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CLINICAL TRIAL REPORT

Effectiveness of Intravenous Ibuprofen on Emergence Agitation in Children Undergoing Tonsillectomy with Propofol and Remifentanil Anesthesia: A Randomized Controlled Trial

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Background: Emergence agitation (EA) has a negative effect on the recovery from general anesthesia in children. This study aimed to evaluate the effectiveness of intravenous ibuprofen in reducing the incidence of EA in children.

Methods: This randomized, double-blind, placebo-controlled, single-center study analyzed data from patients aged 3–9 years undergoing tonsillectomy under general anesthesia with propofol and remifentanil. These patients were randomly assigned to receive either the ibuprofen or the placebo intraoperatively. The primary endpoint was a between-group difference in the incidence of EA at 15 min following extubation. EA was defined as Pediatric Anesthesia Emergence Delirium score ≥10. The secondary endpoint included the associated factors of EA.

Results: Eighty-nine patients were included in the study. Ibuprofen decreased the incidence of EA at 15 min following extubation (8.9% in the treatment group vs 34.1% in the control group; odds ratio [OR], 0.261; 95% confidence interval [CI], 0.094–0.724; P=0.004). Compared with the control group, there was a significant reduction in the number of rescue fentanyl doses (P=0.045), and fewer patients experienced moderate to severe pain at 15 min following extubation in the treatment group (P=0.048). Upon logistic regression analysis, high modified Pediatric Anesthesia Behavior and pain scores following surgery were considered the risk factors related to EA (OR, 8.07; 95% CI, 1.12–58.07, P=0.038 and OR, 2.78; 95% CI, 1.60–4.82, P<0.001, respectively). Ibuprofen administration was the protective factor related to EA (OR, 0.05; 95% CI, 0.01–0.67, P=0.023).

Conclusion: Intraoperative ibuprofen infusion can significantly reduce the incidence of EA following general anesthesia with propofol and remifentanil in children.

Trial Registration: The study was registered with the Chinese Clinical Trial Registry on 7 April 2021 (number: ChiCTR2100045128; https://www.chictr.org.cn/edit.aspx?pid=124595&htm=4).

Keywords: emergence agitation, children, ibuprofen, general anesthesia, protective factor

Introduction

The term emergence agitation (EA) describes an unsettled behavior associated with pain, hunger, thirst, fear owing to the absence of primary caregivers, or unfamiliar surroundings. Pediatric EA is an early negative postoperative behavior and comprises two clinical components, the emergence delirium (ED) and postoperative pain, with different trends in the early postoperative period.[1] ED is considered a behavioral disturbance and neurological complication that occurs in children following general anesthesia and is described as involuntary agitation with shouting, crying, kicking, absence of eye contact with caregivers, inconsolability, and absence of awareness of the surrounding environment.[2] ED is not exactly equivalent to EA; ED can involve hypoactive signs or mixed forms and hyperactive signs similar to agitation.[3]

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The incidence rate of EA in children induced with general anesthesia ranges from 10% to 80%. During EA, children can remove intravenous (IV) catheters and drains, injure the surgical site, and injure themselves or the medical staff.[4] The most commonly known risk factors for EA are the presence of an endotracheal tube, preschool age, volatile anesthetics, ophthalmologic and otolaryngology surgical procedures, a history of behavioral problems, negative behavior on induction, preoperative anxiety level, and postoperative pain.[5–11] Despite the fact that EA can occur in any age group, it is more commonly observed in children aged 3–9 years than in other age groups.[12]

Tonsillectomy is one of the most common surgeries performed in children, when children are diagnosed with moderate or severe obstructive sleep apnea (OSA) and clinical findings are consistent with adenoid and/or tonsil hypertrophy, tonsillectomy and/or adenoidectomy is recommended, the prevalence of pediatric OSA in China was 4.8%.[13] Treatment of pain following tonsillectomy usually requires a combination of opioids and/or non-steroidal anti-inflammatory drugs (NSAIDs). Opioids have traditionally been considered as first-line medications for pain management; however, the side effects associated with opioids limit their overall utility.[14] A study demonstrated that 0.1 $mg \cdot kg^{-1}$ of ramelteon did not have a preventive effect on EA following general anesthesia in children undergoing tonsillectomy.[15] Some previous studies stated that dexmedetomidine could reduce the incidence and severity of ED following surgery.[4,7,16] Moreover, the intraoperative infusion of magnesium sulphate significantly reduced the incidence of EA.[17] Although non-opioid analgesics, such as acetaminophen, may be beneficial, they always do not provide adequate pain relief when used alone. Ibuprofen, an NSAID, has been used in patients undergoing tonsillectomy owing to its analgesic and opioid-sparing effects. The American Academy of Otolaryngology-Head and Neck Surgery has categorically recommended ibuprofen as a safe NSAID for reducing postoperative pain in children undergoing tonsillectomy.[18] The use of propofol was considered beneficial for maintaining anesthesia following induction since it reduces EA; hence, total IV aneshtesia (TIVA) was chosen in our study. Although, this is not the standard anesthetic utilized in the United States and many other countries, it could supplement current studies.

In this randomized, double blind, placebo-controlled study, we hypothesized that IV ibuprofen following induction could reduce the incidence of EA in children undergoing tonsillectomy with or without adenoidectomy using TIVA with propofol and remifentanil. The secondary endpoint included the associated factors of EA in the children.

Methods

Study Design

This was a single-center, double-blind, placebo-controlled, randomized study. The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health (2021-E-015-Y-001). All the methods were carried out following the relevant guidelines and regulations. The procedures were conducted in accordance with the Declaration of Helsinki. The study was conducted at the Beijing Children's Hospital, China, from 9 April to 30 June 2021. Written informed consent was obtained from parents or guardians before performing any study procedures. The study was registered with the Chinese Clinical Trial Registry (number: ChiCTR2100045128, date: April 7, 2021). This article adhered to the Consolidated Standards of Reporting Trials guidelines.

Participants

We enrolled patients aged 3–9 years with an American Society of Anesthesiologists risk score of I–II undergoing elective low-temperature plasma-assisted total tonsillectomy with or without adenoidectomy. Children with autism and developmental delay, cognitive impairment, an abnormal electrolyte balance, preoperative analgesic treatment, previous surgery, allergy to the study drugs, hepatic, renal, neurological, or neuromuscular disease, craniofacial abnormalities, respiratory or cardiac disease, or patients who chose not to participate were excluded. All the patients underwent preoperative laboratory examination (routine blood examination and biochemical examination) and were hospitalized before the day of the surgery.

Randomization, Intervention, and Anesthesia Management

Potential participants were screened the day before the surgery by a study investigator. Patients were randomly assigned in a 1:1 ratio to receive IV ibuprofen or a placebo. The treatment allocation order was generated by permuted block randomization with a block size of 6 and was concealed with sequentially numbered sealed envelopes. On the day of the study, a third-party participant opened the envelope and prepared the study drug, which was indistinguishable from the other drug, and marked with a randomization code known only to the participant. Patients and clinical investigators who collected the clinical information were blinded to patient grouping until the final data analysis.

Lidocaine-prilocaine cream was applied to the venipuncture site to facilitate IV cannulation; thereafter, a peripheral IV was started in the ward. Upon patient arrival at the operating room, conventional monitoring, including electrocardiography, noninvasive blood pressure measurement, pulse oximetry, and bispectral index (BIS) monitoring (BIS Monitor Model A-2000 Aspect Medical Systems Inc., USA), was performed. Anesthesia was induced upon IV administration of propofol 2 $mg \cdot kg^{-1}$, fentanyl 2 $mcg \cdot kg^{-1}$, and cisatracurium 0.1 $mg \cdot kg^{-1}$ to facilitate endotracheal intubation. In addition, dexamethasone 0.5 $mg \cdot kg^{-1}$ (a maximum of 10 mg) was administered. After anesthesia induction, patients in the treatment group received a dose of 10 $mg \cdot kg^{-1}$ of IV ibuprofen slowly infused over 15 min, whereas, in the control group, a volume-matched normal saline infusion was slowly administered. Anesthesia was maintained with propofol and remifentanil, beginning with propofol 10 $mg \cdot kg^{-1} \cdot h^{-1}$ followed by an adjustment in the dose based on the BIS measurements (40–60) and remifentanil 0.3–0.4 $mcg \cdot kg^{-1} \cdot min^{-1}$, with the dose adjusted to analgesic requirements (systolic blood pressure changed within 20% of baseline values). Patients received lactated Ringer's solution as a maintenance fluid. Following the completion of surgery, ondansetron 0.1 $mg \cdot kg^{-1}$ was administered for preventing nausea and vomiting, the patients were transferred to the post-anesthesia care unit (PACU) and extubated once adequate spontaneous breathing was observed. Extubation time was the time interval between discontinuation of anesthetics and extubation. Patients were discharged with a prescription for oral ibuprofen for post-discharge pain management.

Data Collection and Outcomes

Data collected from the electronic anesthesia record included the demographic of the patients, the indication for surgery, the volume of infusion fluid during surgery, anesthesia duration, and extubation time. A modified Pediatric Anesthesia Behavior (PAB) score was used for evaluating the child's behavior and mood state before the induction of anesthesia (Supplemental Table 1). The PAB score had three points: happy, sad, and mad. The PAB scale was converted to the modified PAB score (2-point scale) by merging scale 2 and 3 of the PAB scale in this study. Prior to the study, the member who performed agitation and pain assessments was trained to follow standard procedures and to use the Pediatric Anesthesia Emergence Delirium (PAED) and Face, Legs, Activity, Cry, Consolability (FLACC) scales.[19,20] While the patients were undergoing recovery in the PACU, a similar blinded study team member who was not directly involved in the anesthesia induction measured the agitation and pain degree based on the PAED (Supplemental Table 2) and FLACC scale scores at 15 min and 30 min following extubation. EA was defined as a PAED score ≥10.[17] The restlessness and agitation appeared within 15min or during 15–30 min, an assessment of the agitation and pain degree was started immediately. Fentanyl 0.5 $\mu g \cdot kg^{-1}$ (maximum dose of 2 $\mu g \cdot kg^{-1}$) was administered to patients with EA or FLACC score >3 (moderate-severe pain) and repeated after 10 min if required. The primary outcome was a peak PAED score within 15min or during 15–30 min after extubation in the PACU.

Statistical Analyses

A previous study reported that the incidence rate of EA in pediatric patients undergoing tonsillectomy with propofol and remifentanil anesthesia ranged between 41.4% and 48.3% in the PACU.[16] We assumed that the average incidence rate of EA in this study was 45%. Based on our pilot study of 10 pediatric patients, the incidence of EA in patients receiving ibuprofen during tonsillectomy with TIVA was 20%, we presumed that a reduction in the incidence rate of >25% in the ibuprofen group would indicate a significant effect. The sample size was calculated using the tests for two proportions design model (one-sided, α=0.05, β=0.8, 10% dropout rate), with a group allocation of 1:1 using PASS (NCSS Statistical Software, UT). This resulted in a required sample size of 45 patients per group. Histograms and the Kolmogorov–

Smirnov test were used to assess the normality. Continuous variables are expressed as the mean±standard deviation or median (interquartile interval), as appropriate. To assess the differences between the two groups, the *t*-test was used for normally distributed continuous variables, whereas the Wilcoxon rank-sum test was used for non-normally distributed continuous variables. For categorical variables, the χ^2 test and Fisher's exact test were used. Our secondary analyses were used to create the multivariate logistic regression models to assess the association between EA and perioperative variables. Odds ratios (ORs) with 95% confidence intervals (CIs) for each factor were calculated in the logistic regression. Variables with statistically significant values ($P<0.1$) in the univariate model were entered into the multivariate model. Predictors tested included age, sex, body mass index (BMI), the modified PAB score, the indication for surgery, infusion fluid volume, use of ibuprofen, the FLACC score 15 min following extubation, anesthesia time, and extubation time. Model diagnostics were also reported, including the Hosmer–Lemeshow goodness-of-fit test, a receiver operating characteristic (ROC) curve, and the area under the curve (C-index). Statistical analyses were performed using the International Business Machines Statistical Package for the Social Sciences (SPSS) Statistics version 19.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 9.1 (GraphPad Software Company, San Diego, CA). We selected a significance threshold of $P<0.05$ for comparisons between groups.

Results

Patient Characteristics

Ninety-three patients were assessed for eligibility. One patient declined participation in the study, and two who had previously undergone hernia surgery were excluded. Finally, the 90 remaining patients were randomized. In the control group, one patient only underwent adenoidectomy based on the decision of the otolaryngologist during the surgery. Finally, 45 and 44 patients were included in the treatment and the control groups, respectively (Figure 1). All the surgeries were completed by two senior otolaryngologists. The mean age and BMI of the patients were 5.0 (4.0–7.5) years and 16.6 (14.7–18.0) kg/m^2, respectively. Furthermore, 47 and 42 patients were male and female, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1. There were no statistical differences in the age, sex, BMI, the number of obese children, the modified PAB score, the indication for surgery, the volume of infusion fluid, anesthesia time, and extubation time between the two groups. All patients had no postoperative hemorrhagic complications.

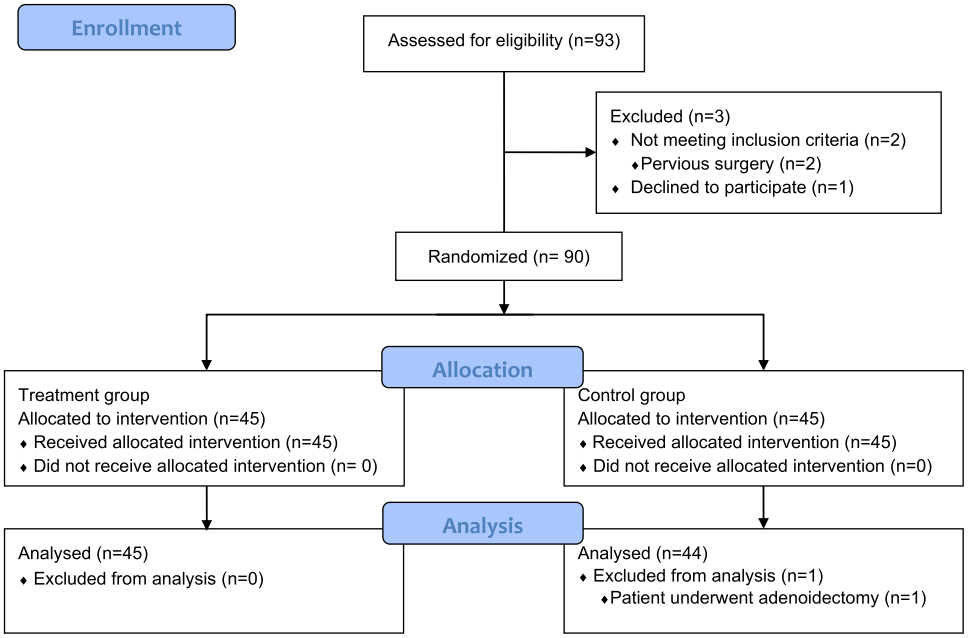

Figure 1 Flow diagram of the patients in the study.

Table 1 Demographic and Clinic Characteristics of the Participants

	Treatment Group (n=45)	Control Group (n=44)	*P* value
Male	24	23	0.920
Female	21	21	
Age (years)	5.0 (4.0–7.5)	5.5 (4.0–7.8)	0.531
BMI	16.6 (14.6–18.1)	16.3 (14.7–18.0)	0.783
Obesity (n)	10	10	0.954
The indication for surgery			
Tonsillitis	9	8	0.827
SDB/OSA	36	36	
The modified PAB score			
1 = happy	34	27	0.149
2 = unhappy	11	17	
The volume of infusion fluid (mL)	105 (75–135)	95 (81.5–135)	0.631
Anesthesia duration (min)	34.0 (30.5–47.0)	35.0 (30.0–45.0)	0.799
Extubation duration (min)	17.0 (12.0–29.0)	14.5 (10.0–19.8)	0.055

Note: Data are presented as median values (interquartile ranges) or number of cases.
Abbreviations: BMI, body mass index; PAB, pediatric anesthesia behavior; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea.

Incidence of Emergence Agitation and FLACC Scores and Rescue Fentanyl

The occurrence of EA and FLACC scale scores are shown in Table 2. The incidence of EA at the PACU was significantly lower in the treatment group than in the control group at 15 min following extubation (8.9% vs 34.1%; OR, 0.261; 95% CI, 0.094–0.724; *P*=0.004). Compared with the control group, fewer patients experienced moderate to severe pain at 15 min following extubation in the treatment group (*P*=0.048). Moreover, the treatment group had a lower FLACC scale score than the control group at this time point (*P*=0.007). Table 3 shows that the number of patients receiving rescue fentanyl did not differ between the two groups (22.2% vs 34.1%; OR, 0.652; 95% CI, 0.329–1.292; *P*=0.213); however, patients in the treatment group received fewer doses of rescue fentanyl compared to those in the control group (*P*=0.045). Besides, more patients required more than one dose of rescue fentanyl in the control group compared to the treatment group (25% vs 0%, *P*<0.001).

Associated Factors of EA

According to the univariate regression analysis, the remaining four predictors (age, the modified PAB score, FLACC score [15 min], and ibuprofen administration) were used as independent variables (Table 4).[21] After the multivariate logistic regression analysis, a high modified PAB and FLACC scores were the risk factors related to EA (OR, 8.07; 95% CI, 1.12–58.07; *P*=0.038 and OR, 2.78; 95% CI, 1.60–4.82; *P*<0.001, respectively). Moreover, IV ibuprofen administration was a protective factor related to EA at the PACU (OR, 0.05; 95% CI, 0.01–0.67; *P*=0.023 [Figure 2]). Pediatric patients with unhappy mood at induction had 8.07 times higher odds of developing EA compared with patients with calm and controlled anesthesia behavior.

Table 2 The Emergence Agitation (EA) and Pain Score at the Post-Anesthesia Care Unit (PACU)

	Treatment Group (n=45)	Control Group (n=44)	*P* value
Incidence of EA, n (%)			
15 min after extubation	4 (8.9%)	15 (34.1%)	0.004*
30 min after extubation	0	0	1.0
FLACC scale			
FLACC 15 min	1.0 (0–3.0)	3.0 (1.0–6.0)	0.007*
FLACC 15 min score >3, n (%)	8 (17.8%)	16 (36.4)	0.048*
FLACC 30 min	0 (0–1.0)	1.0 (0–2.0)	0.002*
FLACC 30 min score >3, n (%)	0	3(6.8%)	0.117

Note: Data are presented as medians (interquartile ranges) or number of cases. *$P<0.05$.
Abbreviations: FLACC, face, legs, activity, cry and consolability scale.

Table 3 The Rescue Analgesia at the Post-Anesthesia Care Unit (PACU)

	Treatment Group (n=45)	Control Group (n=44)	*P* value
Number of patients who received rescue fentanyl, n (%)	10 (22.2%)	15 (34.1%)	0.213
Number of rescue fentanyl doses	0 (0–0)	0 (0–1.8)	0.045*
Number of patients who received, n (%)			
≤1 Dose fentanyl	45 (100%)	33 (75%)	<0.001*
>1 Dose fentanyl	0	11 (25%)	

Note: Data are presented as medians (interquartile ranges) or number of cases. *P<0.05.

Table 4 Univariable and Multivariable Models of Multivariate Logistic Regression

	Univariable Model			Multivariable Model		
	B value	OR (95% CI)	*P* value	B value	OR (95% CI)	*P* value
Age (years)	−0.28	0.75 (0.57–0.99)	0.042	−0.54	0.58 (0.31–1.08)	0.086
Sex (female vs male)	0.01	1.01 (0.37–2.79)	0.986	–	–	–
BMI	−0.02	0.99 (0.84–1.15)	0.846	–	–	–
The modified PAB score (2 vs 1)	2.42	11.20 (3.45–36.35)	<0.001	2.09	8.07 (1.12–58.07)	0.038*
The indication (SDB/OSA vs tonsillitis)	−0.16	0.86 (0.24–3.01)	0.807	–	–	–
The infusion fluid volume (mL)	−0.01	0.99 (0.98–1.01)	0.275	–	–	–
Anesthesia duration (min)	−0.01	0.99 (0.95–1.03)	0.647	–	–	–
Extubation duration (min)	−0.03	0.97 (0.92–1.03)	0.366	–	–	–
FLACC 15 score	0.84	2.31 (1.63–3.28)	<0.001	1.02	2.78 (1.60–4.82)	<0.001*
Ibuprofen administration	−1.67	0.19 (0.06–0.63)	0.006	−3.01	0.05 (0.01–0.67)	0.023*

Notes: Two logistic regression models were fitted separately. In univariable models, variables with statistically significant values (P<0.1) were entered into the final multivariable model. Model diagnostics for final model: P value of Hosmer–Lemeshow goodness-of-fit test=0.998, and area under curve=0.973.*P<0.05.
Abbreviations: BMI, body mass index; PAB, pediatric anesthesia behavior; FLACC 15, face, legs, activity, cry and consolability scale 15 min after extubation; SDB, sleep-disordered breathing; OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval.

Each 1-point increase in the FLACC score was associated with a 1.78-fold increase in EA. Pediatric patients receiving IV ibuprofen were 95% less likely to develop EA than those not receiving ibuprofen. The Hosmer–Lemeshow goodness-of-fit test was non-significant (P=0.998), indicating that the model exhibited a good fit. The predictive ability of the EA risk was examined by generating an ROC curve, and the AUC (C-index) was 0.97 (95% CI, 0.94–1.0). The predictive performance of the EA risk was considered excellent when the C-index was >0.8.

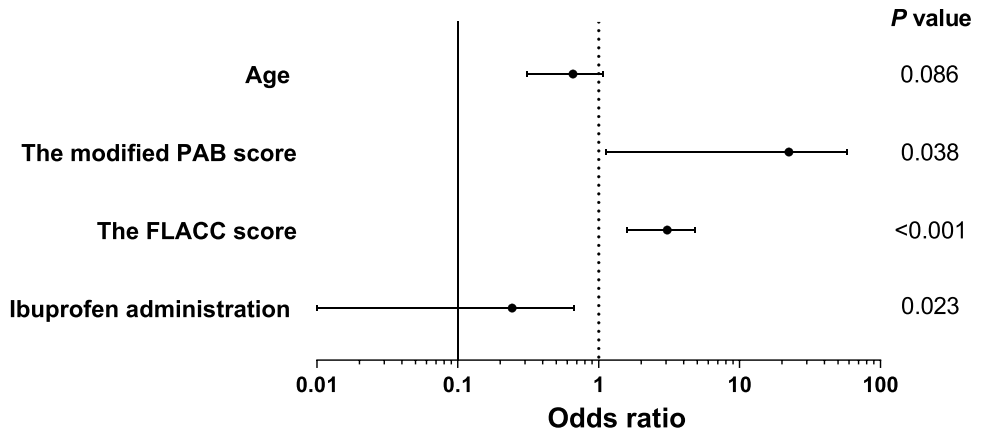

Figure 2 Association between the predictors and emergence agitation.
Abbreviations: FLACC, face, legs, activity, cry, consolability scale; PAB, pediatric anesthesia behavior.

Discussion

In this study, intraoperative infusion of ibuprofen significantly reduced the incidence of EA in pediatric patients aged 3–9 years following tonsillectomy. After IV ibuprofen infusion during surgery, fewer pediatric patients experienced moderate to severe pain following extubation in the treatment group. A review also pointed out that ibuprofen demonstrated a good safety profile and provided evidence for the effectiveness for mild-moderate pain of different origins in children, especially in the presence of inflammatory pathogenesis.[22] In addition, rescue fentanyl doses were significantly reduced in the treatment group compared with the control group, indicating an effective opioid-sparing effect. This was consistent with Moss et al's trial.[23] Interestingly, the number of patients who needed to receive a rescue dose of fentanyl was not significantly different between the two groups. This could be explained by the rescue criteria in our study. We set the FLACC score >3 (moderate to severe pain) as the standard for rescue fentanyl, resulting in six patients in the treatment group with moderate pain and without EA receiving fentanyl. This is an ethical consideration; we desired to relieve the pain of pediatric patients as much as possible. Additionally, in a pediatric randomized placebo-controlled trial by Maya Komazaki et al,[15] the incidence of EA was 67% in the blank control group, and sevoflurane was used for anesthesia maintenance. Here, TIVA with propofol and remifentanil was used for anesthesia maintenance, the incidence of EA was 34.1% in the control group and lower than that in Maya Komazaki's trial. A study from Uezono et al also observed that propofol-based anesthesia induced a significantly lower incidence of EA in children.[24] The PAB score was a simple score for children's behavior during induction of anesthesia, and its reliability and validity had been demonstrated in a previous study.[11] The PAED scale was used in children aged >2 years.[25] The FLACC demonstrated good interrater reliability and validity in children aged 2–6 years;[26] besides, a study from Nilsson et al supported the use of FLACC as a valid and reliable tool for assessing procedural pain in children aged 5–16 years;[27] thus, the PAB, PAED and FLACC scales can be used in our study cohort.

Optimal pain management in children with tonsillectomy remains a challenge. NSAIDs are a promising option for the treatment of postoperative pain in children. The opioid-sparing effect of NSAIDs has been observed in a previous study.[28] Reducing the use of opioids could lead to a reduction in opioid-related complications, including vomiting and respiratory system issues. Previous studies stated that remifentanil infusion during surgery was associated with higher postoperative pain scores, acute opioid tolerance, and hyperalgesia.[29,30] A better intraoperative prophylactic analgesic regimen for postoperative pain control was necessary in our study. Ibuprofen has anti-inflammatory properties that can limit the inflammatory cascade caused by surgical trauma and reduce the development of postoperative pain, making it a convincing option. In our institution, several anesthesiologists are hesitant to use ibuprofen in tonsillectomies owing to their potential for hemorrhage. A recent Cochrane review concluded that NSAIDs did not induce any increase in bleeding that required surgical intervention in pediatric tonsillectomy.[31]

EA has been considered as a behavioral and mental disturbance during recovery from general anesthesia that may manifest as agitation, delusion, inconsolable, crying restlessness, disorientation, and cognitive impairment.[25] To predict the incidence of EA in children aged 3–9 years following tonsillectomy with propofol-based anesthesia, we established a logistic regression prediction model, which demonstrated excellent predictive performance (C-index >0.8). In this randomized controlled study, some risk factors of EA, which had been revealed through various previous studies, were consistent between patients with or without EA, such as an endotracheal tube, operative procedure, and anesthetics (TIVA or inhalation).[32–34] Among the candidate predictors of EA, the FLACC scores and dose of rescue fentanyl were highly correlated with each other. Thus, the dose of rescue fentanyl was excluded in the univariate model to avoid multicollinearity. In the multivariate model, the risk factors for EA were the high modified PAB and FLACC scores. With an unhappy mood at induction and increasing pain following surgery, the probability of EA increases. A prospective observational study also revealed that the PAB score was associated with EA.[21] In addition, our study confirmed that the patients who received intraoperative IV ibuprofen infusion to relieve postoperative pain were less likely to develop EA than patients in whom the pain was not controlled, which was consistent with many previous studies. They demonstrated that some medications or methods to relieve postoperative pain, such as ketamine, dexmedetomidine, acupuncture management, and intraoperative auditory stimulation, can reduce the occurrence of EA in children.[35–38] Interestingly, age was not a risk factor in the logistic regression model, possibly because most of the patients in this study were of preschool age, and according to previous studies, preschool age is a risk factor.

Moreover, contrary to the results of Hino et al's study,[21] the duration of anesthesia was not a risk factor in our study. They found that the incidence of EA increased only when the duration of anesthesia was >1 h in children. In our study, most of the patients were anesthetized for less than an hour; thus, the duration of anesthesia was not considered a risk factor in our study. In addition, a previous study developed and validated an EA risk scale for children; anesthesia time was one of the scale points, the score for anesthesia less than 1 hour was 0 indicating that anesthesia duration less than 1 hour was not a risk factor for EA, which was consistent with our study.

This study has some limitations. First, this was a single-center study, and the anesthesia duration was consistent (<1 h) in our institution. Therefore, if the duration of anesthesia is prolonged in tonsillectomy at other centers, the predictive power of anesthesia duration needs to be reanalyzed. Second, all the patients were anesthetized with propofol and remifentanil; therefore, the outcome of the study cannot be applied to patients anesthetized with other anesthesia techniques, such as volatile anesthetics, and the administration of remifentanil might increase the between-group difference of the postoperative pain score and doses of rescue fentanyl. Third, enrolling more preschool patients at risk for EA may provide better data than lower-risk patients aged 7–9 years. Fourth, the PAED sensitivity typically had a very narrow range with sensitivity dropping significantly between a score of ≥10 and >12;[39] we set PAED score ≥10 as a threshold, which could increase the positive outcomes. Additional limitations of the study included the small sample size of our study considering the secondary endpoint, and the OR value of the modified PAB score had a slightly wide CI. Besides, for the recommendation from otolaryngologists, a higher dose of dexamethasone was administered routinely during pediatric tonsillectomy in our institution. Lastly, postoperative follow-up to further analyze whether intraoperative ibuprofen administration affected postoperative agitation was not performed.

In conclusion, the intraoperative infusion of ibuprofen can significantly reduce the incidence of EA following general anesthesia with propofol and remifentanil in pediatric patients aged 3–9 years undergoing tonsillectomy.

Data Sharing Statement

The key data are contained in the figures, tables, and additional files. The datasets used and/or analyzed during this study can be further obtained from the corresponding author, Jianmin Zhang, on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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