700 patients, assuming a dropout rate of 10%. Therefore, we believe that

sugammadex is unlikely to have a clinically significant effect on EA.

Conclusion

In conclusion, sugammadex did not affect the EA incidence or severity compared with conventional cholinesterase inhibitors. However, sugammadex had favorable effects on the recovery profile in children undergoing strabismus surgery.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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