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Original Article

Comparison analysis of safety profiles and identification of risk factors for postoperative adverse reactions: propofol versus sevoflurane in pediatric anesthesia

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Abstract: Objective: To compare the safety profiles between propofol and sevoflurane in pediatric anesthesia and to investigate risk factors for postoperative adverse reactions. Methods: The data of 194 children who received surgical treatment in Peking Union Medical College Hospital between January 2019 and May 2022 were analyzed retrospectively. According to the different anesthetic drugs the children received, they were divided into a control group (conventional anesthesia with sevoflurane, n=94) and an observation group (anesthesia with both propofol and sevoflurane, n=100). The two groups were compared in terms of anesthetic effect, heart rate, blood oxygen saturation, Ramsay sedation scale (RSS) score during the recovery of anesthesia, and anesthesia safety. Further, the children were grouped based on RSS score to identify the risk factors for agitation during the recovery of anesthesia via logistics regression. Results: The onset time of anesthesia, spontaneous breathing recovery time, extubation time, eye opening time and awake time in the observation group were all significantly shorter than those in the control group (P<0.05). At T1 (during anesthesia induction), T2 (after tracheal intubation) and T3 (after extubation), the observation group showed relatively stable heart rate and blood oxygen saturation than the control group (P<0.05). At the time of awakening, extubation and 30 minutes after extubation, the observation group exhibited significantly lower RSS score than the control group (P<0.05). The observation group also showed a significantly lower incidence of nausea, vomiting and agitation than the control group (P<0.05). Additionally, age ≤6 years old and anesthesia scheme were independent risks for agitation in children during the recovery of anesthesia. The occurrence group had significantly higher risk scores than the non-occurrence group (P<0.05). According to receiver operating characteristic curve-based analysis, the area under the curve of risk score in predicting agitation during the recovery of anesthesia was 0.733. Conclusion: Anesthesia with both propofol and sevoflurane is effective in children undergoing surgical treatment, because the combination can substantially reduce the agitation of children during the recovery of anesthesia and has high anesthesia safety. Propofol combined with sevoflurane is a protective factor against agitation in children during the recovery of anesthesia.

Keywords: Propofol, sevoflurane, pediatric anesthesia, adverse reactions, agitation during the recovery of anesthesia

Introduction

Surgical treatment is significantly effective for many diseases, and anesthetics have become vital in pain alleviation during surgery [1]. However, in surgical anesthesia among children, there are many uncertainties due to the rapid changes of their conditions, compared with adults [2]. Statistics shows that a large number of children worldwide are in need of surgeries and anesthesia each year. For example, in the United States, about 450,000 children undergo surgeries and examinations every year, of which 95% are conducted under general anesthesia [3].

In pediatric anesthesia, parents are increasingly concerned about postoperative complications in children. Frequently adopted general anesthetics in pediatrics include propofol, fen-

tanyl, muscle relaxants, opioids, and inhalation anesthetics, among which propofol and fentanyl are frequently adopted in pediatric general anesthesia [4]. Research has suggested that these drugs, including propofol and fentanyl, might have potential negative impacts on children's brain development, such as decline in learning and memory abilities and potential permanent neurological damage [5]. Agitation during the recovery of anesthesia is one of the most important adverse effects [6]. Agitation in children during the recovery period occurs in the early period of general anesthesia, and it also manifests as excitement and disorientation in clinical scenarios [7]. In the case of agitation, children may have violent behaviors that hurt themselves and others. In severe cases, agitation can trigger behavioral changes of children, surgical incision dehiscence, catheter removal, etc., prolonging the hospitalization time and incurring additional medical expenses [8]. Sevoflurane is an inhalation anesthetic with advantages of quick onset, strong controllability and stable hemodynamics [9]. Its main mechanism of action is to act on neurotransmitter receptors on neuron cell membranes to produce sedative and anesthetic effects [10]. However, sevoflurane also has its disadvantages. For example, it can easily give rise to agitation and adverse reactions in patients during the recovery of anesthesia [11]. On the contrary, propofol, a new type of fast and short-acting anesthetic for anesthesia induction, anesthesia maintenance and sedation, has the advantages of quick onset, low postoperative adverse reactions, rapid recovery and complete functional recovery [12]. However, the safety profile of propofol combined with sevoflurane in pediatric anesthesia is still unclear.

This study was designed to analyze the safety profile between propofol and sevoflurane in pediatric anesthesia and the risk factors for agitation during postoperative recovery of anesthesia.

Methods and data

Ethical statement

This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital.

Patient information

The data of 194 children who received surgical treatment in Peking Union Medical College Hospital from January 2019 to May 2022 were analyzed retrospectively. Based on different anesthetic drugs the children received, they were divided into a control group (conventional anesthesia with sevoflurane, n=94) and an observation group (anesthesia with propofol combined with sevoflurane, n=100).

Inclusion and exclusion criteria

Inclusion criteria: The age range of the children is from 3 to 12 years old. Patients who met the clinical diagnostic criteria for relevant diseases, underwent preoperative examinations, and met the criteria for general anesthesia; patients who conformed to the indications of relevant surgical treatments, and had good tolerance and stable vital signs; patients who received surgical treatment for the first time; patients without signs of infection and symptoms of poisoning; patients with complete clinical data.

Exclusion criteria: Patients with a history of premature beats or atrial fibrillation; patients with malignant tumor; patients with severe dysfunction of important organs; patients with gastrointestinal bleeding; patients with airway difficulty; patients with abnormal coagulation function; patients with unclear consciousness.

Anesthesia schemes

In order to ensure the safety and success of the surgery, it was essential to provide instructions to the children's families before anesthesia. This included informing them about the necessary precautions, such as prohibiting water intake for 4 hours and fasting for 6 hours prior to the procedure. At 30 minutes before the anesthesia, each child was injected intramuscularly with 0.01 mg/kg atropine (Dalian Huali Jingang Pharmaceutical Co., Ltd., State Food and Drug Administration (SFDA) approval number: H21021193), and a trocar was placed in the vein at the back of the hand for subsequent intravenous injection. After the children entered surgical room, they were injected intravenously with 0.3 mg/kg dexamethasone (Zhejiang Xianju Pharmaceutical Co., Ltd., SFDA approval number: H33020822) and 4 ml 0.9% sodium chloride solution.

The control group was given inhalation anesthesia with 8% sevoflurane (Jiangsu Heng Rui Pharmaceutical Co., Ltd., SFDA approval number: H20040771), which was given through the mask to induce anesthesia, and then 3%-4% sevoflurane was given to maintain anesthesia. The oxygen flow was maintained at 2 L/min. In the process of surgical treatment, the inhalation dose was adjusted according to the anesthesia depth, and the anesthesia state was strictly controlled.

The observation group was anesthetized with propofol combined with sevoflurane. The 8% sevoflurane, provided by Jiangsu Heng Rui Pharmaceutical Co., Ltd. (SFDA approval number: H20040771), was administered through a mask to initiate anesthesia. Subsequently, a maintenance dose of 3%-4% sevoflurane was used to sustain the anesthetic state. Thereafter, an intravenous infusion of 1-2 mg/kg propofol (H20163404, Sichuan Guorui Pharmaceutical Co., Ltd.) alongside long-chain fat emulsion was administered to further ensure anesthesia. During the surgical procedure, children's vital signs, including blood pressure and heart rate, were meticulously monitored. This surveillance facilitated the timely identification and resolution of any unexpected situations, thereby ensuring the smooth progression of the operation.

Collection of data

In this study, the clinical data and related indicators of patients were collected from the electronic medical record system and intraoperative records in Peking Union Medical College Hospital. The clinical data included age, sex, body mass index (BMI), family history of hypertension, education time, type of operation, Ramsay sedation scale (RSS) score and postoperative visual analogue scale (VAS) score. Intraoperative records included the onset time of anesthesia, spontaneous breathing recovery time, extubation time, eye opening time, awake time, heart rate and blood oxygen saturation. Adverse reactions were also recorded.

The Ramsay Sedation Scale (RSS) is used to objectively quantify an individual's sedation levels, which range from 1 (the patient is anxious, restless or both) to 6 (the patient shows no response to light tapping on the forehead or loud auditory stimulation) [13].

The Visual Analog Scale (VAS) is a psychological measurement tool to measure subjective attributes or attitudes that cannot be directly measured. In pain measurement, it consists of a scale line with two endpoints, which define the extremes of the pain experience, with scores ranging from 0-10. Patients were required to mark their pain level on the scale line between the two endpoints representing the severity of pain. The closer the mark is to the endpoint representing the worst pain, the higher the perceived intensity of pain [14].

Outcome measures

Primary outcome measures: The anesthetic effect (onset time of anesthesia, spontaneous breathing recovery time, extubation time, eye opening time and awake time) of the two groups were compared. The heart rate and blood oxygen saturation of them were also compared at T0 (before anesthesia induction), T1 (during anesthesia induction), T2 (after tracheal intubation) and T3 (after extubation).

Secondary outcome measures: The clinical data, incidence of adverse reactions, changes in RSS score were all compared between the two groups. Based on RSS score, the children were regrouped (a score <3 points indicated agitation), and the risk factors for agitation during the recovery of anesthesia were analyzed through logistics regression, and a prediction model was constructed.

Statistical analyses

This study adopted R language software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) for data cleaning and data analysis, used logistic regression methods to screen influencing factors, and constructed a prediction model. The concordance index (C-index) was calculated using the rms package, and its clinical value was verified through the Receiver Operating Characteristic (ROC) curve. Measurement data were expressed as (X±S) and analyzed by the t-test. Count data were presented as rates and analyzed by the Chi-square test. Data visualization was performed using Graph Pad Prism 8.0. A *P*-value less than 0.05 was considered statistically significant.

Table 1. Comparison of baseline data

Factors	Control group (n=94)	Observation group (n=100)	X^2 value	*P* value
Age			0.058	0.808
≥6 years old	36	40		
<6 years old	58	60		
Sex			2.972	0.084
Male	41	56		
Female	53	44		
BMI			1.039	0.308
≥16 kg/m^2	42	52		
<16 kg/m^2	52	48		
Family history of hypertension			0.087	0.767
Yes	49	50		
No	45	50		
Education time			0.031	0.858
≥3 years	35	36		
<3 years	59	64		
Type of operation			1.474	0.478
Abdominal hernia	35	30		
Tonsillectomy	29	38		
Other	30	32		

Note: BMI: Body mass index.

Results

Baseline data

In terms of baseline data, the two groups were not significantly different in age, sex, BMI, family history of hypertension, education time and type of operation (P>0.05, **Table 1**).

Comparison of anesthetic effects

The anesthetic effect of the two groups was compared. According to the results, the onset time of anesthesia, spontaneous breathing recovery time, extubation time, eye opening time and awake time in the control group were all significantly longer than those in the observation group (P<0.001, **Figure 1**).

Comparison of heart rate and oxygen saturation at different time points

The heart rate and blood oxygen saturation were compared between the two groups at different time points. According to the results, at T0 and T3, the heart rate and blood oxygen saturation of the two groups were not significantly different (P>0.05, **Figure 2**), while at T1 and T2, the observation group showed significantly lower heart rate and significantly higher blood oxygen saturation than the control group (P<0.05, **Figure 2**).

Comparison of agitation score and postoperative pain score during the recovery of anesthesia

The RSS score during the recovery of anesthesia was compared between the two groups. Significantly lower RSS score during the recovery of anesthesia was found in the observation group than that in the control group (P<0.05, **Figure 3A**). In addition, the observation group demonstrated significantly lower VAS score than the control group (P<0.05, **Figure 3B**).

Adverse reactions

In terms of adverse reactions, a lower incidence of nausea, vomiting and agitation was found in the observation group than that in the control group (P<0.05, **Table 2**).

Analysis of risk factors for agitation during the recovery of anesthesia and construction of a prediction model

Based on RSS score, the children were grouped into an occurrence group and a non-occurrence group. According to univariate analysis, age, postoperative VAS score, and anesthesia scheme were the risk factors for agitation in the children during the recovery of anesthesia (P<0.05, **Table 3**). Then, through backward LR multivariate logistics regression analysis, age, postoperative VAS score and anesthesia scheme were found to be the independent risk factors (P<0.05, **Table 4**). A risk prediction model was constructed based on β coefficient of logistics regression. The risk formula is: Anesthesia mode * 1.005 + Age * 1.261 + VAS score * 1.093. By calculating the risk score of each child, it was found that the occurrence group

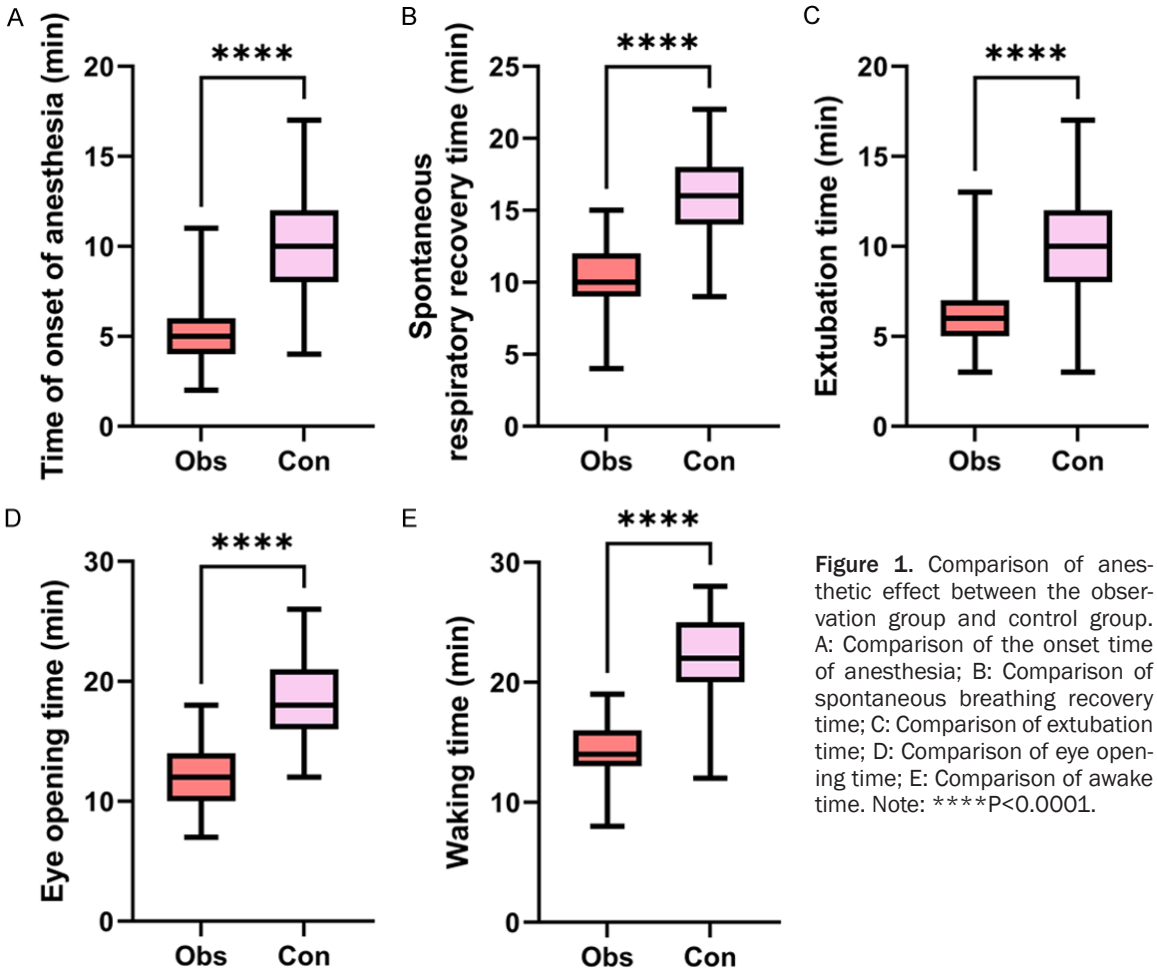

Figure 1. Comparison of anesthetic effect between the observation group and control group. A: Comparison of the onset time of anesthesia; B: Comparison of spontaneous breathing recovery time; C: Comparison of extubation time; D: Comparison of eye opening time; E: Comparison of awake time. Note: ****P<0.0001.

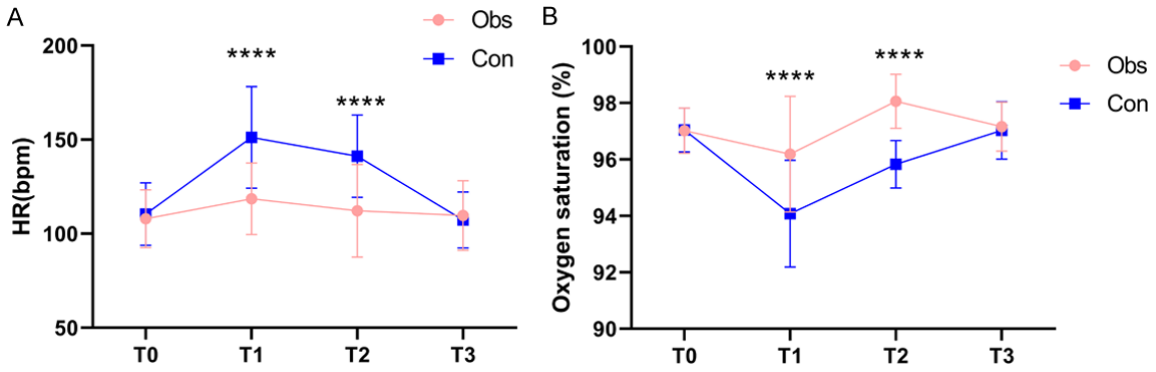

Figure 2. Comparison of heart rate and blood oxygen saturation at different time points. A: Comparison of heart rate; B: Comparison of oxygen saturation. Note: HR: heart rate. ****P<0.0001.

exhibited significantly higher risk scores than the non-occurrence group (P<0.05, **Figure 4A**). In addition, according to ROC curve-based analysis, the area under the curve of the risk score for predicting the agitation in the recovery period was 0.733 (**Figure 4B**). Subsequently, the Bootstrap method (after the original data was repeatedly sampled for 1 000 times) was adopted for internal validation of the model. The results showed that the C-index in internal

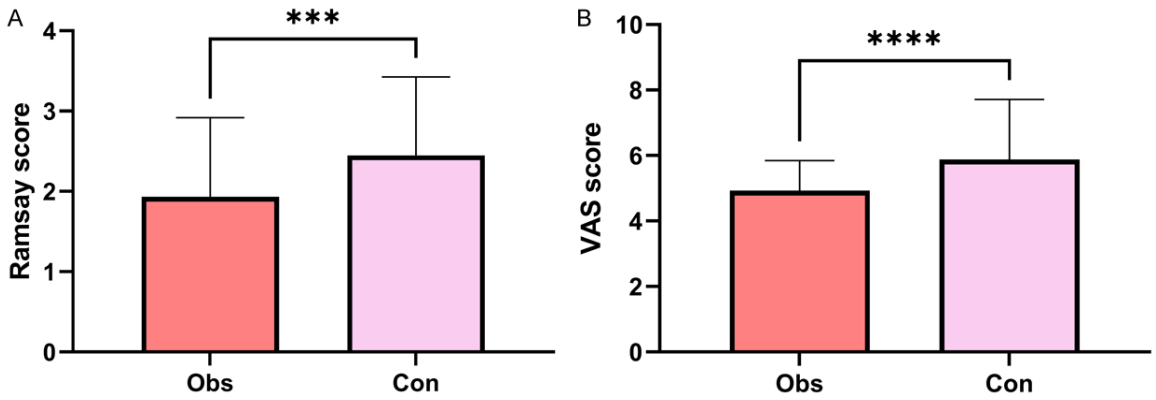

Figure 3. Comparison of RRS and VAS scores between the observation group and control group. A: Comparison of RRS score; B: Comparison of VAS score. Note: ***P<0.001, ****P<0.0001. RSS: Ramsay sedation scale; VAS: Visual analogue scale.

Table 2. Adverse reactions

Group	Nausea and vomiting	Respiratory depression	Hypotension	Agitation during the recovery of anesthesia
Control group (n=94)	10	4	6	44
Observation group (n=100)	3	1	2	27
X^2 value	4.522	2.045	2.354	8.194
P value	0.033	0.152	0.124	0.004

validation was 0.734 (95 CI%: 0.661-0.806), and the calibration curves were well fitted with the ideal curves (**Figure 4C**).

Discussion

With advantages of rapid onset, low irritation, strong controllability and hemodynamic stability, sevoflurane is extensively adopted as an inhalation anesthetic [10]. However, under lax control of the dosage of sevoflurane, children are prone to violent agitation during the recovery of anesthesia, which greatly endangers their safety and prognosis [15, 16]. Therefore, application of sevoflurane should be carried out with other safer and more effective drugs together. In contrast, propofol is an alkyl acid short-acting intravenous anesthetic extensively adopted in clinical scenarios. It has the advantages of rapid recovery, rapid anesthesia induction, low adverse reactions and complete functional recovery [17]. In addition, propofol can strongly protect the cardiovascular system and nervous system, and guarantee the stability of children during surgery, greatly reducing the incidence of agitation after anesthesia [18]. However, the effect of propofol alone is not remarkable. In this study, the onset time of anesthesia, spontaneous breathing recovery time, extubation time, eye opening time and awake time in the observation group were all notably shorter than those in the control group, and the observation group showed notably lower postoperative pain than the control group. Additionally, at T1, T2, and T3, the heart rate of the observation group was lower than that of the control group, and the blood oxygen saturation was significantly more stable than that of the control group. The control group showed a significantly higher incidence of adverse reactions than the observation group. These results indicate that the adoption of propofol combined with sevoflurane for pediatric anesthesia has the advantages of rapid recovery, rapid anesthesia induction, stable heart rate and blood oxygen, and less adverse reactions. Song et al. [19] revealed that compared with the control, the sevoflurane combined with propofol resulted notably shorter time of unconsciousness and recovery. Another study reported that children received propofol and sevoflurane showed a notably lower incidence of adverse reactions (intraoperative cough, breath holding, body movement, bronchospasm and laryngospasm) than those received propo-

Table 3. Univariate analysis of agitation during the recovery of anesthesia

Factors	Occurrence group (n=71)	No-occurrence group (n=123)	X^2 value	*P* value
Age			13.013	<0.001
≥6 years old	16	60		
<6 years old	55	63		
Sex			1.799	0.179
Male	31	66		
Female	40	57		
BMI			0.513	0.473
≥16 kg/m^2	32	62		
<16 kg/m^2	39	61		
Family history of hypertension			0.681	0.409
Yes	39	60		
No	32	63		
Education time			0.388	0.532
≥3 years	28	43		
<3 years	43	80		
Type of operation			1.595	0.450
Ophthalmic surgery	24	50		
Head/neck surgery	25	43		
Other	23	30		
Onset time of anesthesia (min)	8.20±3.78	7.14±3.20	0.488	0.625
Spontaneous breathing recovery time (min)	14.11±3.79	12.49±3.54	0.567	0.571
Extubation time (min)	8.86±3.08	7.87±2.95	0.761	0.447
Eye opening time (min)	15.7±4.10	14.7±4.17	1.626	0.105
Awake time (min)	19.06±4.95	17.35±4.86	0.186	0.852
Postoperative VAS score	6.38±1.47	4.82±1.21	7.994	<0.001
Heart rate at T0 (bpm)	108.2±16.17	109.65±16.06	0.605	0.545
Oxygen saturation at T0 (%)	97.14±0.82	96.97±0.77	1.448	0.149

Notes: BMI: Body mass index; VAS: Visual analogue scale.

Table 4. Multivariate analysis of agitation during the recovery of anesthesia

Factors	β value	Standard error	X^2 value	*P* value	OR value	95% CI	
						Lower limit	Upper limit
Anesthesia mode	1.005	0.330	9.280	0.002	2.733	1.431	5.218
Age	1.261	0.356	12.539	<0.001	3.529	1.756	7.093
VAS score	1.093	0.343	10.167	0.001	2.983	1.524	5.839

Note: VAS: Visual analogue scale.

fol and remifentanil [20]. We believe that this is because propofol mainly acts on GABA receptors and the central nervous system, reducing the release of excitatory transmitters to play a sedative role. Moreover, propofol can substantially reduce the occurrence of nausea and vomiting, as well as the stress reaction during extubation, and thus ensure the stability of hemodynamics after operation [21].

Agitation refers to the separation of behaviors, mental state and consciousness of patients during the recovery of general anesthesia. Patients may have symptoms such as irritability, excitement and delusion, with unconscious movements as the main sign [22]. Compared with adults, children have a relatively higher incidence of agitation after surgical anesthesia due to their relatively poorer brain regulation

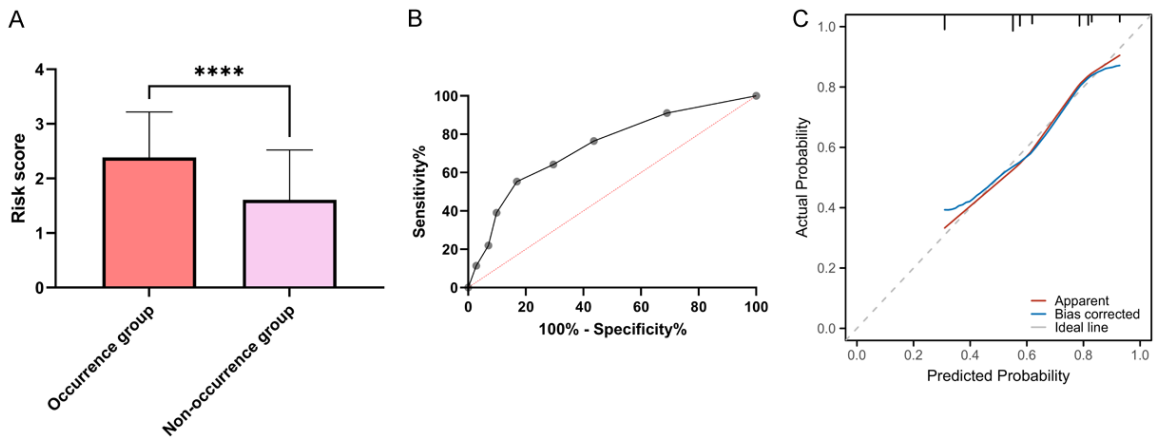

Figure 4. The value of risk model in predicting agitation during the recovery of anesthesia. A: The risk score in children with agitation during the recovery of anesthesia; B: ROC curve of the risk score; C: Risk model correction curve. Notes: ROC: receiver operating characteristic; ****P<0.0001.

capabilities [23]. This study compared the RSS scores of the two groups during recovery. According to the results, the control group exhibited notably higher RSS scores than the observation group. This shows that propofol combined with sevoflurane can substantially lower the incidence of agitation in children after anesthesia. Prior research revealed no significant difference in agitation during recovery and other adverse events between children receiving sevoflurane or propofol alone and those receiving additional propofol [24]. However, another study revealed a lower incidence of agitation during recovery in children receiving propofol anesthesia alone than those receiving sevoflurane [25]. In order to understand the risk factors for agitation during the recovery period, logistics regression analysis was conducted. As a result, age ≥6 years old, postoperative VAS score ≥6 points and anesthesia with sevoflurane were found to be the risk factors for agitation. Age is closely related to the incidence of agitation. Patients at a younger age face a higher rate of agitation. With incomplete physical and psychological development, younger children are prone to agitation because of fear in unfamiliar environment [26]. Postoperative pain is a common symptom that needs to be treated with analgesia. Insufficient analgesia can easily give rise to agitation. For children anesthetized with sevoflurane inhalation, the risk of agitation during recovery is high [7, 27]. This is because anesthesia induction with sevoflurane will cause changes in EEG, similar to seizures. Sevoflurane inhibits different parts of the central nervous system, so the subcortical center can recover normally during awakening, but a few cerebral cortices may still be inhibited, disrupting the sensory response and processing ability of children, and triggering over-excitation and agitation symptoms.

Finally, this study constructed a risk model to predict the agitation in children during awakening. According to comparison, the occurrence group had significantly higher risk scores than the non-occurrence group. In addition, ROC curve analysis revealed that the area under the curve of risk score in predicting the agitation during awakening was 0.734. The internal validation suggested a certain universality of the risk model. However, this study still has some limitations. This is a retrospective study, with all the samples collected from a single center, so whether this model is universal in other settings needs further confirmation. We hope to carry out multi-center experiments in future studies to verify the efficacy of the constructed model.

In conclusion, anesthesia with both propofol and sevoflurane is effective in children undergoing surgical treatment, because this combination can effectively reduce the agitation of children during the recovery of anesthesia, and it shows a high safety profile. Propofol combined with sevoflurane is a protective factor against agitation during the recovery of anesthesia in children.

Disclosure of conflict of interest

None.

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