Effectiveness of Intravenous Ibuprofen On Emergence Agitation in Children Undergoing Tonsillectomy With Propofol Anesthesia: A Double-Blind, Placebo-Controlled, Randomized Study

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Research Article

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Abstract

Background: Emergence agitation (EA) has a negative effect on recovery from general anesthesia in children.

Objectives: 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 study analyzed data from patients aged 3–9 years undergoing tonsillectomy with propofol general anesthesia. These patients were randomly assigned to receive either the ibuprofen or the placebo intraoperatively. The primary endpoint was between-group difference in the incidence of EA after surgery. 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 (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; $P = 0.004$). After the logistic regression analysis, anxiety behavior pre-anesthesia and high pain score after surgery 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). Ibuprofen administration was the protective factor related to EA (OR, 0.05; 95% CI, 0.01–0.67, $P = 0.023$).

Conclusions: In our studied cohort, intraoperatively infusing ibuprofen and relieving preoperative anxiety and postoperative pain can significantly reduce the incidence and severity of EA after propofol general anesthesia.

Trial registration: ChiCTR2100045128 (07/04/2021)

Background

The term emergence agitation (EA) describes an unsettled behavior in children, associated with pain, hunger, thirst, and fear due to the absence of primary caregivers or unfamiliar surroundings. Pediatric EA is an early negative postoperative behavior and consists of 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 after general anesthesia and 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] The terms EA and ED have been used interchangeably in some previous studies.[4, 5] The incidence rate of EA in children induced with general anesthesia ranges from 10–80%. During EA, children can remove intravenous catheters and drains, damage the surgical site, and injure themselves or the medical staff.[6] The most known risk factors for EA are the presence of an endotracheal tube, preschool age, volatile anesthetics, surgical procedures (ophthalmology and otorhinolaryngology), pre-existing

behavior, negative behavior on induction, and postoperative pain.[7–13] Although EA can occur in any age group, it is more generally observed in children aged 3–9 years than in other age groups.[14] The incidence rate of EA is 41.4–48.3% in children undergoing tonsillectomy with propofol and remifentanil anesthesia.[15]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), has been used in patients undergoing tonsillectomy due to its analgesic and opioid-sparing effects; however, in our institution, several anesthesiologists are hesitant to use ibuprofen in tonsillectomies due 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.[16] Moreover, the American Academy of Otolaryngology-Head and Neck Surgery has recommended ibuprofen as a safe NSAID to reduce postoperative pain in children undergoing tonsillectomy.[17]

We performed total intravenous anesthesia (TIVA) with propofol and remifentanil to detect the effectiveness of intravenous ibuprofen 10 $mg{\cdot}kg^{-1}$ in reducing the incidence of EA in children undergoing tonsillectomy with or without adenoidectomy. The secondary endpoint included factors associated with 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, Beijing, China (Chairperson Prof Guojun Zhang) on 23 March 2021 (2021-E-015-Y-001). All methods were performed according to relevant guidelines and regulations. The study was conducted at the Beijing Children’s Hospital, China, from April to June 2021. Written informed consent was obtained from the parents or guardians before the study procedures were performed. The study was registered with the Chinese Clinical Trial Registry (number: ChiCTR2100045128, date: 07/04/2021). 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 tonsillectomy with or without adenoidectomy. Children with an abnormal electrolyte balance, previous analgesic treatment, allergy to the study drugs, hepatic, renal, neurological, or neuromuscular disease; craniofacial abnormalities; respiratory or cardiac disease; and patients who chose not to participate were excluded.

Randomization, intervention, and anesthesia management

Patients were randomly assigned in a 1:1 ratio to receive intravenous ibuprofen or 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 each other and marked with a randomization code known only to the participant. Patients and clinical investigators who collected clinical information were blinded to the patient grouping until the final data analysis.

Upon patient arrival in 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 administered intravenously with propofol 2 $mg \cdot kg^{-1}$, fentanyl 2 $mcg \cdot kg^{-1}$, and cisatracurium 0.1 $mg \cdot kg^{-1}$ to facilitate endotracheal intubation. After the induction of anesthesia, patients in the treatment group received a dose of 10 $mg \cdot kg^{-1}$ of intravenous ibuprofen slowly 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 dose depending on 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). After the completion of surgery, the patients were transferred to the post-anesthesia care unit (PACU) and extubated once adequate spontaneous breathing was observed. Extubation time was defined as the time interval between discontinuation of anesthetics and extubation.

Data collection and outcomes

Statistical analysis

Previous studies have revealed that the incidence rate of EA in pediatric patients undergoing tonsillectomy with propofol anesthesia ranges between 41.4% and 48.3% in the PACU. We assumed that the average incidence rate of EA in this study was 45%. Based on our pilot study, we supposed 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 a two-proportion design model (one-sided, $\alpha=0.05$, $\beta=0.8$, 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 tests were used to assess normality. Continuous variables are expressed as 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 $\chi 2$ test and Fisher's exact test were used. Secondary analyses were used to build 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 using 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), pre-anesthesia score, use of ibuprofen, 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 analysis was 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 to participate in the study, and two patients who did not meet the inclusion criteria were excluded. Finally, 90 patients were randomized. In the control group, one patient only underwent adenoidectomy, depending on the decision of the otolaryngologist during the surgery. Finally, 45 and 44 patients were included in the treatment and control groups, respectively (Figure 1). 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 men and women, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1. There were no statistical differences in age, sex, BMI, pre-anesthesia score, anesthesia time, and extubation time between the two groups.

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
The pre-anesthesia score			
1 = happy	34	27	0.149
2 = unhappy	11	17	
Anesthesia time (min)	34.0 (30.5- 47.0)	35.0 (30.0 - 45.0)	0.799
Extubation time (min)	17.0 (12.0 -29.0)	14.5 (10.0 -19.8)	0.055
Data are presented as median value (interquartile range), or number of cases. BMI, body mass index.			

Incidence of emergence agitation and Pediatric Anesthesia Emergence Delirium and Face, Legs, Activity, Cry, Consolability scores

The PAED and FLACC scores are presented in Table 2. After 15 and 30 min of extubation, the PAED score was lower in the treatment group than in the control group (P = 0.008 and P = 0.012, respectively). Moreover, the treatment group had a lower FLACC scale score than the control group (P = 0.007 and P = 0.002, respectively). The incidence rate of EA at the PACU was significantly lower in the treatment group than in the control group (8.9% vs. 34.1%; OR, 0.261; 95% CI, 0.094–0.724; P = 0.004). 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).

Table 2
The emergence agitation and pain score at the PACU

	Treatment group (n=45)	Control group (n=44)	*P* value
PAED scale			
PAED 15	1.0 (0 -5.0)	3.5 (0.3 - 10.0)	0.008*
PAED 30	0 (0 - 0.5)	0.5 (0 - 3.0)	0.012*
Incidence of EA, n (%)			
PAED 15	4 (8.9)	15 (34.1)	0.004*
PAED 30	0 (0)	0 (0)	1.0
FLACC scale			
FLACC 15	1.0 (0 - 3.0)	3.0 (1.0 - 6.0)	0.007*
FLACC 30	0 (0 - 1.0)	1.0 (0 - 2.0)	0.002*
Number of patients n (%)	10 (22.2)	15 (34.1)	0.213
receiving rescue fentanyl			
Data are presented as median (interquartile range), or number of cases.			
PAED, Pediatric Anesthesia Emergence Delirium; FLACC, Face, Legs, Activity, Cry, Consolability			
*P < 0.05			

Associated factors of EA

According to the univariate regression analysis, the remaining four predictors (age, pre-anesthesia score, FLACC score [15 min], and ibuprofen administration) were used as independent variables (Table 3).[20] After the multivariate logistic regression analysis, a high pre-anesthesia and FLACC score 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, intravenous 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 anxiety had 8.07 times higher odds of developing EA compared to patients with calm and controlled anesthesia behavior. Each 1-point increase in the FLACC score was associated with a 1.78-fold increase in EA. Pediatric patients receiving intravenous ibuprofen were 95% less likely to develop EA than those who did not receive ibuprofen. The Hosmer–Lemeshow goodness-of-fit test was not 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) (Figure 3). The predictive performance of the EA risk was considered excellent when the C-index was > 0.8.

Table 3
Univariable and multivariable model 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 pre-anesthesia score (2 vs 1)	2.42	11.20 (3.45 - 36.35)	<0.001	2.09	8.07 (1.12 - 58.07)	0.038*
Anesthesia time (min)	-0.01	0.99 (0.95 - 1.03)	0.647	-	-	-
Extubation time (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*
Two logistic regression models were fitted separately. In univariate models, variables with statistically significant values ($P < 0.1$) were entered into the final multivariate model. Model diagnostics for final model: *P* value of the Hosmer–Lemeshow goodness-of-fit test = 0.998, and area under curve = 0.973.						
BMI, body mass index; FLACC 15, Face, Legs, Activity, Cry Consolability scale 15 min after extubation.						
*$P < 0.05$						

Discussion

In this study, intraoperative infusion of ibuprofen significantly reduced the incidence and severity of EA in pediatric patients aged 3–9 years after tonsillectomy. The patients who received intravenous ibuprofen had lower PAED and FLACC scores than patients who did not receive ibuprofen, indicating that the agitation level was lower than that in the control group, and intravenous ibuprofen more effectively relieved postoperative pain in pediatric patients after tonsillectomy. 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 used in the present 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 want to relieve the pain of pediatric patients as much as possible. An additional finding of this study was that the

FLACC score was lower in the treatment group than in the control group at 30 min after extubation. According to the data (Table 2), all patients in both groups had mild pain (FLACC score ≤ 3); thus, this difference in score value had no clinical implications.

Optimal pain management in children undergoing tonsillectomy remains a challenge. NSAIDs are a promising option for the treatment of postoperative pain in children. The opioid-sparing effect of NSAIDs was observed in a previous study.[21] Reducing the use of opioids could lead to a reduction in opioid-related complications, including vomiting and respiratory system issues. Ibuprofen has anti-inflammatory properties that can limit the inflammatory cascade caused by surgical trauma and reduce the development of postoperative pain. If intravenous ibuprofen is administered before surgery, therapeutic cerebrospinal fluid and blood levels are assessed by the time a patient arrives in the PACU after this short surgery.[22]

EA has been considered as a behavioral and mental disturbance during recovery from general anesthesia that may manifest as agitation, delusion, inconsolability, crying restlessness, disorientation, and cognitive impairment.[23] To predict the incidence of EA in children aged 3–9 years after tonsillectomy with propofol anesthesia, we established a logistic regression prediction model, which showed 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 endotracheal tube, operative procedure, and anesthesia (TIVA or inhalation).[24, 25] 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 from the univariate model to avoid multicollinearity. In the multivariate model, the risk factors for EA were high pre-anesthesia and FLACC scores. With increasing anxiety before surgery and increasing pain after surgery, the probability of EA increases. Patients who received intraoperative intravenous ibuprofen infusion were less likely to develop EA than those who did not receive ibuprofen infusion. 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 was a risk factor. Moreover, unlike the results of Hino et al.,[20] 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 anaesthetized for less than an hour; thus, anesthesia time was not a risk factor in our study.

This study has some limitations. First, this was a single-center study, and the anesthesia time was consistent (< 1 h) at our institution. Therefore, if the duration of anesthesia is prolonged in tonsillectomy at other centers, the predictive power of anesthesia time needs to be reanalyzed. Second, all patients were anaesthetized with propofol and remifentanil; therefore, the outcome of the study cannot be applied to patients anaesthetized with other anesthesia techniques such as volatile anesthetics. Third, the sample size of our study was small, and the OR value of the pre-anesthesia score had a slightly wider confidence interval. Fourth, postoperative follow-up was not performed to further analyze whether intraoperative ibuprofen administration affected postoperative agitation.

Conclusion

In summary, the intraoperative infusion of ibuprofen can significantly reduce the incidence and severity of EA after general anesthesia induction in pediatric patients aged 3–9 years undergoing tonsillectomy. Pediatric patients with anxiety before anesthesia induction and more pain after surgery have an increased risk of developing EA.

Abbreviations

BIS, Bispectral index

CI, Confidence interval

EA, Emergence agitation

ED, Emergence delirium

NSAID, Non-steroidal anti-inflammatory drug

PACU, Post-anesthesia care unit

PAED, Pediatric Anesthesia Emergence Delirium

ROC, Receiver operating characteristic

SPSS, Statistical Package for the Social Sciences

TIVA, Total intravenous anesthesia

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University, National Center for Children's Health on 23 March 2021 (2021-E-015-Y-001). Written informed consent was obtained from parents or legal guardians before any study procedures were performed. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1964, as revised in 2000. The study was registered with the Chinese Clinical Trial Registry under the number ChiCTR2100045128.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing of interests.

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Authors' contributions: ZZ. G: Study design, data collection and writing up of the manuscript; JM, Z: Study design, analysis and interpretation of data; XL. N: Study design, data analysis and critically revised the manuscript; XH. C: Data collection and analysis, writing up of the manuscript.

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Analg. 2004;99(6):1648–54, table of contents.

Figures

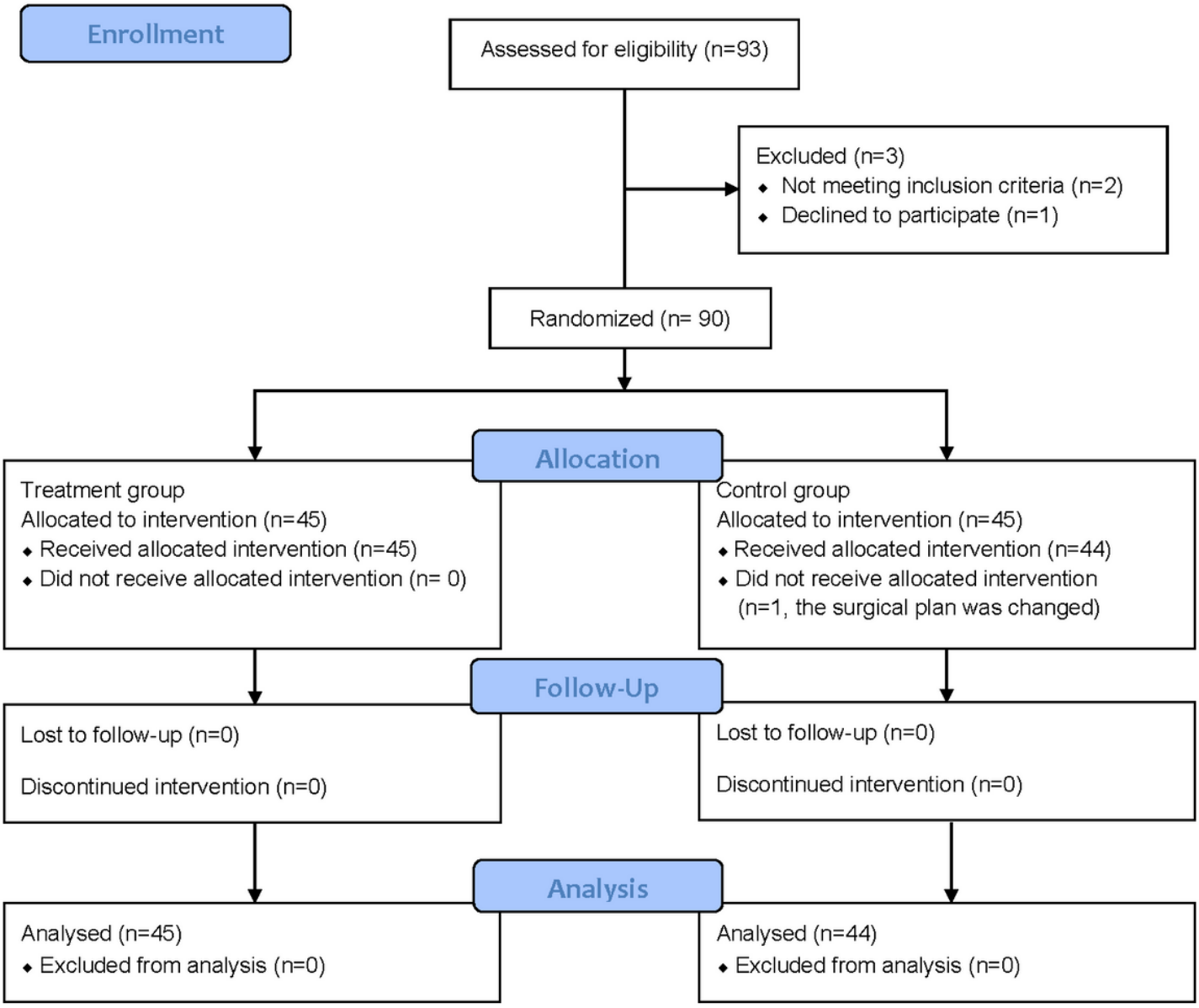

Figure 1

Flow diagram of the patients in the study.

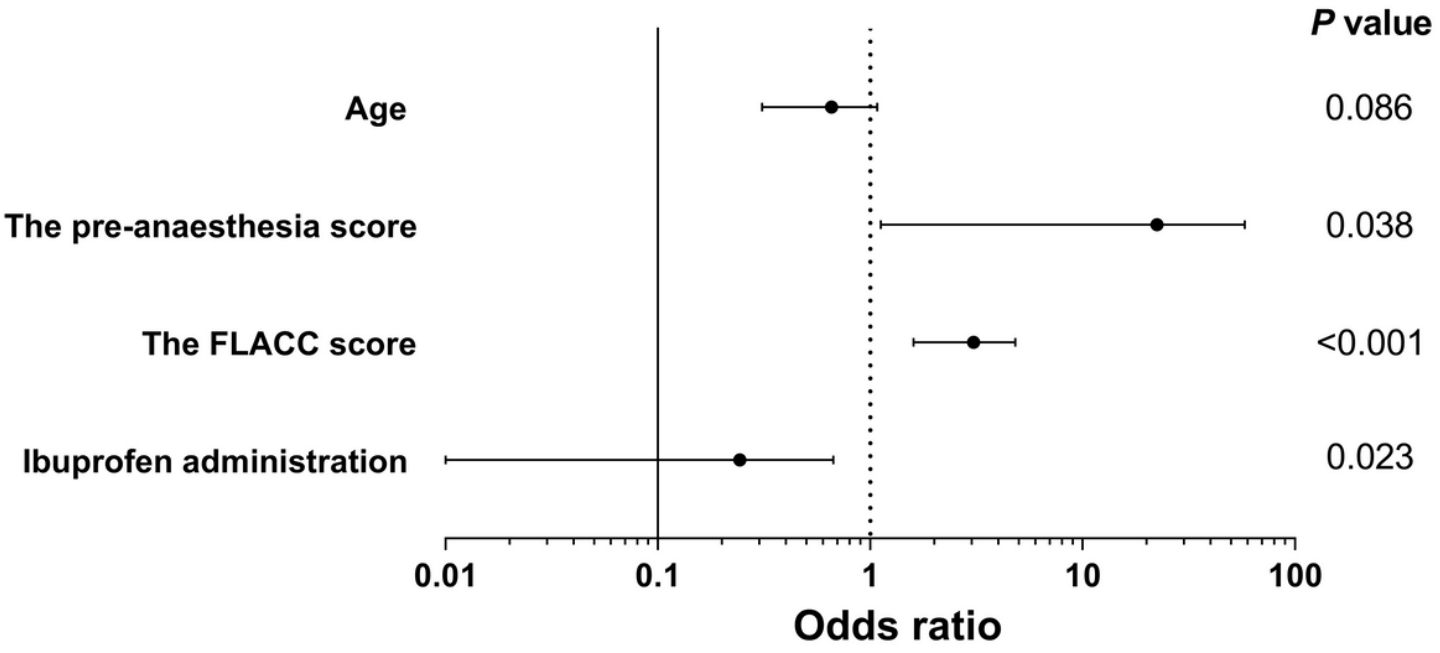

Figure 2

Association between predictors and emergence agitation.

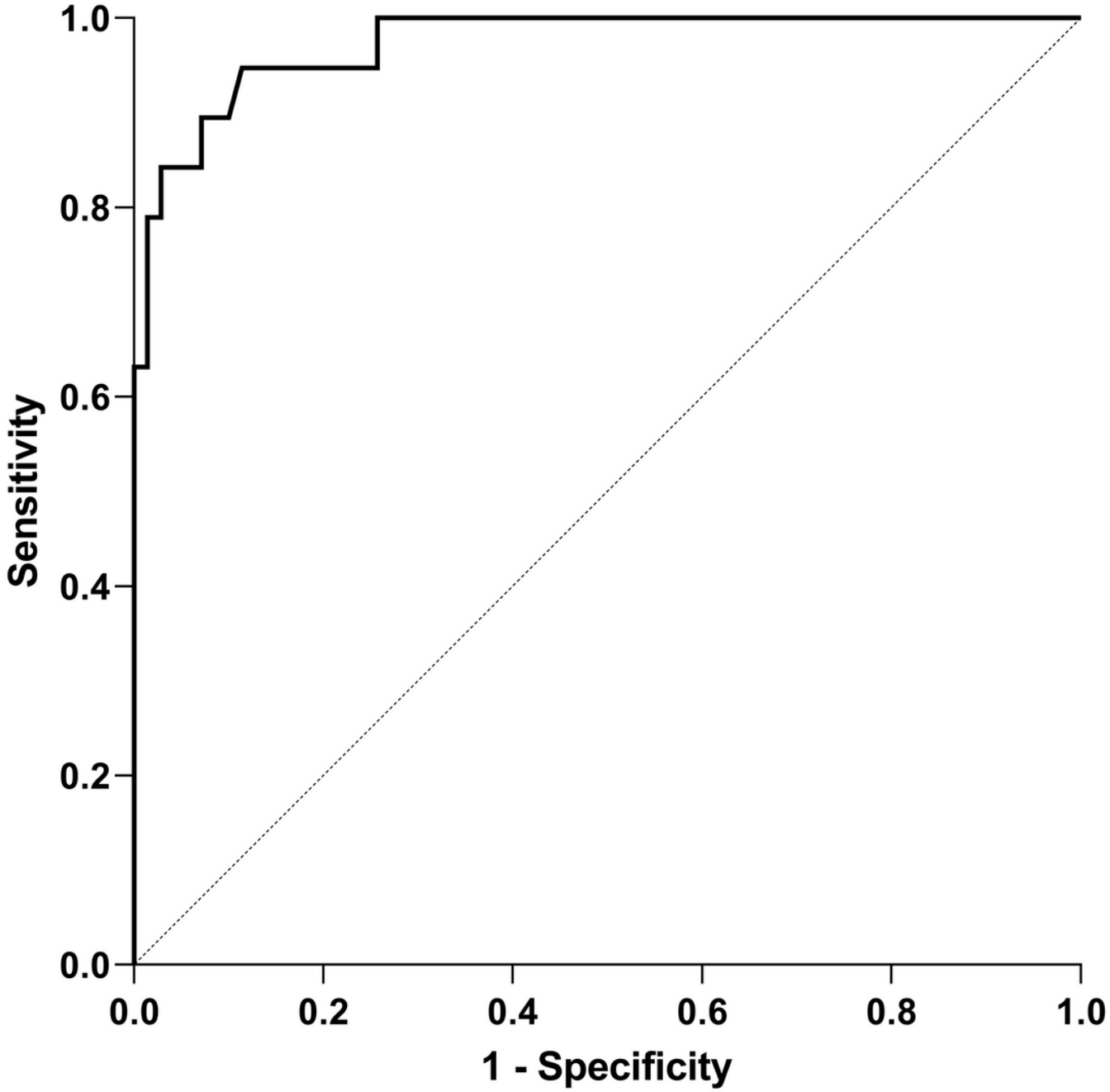

Figure 3

The ROC curve for examining the predictive ability of the final model. The black line indicates the ROC curve. The area under the ROC curve (C-index) was 0.97 (95% CI, 0.94–1.0). ROC, receiver operating characteristic; CI, confidence interval.

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